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Depression in Osteoarthritis and Melatonin or Light Therapy

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Abstract

Osteoarthritis, a chronic condition resulting in considerable disability, particularly in later life, not only impacts life quality significantly and severely, but is also strongly associated with the health conditions most often found in older adults. This review aimed to examine whether melatonin or light based therapies applied to aging adults with osteoarthritis who suffer depression, is likely to be efficacious, in general, and especially among those who cannot exercise readily. A second aim was to provide directives for professionals serving or likely to serve this population at this time in this regards. To this end, the author attempted to include a broad overview of all relevant articles published between January 1, 2016 and July 10, 2021 on these topics, rather than any systematic review. Collectively, these data reveal that while more research may be helpful, the presence of feelings of depression if present should be factored into treatment options as its presence can significantly heighten the adverse physical, social, economic, and psychological consequences of the disease. In particular, melatonin and bright light therapies may be helpful in moderating the onset and/or progression of severe depression and its detrimental effect on features of the osteoarthritis disease process, such as pain, inflammation, and the inability to function physically.

Keywords: aging, depression; disability, intervention, light therapy; melatonin; osteoarthritis, pain.

Introduction

It is well established that among the many health challenges experienced by a high majority of older adults, the disease known as osteoarthritis, the most common of the numerous joint diseases, causes appreciable pain and functional disability in a high percentage of people age 55 [1]. Principally due to symptomatic pathological changes in the articular cartilage lining of freely moving joints such as the hip and knee joints, along with pathological changes of the bone structures of one or more joints, the condition produces high levels of pain and functional disability that is more often than not attributed to the wear and tear processes of aging.

However, while this theory suggests osteoarthritis is thus inevitable in later life, not all older adults suffer from this condition. Rather, it appears a variety of medical comorbidities and biological factors may contribute quite significantly to and/or influence its pathogenesis adversely at any age. In particular, given that reports in the literature on this condition consistently show a discrepancy between the radiographic presentation of the prevailing joint damage, commonly used as the gold standard for diagnosing the condition and its severity [2], factors other than age have been implicated in explaining the extent of the suffering often perceived and reported by the affected individual. Most notably, and of interest in the context of this regard are psychological factors, such as depression, a condition occurring frequently in the general population in various forms, as well as in older people with chronic diseases, and /or chronically painful health conditions such as osteoarthritis.

Yet even though a growing body of research indicates that depression is a potentially highly important osteoarthritis disease correlate, especially in older adults with this disabling joint disease [3-5], the

current evidence base shows very few clinical studies that even broach or discuss the possible mental health component of chronically disabling osteoarthritis and attempt to intervene specifically on this target. As well, a number that do exist have examined samples of osteoarthritis cases alongside cases of inflammatory arthritis [e.g., 6], as well as other comorbid conditions, while many have not examined or discussed depression as a pathogenic factor [eg., 7, 8]. Others that do, commonly fail to discuss the implications or significance of their findings. Moreover, only a few joints have been studied and the samples studied are generally non uniform as to the degree of pathology within and across studies, which is compounded by the diverse modes of assessing both osteoarthritis severity, as well as depressive symptom severity.

Thus, many clinicians may not be prompted to screen for or identify the presence of depression in its various forms in their osteoarthritis cases, and may be unaware of the importance of appropriate follow up treatments in this regard in efforts to alleviate some degree of excess suffering and disability [5]. For example, it is possible psychoactive drug use to combat depressive symptoms, are strong falls injury determinants, which can lead to osteoarthritis damage of one or more joints [9]. Moreover, this issue may be more serious than previously acknowledged given that both osteoarthritis as well as depression are cited as being among the top five comorbid conditions found in Alzheimer's disease [10]. As well, more rapid osteoarthritis disease progression is found in osteoarthritis cases who are obese as well as depressed [11], and in terms of long-term consequences, when comparing osteoarthritis, cardiovascular disease, and cancer, all independent risk factors for incident depression and anxiety in both genders, osteoarthritis tended to pose the highest relative risk for depression [12].

At the same time, given that older people are highly vulnerable to osteoarthritis, and those with long-standing or poorly treated osteoarthritis may be excessively impaired and hence too challenged to pursue physical activity and multiple self-management recommendations [4], especially if they suffer from treatable, but previously overlooked mental health conditions, such as depression [13], the goal of this report was to first to highlight what is known about the health ramifications of depression for adults with

osteoarthritis. A second was to examine the degree of support for intervening in a novel way that may help to mitigate primary or secondary depression effects or both in the context of the older osteoarthritis sufferer.

Because of the unrelenting personal and societal burden imposed by osteoarthritis among the older population, and the ill-effects of both undiagnosed depression and excess or suboptimal medication usage on overall wellbeing in this disabling chronic condition, this review elected to focus specifically on examining the role of depression as a possible highly important key osteoarthritis health outcomes mediator or determinant, as well as the potential for either bright light therapy or melatonin or both to ameliorate any excess feelings of depression, and possibly thereby pain, both depicted to prevail at high rates in this group [6]. To this end, this review describes:

- 1. Some key features of osteoarthritis.
- 2. Findings concerning osteoarthritis and depression
- 3. How light therapy or melatonin or both might help decrease depressive symptoms.
- 4. Implications for practice and research.

