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Review Article

Linking Persistent Pain and Frailty in Older Adults

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Abstract

Objective. In older adults, the impact of persistent pain goes beyond simple discomfort, often contributing to worsening functional outcomes and ultimately frailty. Frailty is a geriatric syndrome that, like persistent pain, increases in prevalence with age and is characterized by a decreased ability to adapt to common stressors such as acute illness, thereby increasing risk for multiple adverse health outcomes. Evidence supports a relationship between persistent pain and both the incidence and progression of frailty, independent of health, social, and lifestyle confounders. **Design and Setting.** In this article, we synthesize recent evidence linking persistent pain and frailty in an effort to clarify the nature of the relationship between these two commonly occurring geriatric syndromes. **Setting.** We propose an integration of the frailty phenotype model by considering the impact of persistent pain on vulnerability toward external stressors, which can ultimately contribute to frailty in older adults. **Results and Conclusions.** Incorporating persistent pain into the frailty construct can help us better understand frailty and ultimately improve care for patients with, as well as those at increased risk for, pain and frailty.

Key Words: Persistent Pain; Frailty; Older Adults

Introduction

The health of aging populations in developed countries has not kept pace with improvements in life expectancy. Many older adults spend their final years coping with and managing the consequences of multiple chronic conditions. One of the most common of these is persistent pain. Persistent pain is associated with numerous age-related chronic conditions, occurring in up to 50% of community-dwelling older adults [1]. Many chronic conditions—such as osteoarthritis, osteoporosis, and stroke—are associated with both nociceptive and neuropathic pain and increase in frequency with age [2,3].

The consequences of untreated or inadequately treated pain are significant and include impaired quality of life and sleep, as well as decreased immune functioning, cognition, and mobility. Pain is by far the most frequently cited symptom causing activity of daily living disability in later life [4]. Persistent pain in older adults should be considered a geriatric syndrome that frequently leads to deleterious outcomes, including loss of mobility and independence, sarcopenia, and declines in strength [5]. These pain-related consequences have a close relationship with and are similar to those found in older adults with frailty.

What is frailty? Frailty is a geriatric syndrome that, like persistent pain, increases in prevalence with age [6]. Frailty is a conceptual framework in modern geriatric medicine; frailty represents a state where an individual is independent but at high risk of developing disability [7]. Once frailty develops, affected individuals are more vulnerable to external stressors; they are also prone to developing dependency and having a reduced life expectancy [8]. Frailty is thought to be the final result of dysregulation in diverse physiological systems and increases the risk of adverse health outcomes, including institutionalization and mortality [9].

Several definitions of frailty have been proposed. The most recognized and accepted definition is "a state of increased vulnerability to poor resolution of homeostasis after a stressor event, resulting from cumulative loss of physiological reserve" [10]. Furthermore, the phenotypic

model is the most widely validated and accepted construct for frailty. In this model, frailty is viewed as a physiological syndrome, defined by the presence of least three of the following: weight loss, slow gait speed, low activity level, exhaustion, and weakness [11]. The phenotypic model—first proposed by Fried and colleagues—provides a basis for examining the underlying causes of (and identifies specific targets for interventions aimed at reducing) vulnerability to external stressors [12].

In this narrative review, we synthesize recent evidence linking persistent pain and frailty in an effort to clarify the nature of the relationship between these two commonly occurring geriatric disorders. A growing evidence base supports the notion that pain is an important contributor to both frailty onset and progression. We call for more appropriate frailty assessments and the development of interventions to address individuals with as well as those who are at risk for frailty.

Linking Pain and Frailty: Pain Homeostenosis

Homeostenosis is a well-established geriatric concept referring to the characteristic and progressive reduction of homeostatic reserve that occurs with aging in organ systems. This concept was first described by Cannon in the 1940s [13]. Homeostenosis manifests as an impaired ability to compensate in the face of internal or external challenges, restricting an individual's ability to successfully respond to stressors in biological, psychological, and social systems. Frail older adults who experience homeostenosis are unable to regain a steady state after experiencing a stressor such as an infection, malnutrition, hospitalization, or surgery [14], which stands in contrast to the usual ability to recover homeostasis. Unable to recover equilibrium, affected individuals often spiral into further decline and disability [15].

Persistent pain is a well-known stressor that makes maintaining homeostasis difficult for many older adults. It has been observed that persistent pain may precipitate frailty onset and accelerate its progression through several combined mechanisms, such as impaired mobility, depression, and decreased nutritional intake. These changes could in turn predispose older adults to experiencing greater levels of vulnerability, making them less able to effectively respond to physiological stressors [5,16]. This phenomenon was first described in 2012 by Shega and colleagues and defined as "pain homeostenosis" [17].