It was felt this information would be consistent with the need for continuing efforts to broaden our knowledge base concerning factors that impact osteoarthritis disability, particularly with respect to the long term prognosis of this condition. The information was also deemed consistent with the goal of identifying what prevention/intervention strategies other than those currently considered standard practice might prove efficacious in the future for maximizing the affected individuals' functional status and overall life quality, while minimizing the extent of the anticipated disease progression. Commonly a neglected area of therapeutic concern, and often not even mentioned in the context of clinical practice recommendations, the author's purpose was to provide a firm rationale for supporting continuing efforts to routinely screen for and treat any prevailing signs or symptoms of depression in this population.

Accordingly, in the first section of this work, some background information on the topic of osteoarthritis followed by the topic of depression and the linkage of depression to common symptoms associated with osteoarthritis of one or more joints is presented. Then some recent data from clinical observations of selected cohorts classified as having depression and their possible response to light therapy or melatonin are described. The work concludes by summarizing the key findings from these data and by providing related guidelines for clinical practice and future research endeavors.

The desired information was compiled from an extensive review of the English language literature embedded in the PUBMED, predominantly over the years 2016-2021. The goal was to provide a comprehensive overview of the proposed link between depression and osteoarthritis disability, and how melatonin or light may be used to help this group of adults. Using the keywords: Osteoarthritis and Depression and Bright Light therapy/Melatonin, alone or in combination the following key sources located as of July 8, 2021 were examined. Articles that did not focus on these issues in a distinctive manner, surgical based studies, and incomplete reports were excluded. Only one data base was used, as most articles of relevance are included in this extensive database, and only current data were sought in order to reflect prevailing insights.

FINDINGS

In general, many articles categorized according to the current keywords were not strictly of present interest. Those below were selected to represent current observations and conclusions and to support the idea that more needs to be done to screen for, and intervene upon the presence of depression or its symptoms in older osteoarthritis cases, and in a manner that is practical, safe, and accessible. The numbers of **PUBMED** listings found for the periods 2016-2021 were:

Osteoarthritis as key term: 30, 675

Depression as key term: 134, 528

Osteoarthritis and Depression as key term: 719
 [2.34% all osteoarthritis literature]

The knee was the most studied joint 2016-2021 with 395 publications. There were 125 articles on hip osteoarthritis and depression and 34 for hand osteoarthritis. There were 267 articles on joint surgery and depression.

Osteoarthritis

Among the many manifestations of osteoarthritis shown in Box 1, current reports are beginning to stress an important role for mental health issues, among others. Indeed, cumulative data continue to affirm that osteoarthritis, the most common joint disease, commonly produces periods of chronically intractable pain, joint stiffness and swelling, as well as multiple functional, social, occupational, and emotional challenges and restrictions, plus a low life quality, and feelings of depression [14] despite years of study and efforts to intervene in this regard.

PHYSICAL MANIFESTATIONS

Decreased mobility and flexibility Impaired balance/proprioception Muscle atrophy, weakness/poor endurance Muscle spasm, contractures Joint inflammation, swelling, and tenderness Pain/stiffness in one or more joints

MENTAL/EMOTIONAL MANIFESTATIONS

Depression and/or anxiety
Diminished vitality/life quality
Excess fatigue
Fear of movement/avoidance behaviors
Reduced self-efficacy/coping ability
Sleep disturbances

FUNCTIONAL MANIFESTATIONS

Difficulties performing daily tasks
Diminished work capacity
Occupational, social, and recreational limitations
Diminished social interactions
Diminished participation in leisure activities

Box1. Summary of key interactive potentially treatable manifestations of osteoarthritis pathology of one or more joints that may induce or perpetuate depression [Source: Author]

Osteoarthritis and Depression

Although not a 'death sentence', it is increasingly clear, depression, found to exist in a considerable percentage of adults with osteoarthritis [15], is a significant overlapping and negative health correlate of this disease, wherever it exists. Affecting the physical, economic, psychological, and social wellbeing of the affected adult, the presence of depression, often associated with low activity participation, may significantly hamper intervention effects [16], while increasing the needs for office visits, and increasing their costs, as well as fostering sleep problems, as discussed by Liu et al. [17] and Fertelli et al. [18].

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In addition, depression leading to learned helplessness, lack of vitality and motivation may be expected to heighten both adverse joint symptoms and joint destructive processes according to compelling research by Power et al. [19], and Rathbun et al. [20] who confirmed that there is likely to be a faster disease progression as measured by either worsening structural severity or decreasing physical performance that corresponds to an increased presence of depression among individuals with radiographic knee osteoarthritis. As in the study by Power et al. [19] where joint destruction was exaggerated in those with comorbid obesity and depression, Rathbun et al. [20] found the highest quintile (relative to the lowest) of joint space width, indicative of joint erosion to be significantly associated with the onset of depression. Unsurprisingly, as outlined by Tsuji et al. [21] depression was found to heighten the health-related burden of those cases with osteoarthritis that were studied, and is well correlated with pain, functional limitations, and inflammation [22-24]. Moreover, those who remain untreated are likely to be at an elevated risk for incidental major depression and/or anxiety disorders, rather than for reactive secondary depression alone [25]. They may in turn, adopt a lower than desirable activity participation rate [26, 27], and experience poor sleep quality as well as excess pain [28, 29].

That is, while rates of depressive symptoms tend to vary in different osteoarthritis samples, it seems safe to say, not only will a modest proportion be affected negatively by their disease in terms of mood states, but since many older adults with osteoarthritis suffer from impairments other than musculoskeletal impairments, as well as from various forms of primary depression, the likelihood of older osteoarthritis cases exhibiting both cognitive as well as functional impairments is increased [30]. Moreover, those osteoarthritis cases who do not obtain adequate pain relief, as well as those with worse radiographic signs of the disease will be more prone to depression than those with less severe disease findings [31, 32].

Increasing evidence shows a moderate positive correlation between pain severity and depressive symptomatology, and that having severe depression can impact the pathology of the affected joint quite negatively [17, 18, 33-37], as well as possible frailty in the older adult [38]. Indeed, as outlined in Figure 1 numerous adverse effects can be readily anticipated in the event of unrecognized or undertreated or improperly treated pain. In addition to the onset of depressive symptoms, one can expect a parallel increasing prevalence of both factors, as well as increased hospital visits, and medications to avert experiencing extraneous adverse health outcomes [34].

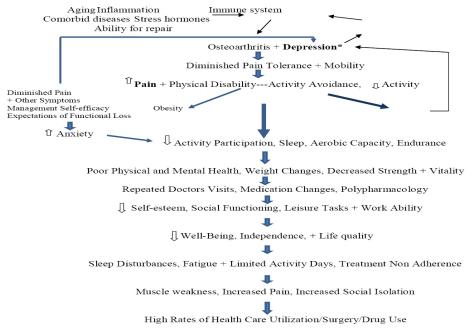


Figure 1. Proposed complex set of health related interactions occurring between pain and depression that can be anticipated to lead to considerable disability, especially if untreated

At the same time, even though more than 70 percent of persons with osteoarthritis may be in constant pain at rest, as well as pain on movement, those with higher pain levels in particular, may consequently have immense difficulty in accomplishing everyday tasks. They may suffer unanticipated disability consequences, especially if all current treatment options fail to provide adequate pain relief or relief for unrelenting feelings distress that can increase pain as per Figure 1. As a result, they may require surgery, as well as a possible increased demand for psychoactive drugs and opioids [17, 39].

Fortunately, the extent of any prevailing depressive symptoms, although not mentioned as a remediable risk factor by Georgiev and Angelov [33] can be reasonably well recognized as well as diagnosed by taking a careful history, and by applying one or more validated scales to examine if indeed the individual is depressed, and if so, how severe the condition is. According to Akintayo et al. [29], depression, which is common among patients with knee osteoarthritis, can not only be predicted by multiple screening methods, but can be predicted by persistent complaints of poor sleep quality and moderate to severe pain. As such, treatments including counselling, psychotherapy, exercise, stress counselling, acceptance therapy, and social support may be especially helpful in efforts to minimize the combined medical costs of low physical activity participation, excess pain sensitivity, poor walking capacity, and sleep challenges [33, 40-44] and their early rather than later implementation is deemed especially desirable [36]. What is not evident in the literature are efforts to address depression directly via the application of melatonin derivatives and/or light therapies.

Melatonin

Melatonin, a hormone produced in response to the sleep wake cycle may arguably be of immense relevance in the context of painful inflammatory diseases, including osteoarthritis [49] and its presence and timely production may have direct benefits on its structural features [50-55] as well as sleep associated problems [56]. Also being used for depression, its direct or indirect application may prove highly valuable in the elderly where melatonin levels are commonly depleted or suboptimal [56]. This is owing to the fact that melatonin, an indolamine synthesized by the pineal gland during the night, greatly

contributes to synchronization of body rhythms with the environmental light/dark cycle [57] as well as to its physiology and mood in multiple ways.

In this regard, the rationale for considering melatonin in the context of depression in its own right is the fact that circadian rhythm disruption is believed to underlie the pathophysiology of various psychiatric disorders, especially depression. In this regard, antidepressants focused on a melatonergic system known to be altered in depression has led to a potential option for treatment of depression that appears to resynchronize the circadian rhythm and possibly to alleviate depressive symptoms in depressed subjects [58].