Persistent pain shares several similarities with frailty: Both are multidimensional in nature, share interconnected etiological relationships that lead to heightened vulnerability to external stressors, and increase risk for deleterious clinical and functional outcomes. A growing body of evidence indicates a causal relationship between pain and frailty that is briefly summarized below.

Evidence of an association between pain and frailty was first published in 2008. Blyth and colleagues analyzed data from the CHAMP study (participants included 1,705 Australian men aged 70 and above) and demonstrated an independent association between intrusive pain and frailty, after adjusting for relevant confounders [18]. Shega and colleagues further documented a cross-sectional association between pain, frailty, and mortality [19]. Other cross-sectional studies confirmed these findings in both European and Asian populations [20].

In 2016, a well-conducted prospective study documented that persistent pain is associated with the development, and also worsening, of frailty. To our knowledge, this longitudinal study was the first to confirm an independent association between persistent pain measured at baseline and the development of frailty over a 4.3-year follow-up period [21]. In addition, a large observational study of community-dwelling older adults found that those with (vs without) persistent pain were significantly more likely to endorse each frailty criterion and to be considered frail [22]. In this study, persistent pain was considered to be a sixth frailty criterion, and both the construct and predictive validity of this updated phenotypic frailty model were established. Recently, a systematic review of five prospective studies with >13,000 participants demonstrated that participants with persistent pain at baseline had a twofold increased risk of developing frailty [23]. Collectively, these data support a causal relationship between persistent pain and frailty. In the next section, we describe possible mechanisms underlying the persistent pain–frailty relationship and propose an update of the traditional paradigm of frailty.

Incorporating Persistent Pain into the Frailty Construct: A New Paradigm

Persistent pain and its sequelae (e.g., loss of mobility, sleep disturbance, social isolation) heighten an older individual's vulnerability to stressors, which can in turn increase their risk of developing, or experiencing worsening, frailty. Consistent with this hypothesis, Karp and colleagues have argued that, due to its multidimensional impact on older adults, persistent pain negatively impacts physiologic systems, reduces reserve, and decreases an individual's ability to maintain homeostasis [24]. These effects provide a mechanistic interpretation for the evidence of a dose–response relationship between pain intensity and frailty [22]. That is to say, the greater the severity of pain an older adult experiences, the greater the decline in physical activities and autonomy, which in turn increases the individual's risk of sarcopenia and ultimately frailty [25]. Older adults with (vs those without) persistent pain are less physically active and experience more comorbidities as well as worse functional mobility [26]. In addition, pain of higher (vs lower) intensity is more disabling [27], increasing the risk of frailty onset [28].

But what biological mechanisms link persistent pain with frailty? Several observations offer clues regarding possible underlying mechanisms. First, persistent pain

results in impaired mobility, decreased resting metabolic rate, and decreased protein and caloric intake, as well as social isolation. Second, it has been observed that frailty onset causes brain changes, which may alter the experience of pain by impairing the descending inhibitory system and pain modulation [16]. Third, perturbations in the hypothalamic pituitary adrenal (HPA) axis have been linked with persistent pain [29]. Persistent pain and associated conditions (e.g., psychological distress, poor sleep, and obesity) [30] can activate the HPA axis, thereby increasing cortisol levels. HPA axis dysregulation is also a mechanism thought to be important in the onset of frailty [31]. Fourth, persistent pain and frailty are linked through the immune-inflammatory response. Inflammation through cytokine release, which occurs in the setting of painful conditions, is associated with greater pain-related psychological distress, and this condition typically also occurs in the frailty syndrome [32]. This evidence—both clinical and pathophysiological—supports a strong bidirectional link between persistent pain and frailty in older adults. The current evidence suggests that persistent pain plays an important role in the development and worsening of frailty and supports the proposed implementation of persistent pain into the frailty pathway. For these reasons, we propose an integration of persistent pain as an external contributor in the cycle of frailty.

The presence of comorbidities may directly contribute to pain. In later life, socioeconomic and psychological conditions directly impact pain and health status as well. In fact, the experience of depression and social losses (e.g., status, independence, spouse/partner, friends, financial income) constitute significant stressors in later life. When these negative issues overwhelm psychological, cognitive, and physical resources, descending inhibition of persistent pain conditions may be compromised and represent the first step toward pain development and chronicization and frailty onset.