According to Cardinali et al. [59], one melatonergic antidepressant agent called agomelatine, was found effective in the treatment of depression. As discussed by Mendoza et al. [60], this may be because depressive symptoms, which may range from a loss of motivation and energy to suicidal thoughts may implicate the desirable level of daily hormonal secretions such as melatonin that is regulated by an internal biological clock. As such, it is possible that substances that have the ability to reset the biological clock(s), such as melatonin, can also help to improve mood, which is regulated by the internal clock.

Valdes-Tovar et al. [57] thus argued in favor of the circadian modulation of neuroplasticity by melatonin, as a possible key target in the treatment of depression given the observation that mood disorder patients commonly present with an uncoupling of their circadian rhythms. Evidence implies moreover that there are antidepressant-like actions of melatonin related to neural circadian modulation cycles, plus melatonin receptors and their signaling pathways that might be amenable to modulatory effects in cases where circadian disruption and mood disorders prevail.

Interestingly, adults classified as being depressed have been shown to have decreased levels of melatonin, thus lessening its purported anti-depressant effects [61], while possibly further disrupting sleep-wake cycles that predict more depressive symptoms in the future [62]. That is, increasing evidence points to a key role of the biological clock in the development of depression and possible mood disturbances caused by circadian malfunction. Alternately, these disturbances have the

potential to be treated by manipulating the circadian system using chronobiotic drugs, chronotherapy or bright light therapy. Melatonin may also influence depression indirectly due to its important role in pain modulation [63] and should have a positive effect on osteoarthritis pain based on evidence from fibromyalgia research [64].

In short, melatonin and melatonin agonists which are said to have chronobiotic effects, can potentially be mobilized to help readjust the circadian system, often linked to affective disorders and mood disturbances. Thus it is possible that those cases of osteoarthritis who exhibit depressive symptoms and sleep disturbances and do not improve in response to standard therapeutic approaches, may well benefit by being exposed to some form of chronotherapy such as melatonin, or bright light therapy [65].

Bright Light Therapy

In terms of bright light therapy, Penders et al. [66] reports this form of treatment has demonstrated efficacy and is an accepted approach for reducing seasonal depression. It has been suggested therefore that bright light therapy may have efficacy in nonseasonal depressions, in that it may improve responsiveness to antidepressant pharmacotherapy. An analysis of pooled data from randomized trials did tend to provide evidence for the efficacy of use of bright light therapy $\geq 5,000$ lux for periods ≥ 30 minutes when used as augmentation to standard antidepressant pharmacotherapy in the treatment of major depressive disorder and bipolar depression without a seasonal pattern.

Tsai et al. [67] and Zhao et al. [68] further support the idea that light therapy, which has become an increasingly common treatment for adults with depression has a positive effect on geriatric nonseasonal depression as well as seasonal depression. Tao et al. [69] too found light therapy was significantly more effective than comparative treatments, and provided mild to moderate treatment effect in reducing depressive symptoms in non-seasonal depression. New experimental data also show that pain-a strong depression determinant may safely be reduced by applications of green light therapy [70], while reducing depressive symptoms and sleep disturbances in the chronically disabled elderly individual [71]. In addition, Henderson et al. [72] report that near multi-

watt infra red phototherapy showed high efficacy for alleviating depression, wherein patients saw benefits often within four treatments and experienced resolution of depressive symptoms within 4 weeks in some cases.

Salehpour et al. [73] further note that brain photobiomodulation (PBM) therapy using red to near-infrared (NIR) light is an innovative form of light therapy that can be applied to a wide range of neurological and psychological conditions. Red/ NIR light is able to able to have beneficial cognitive effects due to its impact on brain cellular mechanisms involved in brain function and enhances the metabolic capacity of neurons, stimulates anti-inflammatory, anti-apoptotic, and antioxidant responses, as well as neurogenic and synaptogenic processes. Its therapeutic role in disorders such as depression is thus garnering increasing interest to study and apply. Potentially useful for intervening in major depressive disorder [74, 75], the use of transcranial and systemic photobiomodulation for depressive symptoms in selected cases of osteoarthritis with clinical depression which has not been studied, warrants exploration.

DISCUSSION

Although the radiographs of most individuals seeking medical help for painful symptomatic osteoarthritis consistently exhibit some degree of bone damage and joint space narrowing consequent to progressive degeneration of the articular cartilage lining the joint, the degree of observable joint damage alone may be very minor. In addition, given that the cartilage tissue implicated in the disease process as the primary source of the condition has no actual nerve related constituent it is consequently assumed some of the pain experience accompanying osteoarthritis may stem, from sources other than the diseased joint. That is, alone or in combination, the destruction of a joint and its effect on the surrounding joint structures that results in varying degrees of joint swelling and tenderness, inflammation, and pain may herald the onset of comorbid depressive symptoms often found among those who seek treatment or participate in research studies [36, 78].

Indeed, based on many years of research in the realm of chronic pain and other chronically painful health conditions, it is proposed that prolonged periods of unrelenting pain, can produce feelings of depression, which in turn magnify the pathology and overall pain experience and resulting disability of the individual. These feelings are not only disruptive in the daily lives of those affected, but clearly worsen the prognosis of the disease in the long term [45]. As well, many older adults with osteoarthritis have multiple comorbid conditions that renders them prone to depression. A fair proportion may suffer independently from depression, a very common disturbance in the elderly.

That is, although most studies rely on self-report, and may not be truly capture the magnitude and severity of depression as this affects the older population affected by osteoarthritis, it appears safe to assume that even if only a modest number of older osteoarthritis cases exhibit depressive symptoms, the presence of negative affect and associated perceptions, plus negative disease outcome interpretations, expectations, and fearful reactions of the affected individual may be expected to interact with a variety of pain stimuli and local disease correlates to produce or heighten the painful experience, as well as the extent of prevailing disability, if this remains undetected or poorly treated. This in turn, potentially heightens the nature of any reactive depression, as well as joint inflammation and pathology, and low life quality attributes along with the degree of possible motivation to comply with health recommendations, especially physical activity participation. A low self-efficacy and/or motivation towards participating in self-help or care strategies, along with persistent feelings of helplessness, may in turn foster a feeling of being overwhelmed, with a subsequent decline in the ability to cope with their disease. Coupled with excess fears, anxiety, and stress, plus sleep disturbances, a proclivity towards excess joint destruction, excess weight gain, plus further depression can be readily predicted [33] as can a possible excess need for psychoactive drugs, destructive antiinflamamtory medications, opioids to avert pain [76, 77]. This situation may further induce more non-compliant behavior than not, including the adoption of negative or impulsive behaviors, activity avoidance behaviors, and passive, rather than active coping practices.

By contrast, clear support for improved efforts to identify, quantify, qualify, and treat this psychosocial factor may greatly help to spark a greater belief in the patient's overall long term prognosis, plus their motivation to pursue recommended health behaviors, that can further minimize the extent of any reactive depression that might be experienced in the context of unrelenting osteoarthritis pain [36].

While many approaches have been recommended, these should not be neglected, but their application carefully considered and tailored where possible. In this regard, we specifically advocate further examination of the potential efficacy of melatonin and/or light therapy, interventions that might safely help to mitigate depressive feelings in a least a proportion of older adults with osteoarthritis in a safe manner. This approach was chosen for exploration, in spite of many other options, because standard approaches [Box 2], while somewhat helpful, have not proven universally effective in all cases, and may not be practical or feasible in the case of some homebound older osteoarthritis sufferers [46]. Melatonin, for example may be extracted from many food items directly, and light therapy may be easily set up in most homes in communities, and even if administered as a supplement or a form of therapy are deemed safe and cost effective.

Moreover, not only can older adults who live in the community ably apply these strategies and others if they find they do suffer less from their osteoarthritis as a result, but we feel this approach may prove especially important for those older adults who may already have a long standing depression diagnosis, as well as low circulating levels of melatonin, and immense pain [32]. Since osteoarthritis impacts one's physical, as well as social and economic health quite markedly at any age, this approach may have far reaching beneficial effects if applied sooner later. In particular, it may help to reduce the need for high doses of pain relieving medications, as well as more health services than those with no depression, while building selfefficacy. It may also impact the ability to maintain a healthy weight indirectly, as well as a sleep health and the circadian wake-sleep cycle, while decreasing excess feeling of fatigue [4, 18], or falls risk [47] or both, comorbid or systemic disease manifestations, as well as pain and inflammation. In this regard, we strongly advocate for more careful research to examine depression as key health predictor in older adults at risk for osteoarthritis, as well as the possible utility of the multidimensional hormone, melatonin, along with bright light therapy on prevailing depression, pain, inflammation, and activity associated fatigue, as well as

structural indicators in this population. In turn, it may be useful to test these therapies as possible gateway methods of encouraging more healthy behaviours in older adults with chronically painful inflamed joints, such that traditional therapies used in continuing efforts to foster more optimal osteoarthritis wellbeing as per Box 2.

In short, rather than assuming that osteoarthritis, the most common joint disease and one that causes appreciable disability in a high percentage of older individuals is irreversible and inevitable, if the disease is only considered to be a physical disease, but also potentially an emotional one requiring treatment where present, one can expect a great decrement in the overall personal health burden, as well as the collective health burden attributable to this condition. Life quality may be enhanced, especially if depression is routinely sought and thus uncovered sooner, rather than later. Alternately, much distress will continue to prevail, in a fair percentage of older osteoarthritis cases, by failing to accept this possibility. In this regard, it can also be assumed that a one size fits all intervention approach will possibly fail to foster optimal outcomes, given the multiple overlapping interacting disease correlates shown in Box 1, as may a uni-dimensional intervention approach. However, efforts to assess and normalize melatonin levels if deficient, as well as applications of bright light therapy to stimulate the sleep wake cycle, a major cause or consequence of this painful disease may produce previously unrecognized multiple benefits in our view. While this is clearly hypothetical at this point, given that the role of melatonin and bright light therapy in mediating or moderating many similar symptoms is quite well supported in other spheres, a strong rationale surely exists for testing these approaches in the context of painful chronically disabling osteoarthritis. Until then, given the anticipated widespread negative repercussions of unrelieved feelings of depression that may arise consequent to the disease and its disabling impacts on multiple body systems as well as mobility, timely and periodic screening of at risk older adults using an agreed upon screening tool, is strongly advocated to avert more rapid, extensive, and severely disabling and painful outcomes, including worse mobility outcomes or no definite mobility change outcomes despite the application of standard forms of therapy [48].