Interventions Targeting Frailty

To analyze further the persistent pain–frailty relationship, it is important to consider interventions directed at ameliorating frailty and their effects among older adults with persistent pain. Despite the paucity of evidence to guide interventions seeking to reduce frailty, the most frequently recommended approaches employ physical exercise and nutritional support (e.g., foods rich in energy and proteins).

If we look at ameliorating pain, there is strong clinical evidence that physical exercise plays an important role in mitigating pain levels in patients with knee or hip osteoarthritis [33]. In particular, resistance training is beneficial in reducing pain, improving proprioception, and enhancing older osteoarthritic adults' abilities to perform activities of daily living [34]. Resistance training contributes to the maintenance of functional abilities, preventing older adults from developing sarcopenia, falls, fractures, disabilities, and persistent pain [35].

Other evidence, although preliminary, suggests that nutrition and nutraceuticals may also play a role in pain management and could help older patients to mitigate the impact of persistent pain and improve quality of life. Nutritional elements may help to improve persistent pain management through antioxidant and anti-inflammatory properties [36]. The amino acid precursors of pain-modulating neurotransmitters have been shown to potentiate pain medications, sometimes reducing the amount of opioids needed [37,38]. Several trials have also identified an association between vitamin D level and nociceptive pain (e.g., low back pain), but less is known about vitamin D analgesic properties [39,40]. The novel properties of food and nutrients deserve greater attention as interventions to mitigate pain from both clinicians and scientists.

Clinical Implications of Linking Persistent Pain and Frailty

Developing effective treatments that reduce frailty occurrence and progression is challenging because of frailty's complexity and multifaceted nature. As a consequence, therapeutic interventions targeting frailty in older adults are often difficult to implement in practice. In contrast, pain can be more easily measured and managed than frailty: A range of treatments—both pharmacological and nonpharmacological—are available with demonstrated ability to improve patient outcomes [41].

Recognizing persistent pain as a contributor to frailty has clinical implications.

It is universally accepted that Comprehensive Geriatric Assessment (CGA) is the best way to assess overall health in older adults. A CGA helps to identify care needs and establish goal-oriented management plans [42]. While conducting the CGA, clinicians should screen for the presence of frailty. For that purpose, several tools have been identified and validated; upwards of 20 frailty tools have been developed to measure frailty, and they generally focus on one or more of the five core domains that define the frailty phenotype: slowness, weakness, low physical activity, exhaustion, and weakness [43].

For health care providers, viewing persistent pain as a risk factor for frailty onset and progression should encourage a broader perspective when assessing and treating older adults with persistent pain. In these patients, pain should not be seen as an isolated symptom due to an acute or chronic disease, but rather it should be viewed as a condition that predicts heightened vulnerability to stressors and worsening health status [44]. In all older patients with persistent pain, a frailty assessment is strongly advocated; in particular, performing simple physical tests (e.g., handgrip strength test using a dyanometer [45], or measuring speed gait, or performing Timed Up and Go [46]) or multidomain questionnaires

(e.g., Edmonton Frail Test [47], Prisma-7 [48]) may be helpful for calibrating better treatment and also for measuring clinical outcomes.

This approach would allow clinicians to routinely incorporate pain management strategies, when appropriate, in individuals with frailty (or prefrailty), and it could potentially contribute to a delay or prevent several frailty-related deleterious outcomes, including disability dependence and reliance on long-term care [49].

In older adults, better pain control has been associated with better functional abilities [50]. However, the management of persistent pain in older adults is a complex task because of concurrent comorbidities, age-related physiological changes, cognitive decline, narrow therapeutic and safe index of current drugs (e.g., nonsteroidal anti-inflammatory drugs, opioids), and limited access to nonpharmacological therapies in the health care setting.

For these reasons, a significant minority of community-dwelling older adults with persistent pain do not receive any analgesia at all, and others also experience pain that is undertreated [51]. Nevertheless, untreated (or undertreated) pain may reduce the effectiveness of traditional interventions targeting frailty, which are aimed at increasing strength and muscle mass and promoting adequate intake of proteins and nutrients [24].

Although older adults with persistent pain may experience only modest reductions in pain through the use of pharmacological treatments, even small improvements in pain can translate into large benefits overall [52]. This geriatric principle is due to the clinical observation of a dose–response relationship between pain severity and interference with function [53].

However, to our knowledge, little attention has been paid to frailty-directed interventions that incorporate pain management components [54,55]. Considering the mutual relationship between persistent pain and frailty, such programs are—in our opinion—strongly needed.