PERIODIC ASSESSMENT PLUS:

Cognitive behavioral therapy
Counseling
Education
Minimize stress
Promote coping/self-efficacy skills
Promote healthy nutrition
Promote relaxation
Promote sleep health+
Promote joint sparing techniques
Promote physical fitness
Prevent/treat obesity
Social support
Treat comorbid conditions+
Treat comorbid pain
+-where melatonin/light therapy may help

Box2. Selected strategies for preventing/treating osteoarthritis and depression

+Target older overweight cases with multiple morbidities and unrelenting pain.

CONCLUSION

From the present literature base we conclude that:

The presence of oftentimes substantive rates of depression in cases with osteoarthritis may be expected to heighten its pathology and consequences, producing less than optimal health outcomes, including, greater levels of fatigue and pain. Conversely, those cases who exhibit depressive symptoms and who do receive appropriate treatments and treatment recommendations may experience more optimal well-being than those who do not. They may be more rather than less willing to pursue activities deemed beneficial to them over time. In this regard the role of melatonin and light therapy should be explored further, while more importance should be given to routine screening for depression among older adults seeking clinical care for osteoarthritis, especially in cases with physical comorbidities or a coexisting medical condition. Meantime, given that antidepressants used to treat depression may foster weight gain, or falls, or both, the importance of minimizing depression safely without side effects cannot be underestimated in the context of both weight, as well as pain control, which are both pathogenic predictors of excess osteoarthritis disability.

We further conclude that more specific exploration of

these variables among different samples at different disease stages may help us to better discern those who need treatment, and will benefit from this, from those that do not need treatment.

REFERENCES

- [1] Vina ER, Kwoh CK. Epidemiology of osteoarthritis: literature update. Current Opinion in Rheumatology. 2018;30(2):160-167. doi: 10.1097/BOR.0000000000000479.
- [2] McDonough CM, Jette AM. The contribution of osteoarthritis to functional limitations and disability. Clinics in Geriatric Medicine. 2010;26:387-399.
- [3] Lentz TA, George SZ, Manickas-Hill O, Malay MR, O'Donnell J, Jayakumar P, Jiranek W, Mather RC 3rd. What general and pain-associated psychological distress phenotypes exist among patients with hip and knee osteoarthritis? Clinical Orthopedics and Related Research. 2020;478(12):2768-2783. doi: 10.1097/CORR.000000000001520.
- [4] Hawker GA. Osteoarthritis is a serious disease. Clinical and Experimental Rheumatology. 2019;37 Suppl 120(5):3-6.
- [5] Jesus C, Jesus I, Agius M. Treatment of depression in patients with osteoarthritis: the importance of an early diagnosis and the role of Duloxetine.. Psychiatrina Danubina. 2016;28(Suppl-1):149-153.
- [6] Pérez-García LF, Silveira LH, Moreno-Ramírez M, Loaiza-Félix J, Rivera V, Amezcua-Guerra LM. Frequency of depression and anxiety symptoms in Mexican patients with rheumatic diseases determined by self-administered questionnaires adapted to the Spanish language. Revista de Investigación Clínica; Organo Del Hospital de Enfermedades de la Nutrición.. 2019;71(2):91-97. doi: 10.24875/RIC.18002698.
- [7] O'Neill TW, McCabe PS, McBeth J. Update on the epidemiology, risk factors and disease outcomes of osteoarthritis. Best Practices in Research and Clinical Rheumatology. 2018;32(2):312-326. doi: 10.1016/j.berh.2018.10.007.
- [8] Martel-Pelletier J, Barr AJ, Cicuttini FM, Conaghan PG, Cooper C, Goldring MB, Goldring SR, Jones G,