Perspectives for Translating Research into Practice

As discussed above, pain and frailty share common mechanisms. Persistent pain represents both an important risk factor and a potential target for frailty-directed interventions. Little is currently known, however, about whether reducing pain can lead to a reduction in the development (or progression) of frailty. Studies are needed in this area.

Opioid therapy has proved to be—in some cases—of benefit in older patients with persistent pain. For example, in older patients treated with hydrocodone, moderate or substantial levels of pain relief have been associated with the greatest functional improvements [56]. In a 28-day open-label prospective study of 53 older adults with severe persistent pain, use of oxycodone/naloxone was associated with significant improvement in daily functioning (Barthel Index from 53.3 ± 14.1 to 61.3 ± 14.3, $P < 0.01$) [44]. In agitated people with dementia, a stepwise protocol of treating pain conferred significant benefit in the treatment of associated neuropsychiatric symptoms; improvements in mood, apathy, night-time behaviors, and appetite items have been observed [57]. In older adults, a comprehensive multidisciplinary pain management program has been shown to be well tolerated and to produce superior outcomes [58], including short-term improvements in physical and emotional functioning, better pain coping, and reduction in analgesic medication use [59].

These results provide support for the hypothesis that effectively managing pain in older adults produces effects beyond simply lowering pain intensity scores.

In particular, in older adults with frailty, mitigating pain to improve health conditions and quality of life (e.g., function, nutritional status, muscle strength, mood disorder, sleep disturbance) is the appropriate goal [60]. These frailty-related conditions have to be assessed when managing pain in older adults and have to be considered themselves as desired outcomes once a care plan has been put in place. These findings are consistent with the rehabilitation philosophy of improving function and a sense of well-being. Again, we highlight that performing a CGA and frailty assessment may help when trying to determine the efficacy of a given pain management strategy. Pain in older adults is more than simply the sensory experience of pain.

In conclusion, if effective pain management yields benefits beyond pain reduction, we hypothesize that treating pain in older adults could have a salutary impact on preventing frailty onset or reducing its progression.

To our knowledge, no study has examined the impact of pain management on frailty prevention. Research is now needed to determine whether pain therapy when added to existing frailty treatment protocols reduces frailty onset and progression.

Conclusions

The impact of persistent pain in older adults goes beyond simple discomfort, often contributing to worsening functional outcomes and ultimately frailty. Evidence supports a relationship between persistent pain and both incident and worsening frailty, independent of health, social, and lifestyle confounders. Incorporating persistent pain into the frailty process is, in our opinion, an additional contribution to a better understanding of frailty, as, importantly, it has the potential to improve patient care for both conditions. Further studies are needed to clarify the mechanisms underlying the persistent pain–frailty relationship, and clinical trials are needed to evaluate effective management strategies.

References

1. Sawyer P, Bodner EV, Ritchie CS, Allman RM. Pain and pain medication use in community-dwelling older

adults. Am J Geriatr Pharmacother 2006;4 (4):316–24.
2. Ethgen O, Reginster J-Y. Degenerative musculoskeletal disease. Ann Rheum Dis 2004;63(1):1–3.
3. Donal JP, Foy C. A longitudinal study of joint pain in older people. Rheumatology 2004;43(10):1256–60.
4. Reid MC, Eccleston C, Pillemer K. Management of chronic pain in older adults. BMJ 2015;350:h532.
5. Guerriero F. Guidance on opioids prescribing for the management of persistent non-cancer pain in older adults. World J Clin Cases 2017;5(3):73–81.
6. Bortz WM. A conceptual framework of frailty: A review. J Gerontol A Biol Sci Med Sci 2002;57 (5):M283–88.
7. Puts MTE, Hardt J, Monette J, Girre V, Springall E, Alibhai SMH. Use of geriatric assessment for older adults in the oncology setting: A systematic review. J Natl Cancer Inst 2012;104:1133–63.
8. Lally F, Crome P. Understanding frailty. Postgrad Med J 2007;83(975):16–20.
9. Rockwood K, Stadnyk K, MacKnight C, McDowell I, Hébert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. Lancet 1999;353 (9148):205–6.
10. Clegg A, Young J, Liffe S, Rijkkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381 (9868):752–62.
11. Fried LP, Tangen C, Waltson J. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:146–56.
12. Walston JD, Bandeen-Roche K. Frailty: A tale of two concepts. BMC Med 2015;13:185.
13. Cowdry EV. Problems of Ageing: Biological and Medical Aspects. 2nd ed. Baltimore: Williams & Wilkins; 1942.
14. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg 2010;210(6):901–8.
15. Xue QL. The frailty syndrome: Definition and natural history. Clin Geriatr Med 2011;27(1):1–15.
16. Rudy TE, Weiner DK, Lieber SJ, Slaboda J, Boston JR. The impact of low back pain on older adults: A comparative study of patients and controls. Pain 2007;131(3):293–301.
17. Shega JW, Dale W, Andrew M, Paice J, Rockwood K, Weiner DK. Persistent pain and frailty: A case for homeostenosis. J Am Geriatr Soc 2012;60(1):113–7.
18. Blyth FM, Rochat S, Cumming RG, et al. Pain, frailty and comorbidity on older men: The CHAMP Study. Pain 2008;140(1):224–30.
19. Shega JW, Andrew M, Kotwal A, et al. Relationship between persistent pain and 5-year mortality: A population-based prospective cohort study. J Am Geriatr Soc 2013;61(12):2135–41.
20. Tian X, Wang C, Qiao X, et al. Association between pain and frailty among Chinese community-dwelling older adults: Depression as a mediator and its interaction with pain. Pain 2018;159(2):306–13.
21. Wade KF, Lee DM, McBeth J, et al. Chronic widespread pain is associated with worsening frailty in European men. Age Ageing 2016;45(2):268–74.
22. Lohman MC, Whiteman KL, Greenberg RL. Incorporating persistent pain in phenotypic frailty measurement and prediction of adverse health outcomes. J Gerontol Ser A 2017;72(2):216–22.
23. Saraiva MD, Suzuki GS, Lin SM, et al. Persistent pain is a risk factor for frailty: A systematic review and meta-analysis from prospective longitudinal studies. Age Ageing 2018;47(6):785–93.
24. Karp JF, Shega JW, Morone N, et al. Advances in understanding the mechanisms and the management of persistent pain in older adults: The critical role of descending inhibition. Br J Anaesth 2008;101 (1):111–20.
25. Wade KF, Marshall A, Vanhoutte B. Does pain predict frailty in older men and women? Findings from the English Longitudinal Study of Ageing (ELSA). J Gerontol 2017;72(3):403–9.
26. Stubbs B, Binnekade TT, Soundy A, et al. Are older adults with chronic musculoskeletal pain less active than older adults without pain? A systematic review and meta-analysis. Pain Med 2013;14(9):1316–31.
27. Hicks GE, Simonsick EM, Harris TB, et al. Trunk muscle composition as a predictor of reduced functional capacity in the Health, Aging and Body Composition Study: The moderating role of back pain. J Gerontol A Biol Sci Med Sci 2005;60 (11):1420–4.
28. Coyle PC, Sions JM, Velasco T, et al. Older adults with chronic low back pain: A clinical population vulnerable to frailty. J Frailty Aging 2015;4(4):188–90.
29. McBeth J, Chiu YH, Silman AJ, et al. Hypothalamic-pituitary-adrenal stress axis funtcion and the relationship with chronic widespread pain and its antecedents. Arthrits Res Ther 2005;7(5):R992–1000.
30. Choi C-J, knutsen R, Oda K, fraser GE, Knutsen SF. The association between incident self-reported fybromialgia and nonpsychiatric factors: 25 years follow-up of the Adventist Health Study. J Pain 2010;62 :611–7.
31. Varadhan R, Walston J, Cappola AR, et al. Higher levels and blunted diurnal variation of cortisol in frail older women. J Gerontol Med Sci 2008;63(2):190–5.
32. Edwards RR, Kronfli T, Haythornthwaite JA, et al. Association of catastrophizing with interleukin-6 responses to acute pain. Pain 2008;140(1):135–44.
33. Montero-Fernandez N, Serra Rexach JA. Role of exercise on sarcopenia in the elderly. Eur J Phys Rehabil Med 2013;49:131–43.
34. Latham N, Liu CJ. Strength training in older adults: The benefits for osteoarthritis. Clin Geriatr Med 2010;26(3):445–9.