- Teichtahl AJ, Pelletier JP. Osteoarthritis. Nature Reviews Disease Primers. 2016;2:16072. doi: 10.1038/nrdp.2016.72.
- [9] Hoffman GJ, Hays RD, Wallace SP, Shapiro MF, Ettner SL. Depressive symptomatology and fall risk among community-dwelling older adults. Social Science and Medicine. 2017;178:206-213. doi: 10.1016/j.socscimed.2017.02.020.
- [10] Wang JH, Wu YJ, Tee BL, Lo RY. Medical comorbidity in Alzheimer's Disease: a nested case-control study. Journal of Alzheimers Disease. 2018;63(2):773-781. doi: 10.3233/JAD-170786.
- [11] Jacobs CA, Vranceanu AM, Thompson KL, Lattermann C. Rapid progression of knee pain and osteoarthritis biomarkers greatest for patients with combined obesity and depression: data from the Osteoarthritis Initiative. Cartilage. 2020;11(1):38-46. doi: 10.1177/1947603518777577.
- [12] Shang X, Peng W, Hill E, Szoeke C, He M, Zhang L. Incidence, progression, and patterns of multimorbidity in community-dwelling middle-aged men and women. Frontiers in Public Health. 2020;8:404. doi: 10.3389/fpubh.2020.00404.
- [13] Jung JH, Seok H, Kim JH, Song GG, Choi SJ. Association between osteoarthritis and mental healthina Korean population: a nationwide study. International Journal of Rheumatic Diseases. 2018;21(3):611-619. doi: 10.1111/1756-185X.13098.
- [14] Park HM, Kim HS, Lee YJ. Knee osteoarthritis and its association with mental health and health-related quality of life: a nationwide cross-sectional study. Geriatrics and Gerontology International. 2020;20(4):379-383. doi: 10.1111/ggi.13879.
- [15] Aqeel M, Rehna T, Sarfraz R. The association among perception of osteoarthritis with adverse pain anxiety, symptoms of depression, positive and negative affects in patients with knee osteoarthritis: a cross sectional study. Journal of the Pakistan Medical Association 2021 Feb;71(2(B)):645-650. doi: 10.47391/ JPMA.862.
- [16] Chen YP, Huang YY, Wu Y, Kuo YJ, Lin CY.

- Depression negatively affects patient-reported knee functional outcome after intraarticular hyaluronic acid injection among geriatric patients with knee osteoarthritis. Journal of Orthopedic Surgery Research. 2019 Nov 27;14(1):387. doi: 10.1186/s13018-019-1419-z.
- [17] Liu M, McCurry SM, Belza B, Dobra A, Buchanan DT, Vitiello MV, Von Korff M. Effects of osteoarthritis pain and concurrent insomnia and depression on health care use in a primary care population of older adults. Arthritis Care and Research (Hoboken). 2019;71(6):748-757. doi: 10.1002/acr.23695..
- [18] Fertelli TK, Tuncay FO. Fatigue in individuals with knee osteoarthritis: Its relationship with sleep quality, pain and depression. Pakistan Journal of Medical Science. 2019;35(4):1040-1044. doi: 10.12669/pjms.35.4.383.
- [19] Power JD, Kudesia P, Nadeem A, Perruccio AV, Sundararajan K, Mahomed NN, Ribeiro IC, Coimbra AMV, Costallat BL, Coimbra IB. Relationship between radiological severity and physical and mental health in elderly individuals with knee osteoarthritis. Arthritis Research and Therapy. 2020;22(1):187. doi: 10.1186/s13075-020-02280-2.
- [20] Rathbun AM, Shardell MD, Ryan AS, Yau MS, Gallo JJ, Schuler MS, Stuart EA, Hochberg MC. Association between disease progression and depression onset in persons with radiographic knee osteoarthritis. Rheumatology (Oxford). 2020;59(11):3390-3399. doi: 10.1093/rheumatology/keaa141.
- [21] Tsuji T, Nakata K, Vietri J, Jaffe DH. The added burden of depression in patients with osteoarthritis in Japan. ClinicoEconomics and Outcomes Research. 2019;11:411-421. doi: 10.2147/CEOR.S189610.
- [22] Iijima H, Aoyama T, Fukutani N, Isho T, Yamamoto Y, Hiraoka M, Miyanobu K, Jinnouchi M, Kaneda E, Kuroki H, Matsuda S. Psychological health is associated with knee pain and physical function in patients with knee osteoarthritis: an exploratory cross-sectional study. BMC

- Psychology. 2018;6(1):19. doi: 10.1186/s40359-018-0234-3.
- [23] Aykut Selçuk M, Karakoyun A. Is There a relationship between kinesiophobia and physical activity level in patients with knee osteoarthritis? Pain Medicine. 2020 Dec 25;21(12):3458-3469. doi: 10.1093/pm/pnaa180.
- [24] Harth M, Nielson WR. Pain and affective distress in arthritis: relationship to immunity and inflammation. Expert Review of Clinical Immunology. 2019;15(5):541-552. doi: 10.1080/1744666X.2019.1573675.
- [25] Karp JF, Zhang J, Wahed AS, Anderson S, Dew MA, Fitzgerald GK, Weiner DK, Albert S, Gildengers A, Butters M, Reynolds CF 3rd. Improving patient reported outcomes and preventing depression and anxiety in older adults with knee osteoarthritis: results of a sequenced multiple assignment randomized trial (SMART) study. American Journal of Geriatric Psychiatry. 2019;27(10):1035-1045. doi: 10.1016/j. jagp.2019.03.011.
- [26] Zheng S, Tu L, Cicuttini F, Zhu Z, Han W, Antony B, Wluka AE, Winzenberg T, Aitken D, Blizzard L, Jones G, Ding C. Depression in patients with knee osteoarthritis: risk factors and associations with joint symptoms. BMC Musculoskelet Disorders. 2021;22(1):40. doi: 10.1186/s12891-020-03875-1.
- [27] Vaughan MW, LaValley MP, Felson DT, Orsmond GI, Niu J, Lewis CE, Segal NA, Nevitt MC, Keysor JJ. Affect and incident participation restriction in adults with knee osteoarthritis. Arthritis Care and Research (Hoboken). 2018;70(4):542-549. doi: 10.1002/acr.23308.
- [28] Akintayo RO, Yerima A, Olaosebikan HB, Uhunmwangho C, Akpabio AA. How much gloom is in groans? Depression and its determinants in Nigerian patients with knee osteoarthritis: a multi-center cross-sectional study. Clinical Rheumatology. 2019;38(7):1971-1978. doi: 10.1007/s10067-019-04497-2.
- [29] Akintayo RO, Yerima A, Uhunmwangho C, Olaosebikan H, Akpabio AA. Tossing and turning