35. Peterson MD, Sen A, Gordon PM. Influence of resistance exercise on lean body mass in aging adults: A metaanalysis. Med Sci Sports Exerc 2011;43 (2):249–58.
36. De Gregori M, Muscoli C, Schatman ME, et al. Combining pain therapy with lifestyle: The role of personalized nutrition and nutritional supplements according to the SIMPAR Feed Your Destiny approach. J Pain Res 2016;9: 1179–89.
37. Chen TJ, Blum K, Payte JT, et al. Narcotic antagonists in drug dependence: Pilot study showing enhancement of compliance with SYN-10, amino-acid precursors and enkephalinase inhibition therapy. Med Hypotheses 2004;63(3):538–48.
38. Nicolodi M, Sicuteri F. Fibromyalgia and migraine, two faces of the same mechanism. Serotonin as the common clue for pathogenesis and therapy. Adv Expn Med Biol 1996;398:373–9.
39. Winzenberg T, van der Mei I, Mason RS, Nowson C, Jones G. Vitamin D and the musculoskeletal health of older adults. Aust Fam Physician 2012;41(3):92–9.
40. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: A meta-analysis of randomised controlled trials. Br Med J 2009;339:843–6.
41. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc 2009; 57(8):1331–46.
42. Welsh TJ, Gordon AL, Gladman JR. Comprehensive geriatric assessment–a guide for the non-specialist. Int J Clin Pract 2014;68(3):290–3.
43. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. J Am Coll Cardiol 2014;63(8):747–62.
44. Thielke SM, Unutzer J. Pain is not a benign symptom among older adults. Pain 2008;140(1):1–2.
45. Ling CHY, Taekema D, de Craen AJM, Gussekloo J, Westendorp RGJ, Maier AB. Handgrip strength and mortality in the oldest old population: The Leiden 85-Plus Study. CMAJ 2010;182(5):429–35.
46. Abellan van Kan G, Rolland Y, Andrieu S, et al. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people: An International Academy on Nutrition and Aging (IANA) Task Force. J Nutr Health Aging 2009;13 (10):881–9.
47. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing 2006;35(5):526–9.
48. Raîche M, Hébert R, Dubois M-F; And the PRISMA Partners. User guide for the PRISMA-7 questionnaire to identify elderly people with severe loss of autonomy. In: Hébert R, Tourigny A, Gagnon M, eds. Integrated Service Delivery to Ensure Persons' Functional Autonomy. Quebec: Edisem; 147–65.
49. Lang P-O, Michel J-P, Zekry D. Frailty syndrome: A transitional state in a dynamic process. Gerontology 2009;55(5):539–49.
50. Guerriero F, Sgarlata C, Marcassa C, Ricevuti G, Rollone M. Efficacy and tolerability of low-dose oral prolonged-release oxycodone/naloxone for chronic nononcological pain in older patients. Clin Intervent Aging 2015;10:1–11.
51. Maxwell CJ, Dalby DM, Slater M, et al. The prevalence and management of current daily pain management among older home care clients. Pain 2008;138 (1):208–16.
52. Resnick NM, Marcantonio ER. How should clinical care of the aged differ? Lancet 1997;350 (9085):1157–8.
53. Weiner DK, Haggerty CL, Kritchevsky SB, et al. How does low back pain impact physical function in independent, well-functioning older adults? Evidence form Health ABC Cohort and implications for the future. Pain Med 2003;4(4):311–20.
54. Rastogi R, Meek BD. Management of chronic pain in elderly, frail patients: Finding a suitable, personalized method of control. Clin Interv Aging 2013; 8:37–46.
55. Cesari M, Prince M, Thiyagarajan JA, et al. Frailty: An emerging public health priority. J Am Med Dir Assoc 2016;17(3):188–92.
56. Argoff C, Arnstein P, Stanos S, et al. Relationship between change in pain intensity and functional outcomes in patients with chronic pain receiving twice daily extended-release hydrocodone bitartrate. J Opioid Manag 2015;11(5):417–24.
57. Husebo BS, Ballard C, Fritze F, et al. Efficacy of pain treatment on mood syndrome in patients with dementia: A randomized clinical trial. Int J Geriatr Psychiatry 2014;29(8):828–36.
58. Kaiser U, Arnold B, Pfingsten M, Nagel B, Lutz J, Sabatowski R. Multidisciplinary pain management programs. J Pain Res 2013;6:355–8.
59. McCormick ZL, Gagnon CM, Caldwell M, et al. Short-term functional, emotional, and pain outcomes of patients with complex regional pain syndrome treated in a comprehensive interdisciplinary pain management program. Pain Med 2015;16 (12):2357–67.
60. Guerriero F, Reid MC. New opioid prescribing guidelines released in the US: What impact will they have in the care of older patients with persistent pain? Curr Med Res Opin 2017;33(2):275–8.