- with degenerative arthropathy: an assessment of poor sleep quality in knee osteoarthritis. Reumatologia. 2019;57(4):207-213. doi: 10.5114/reum.2019.87615.
- [30] Calders P, Van Ginckel A. Presence of comorbidities and prognosis of clinical symptoms in knee and/or hip osteoarthritis: a systematic review and meta-analysis. Seminars in Arthritis and Rheumatism. 2018;47(6):805-813. doi: 10.1016/j.semarthrit.2017.10.016.
- [31] Laires PA, Laíns J, Miranda LC, Cernadas R, Rajagopalan S, Taylor SD, Silva JC. Inadequate pain relief among patients with primary knee osteoarthritis. Revista Brasileira de Reumatologia Engl Ed. 2017;57(3):229-237. English, Portuguese. doi: 10.1016/j.rbre.2016.11.005.
- [32] Abd El Monaem SM, Hashaad NI, Ibrahim NH. Correlations between ultrasonographic findings, clinical scores, and depression in patients with knee osteoarthritis. European Journal of Rheumatology. 2017;4(3):205-209. doi: 10.5152/eurjrheum.2017.160097.
- [33] Taylor SS, Hughes JM, Coffman CJ, Jeffreys AS, Ulmer CS, Oddone EZ, Bosworth HB, Yancy WS Jr, Allen KD. Prevalence of and characteristics associated with insomnia and obstructive sleep apnea among veterans with knee and hip osteoarthritis. BMC Musculoskeletal Disorders. 2018;19(1):79. doi: 10.1186/s12891-018-1993-v.
- [34] Sharma A, Kudesia P, Shi Q, Gandhi R. Anxiety and depression in patients with osteoarthritis: impact and management challenges. Open Access Rheumatology. 2016;8:103-113. doi: 10.2147/OARRR.S93516.
- [35] Georgiev T, Angelov AK. Modifiable risk factors in knee osteoarthritis: treatment implications. Rheumatology International. 2019;39(7):1145-1157. doi: 10.1007/s00296-019-04290-z.
- [36] Fonseca-Rodrigues D, Rodrigues A, Martins T, Pinto J, Amorim D, Almeida A, Pinto-Ribeiro F. Correlation between pain severity and levels of anxiety and depression in osteoarthritis patients: a systematic review and meta-analysis.

- Rheumatology (Oxford). 2021:keab512. doi: 10.1093/rheumatology/keab512.
- [37] Stubbs B, Aluko Y, Myint PK, Smith TO. Prevalence of depressive symptoms and anxiety in osteoarthritis: a systematic review and meta-analysis. Age Ageing. 2016;45(2):228-235. doi: 10.1093/ageing/afw001.
- [38] Soysal P, Veronese N, Thompson T, Kahl KG, Fernandes BS, Prina AM, Solmi M, Schofield P, Koyanagi A, Tseng PT, Lin PY, Chu CS, Cosco TD, Cesari M, Carvalho AF, Stubbs B. Relationship between depression and frailty in older adults: a systematic review and meta-analysis. Ageing Research Reviews. 2017;36:78-87. doi: 10.1016/j.arr.2017.03.005.
- [39] Hadlandsmyth K, Sabic E, Zimmerman MB, Sluka KA, Herr KA, Clark CR, Noiseux NO, Callaghan JJ, Geasland KM, Embree JL, Rakel BA. Relationships among pain intensity, pain-related distress, and psychological distress in pre-surgical total knee arthroplasty patients: a secondary analysis. Psychology Health & Medicine. 2017;22(5):552-563. doi: 10.1080/13548506.2016.1189581.
- [40] Tang HJ, McCurry SM, Pike KC, Von Korff M, Vitiello MV. Differential predictors of nighttime and daytime sleep complaints in older adults with comorbid insomnia and osteoarthritis pain. Journal of Psychosomatic Research. 2017;100:22-28. doi: 10.1016/j.jpsychores.2017.06.020.
- [41] Parmelee PA, Tighe CA, Dautovich ND. Sleep disturbance in osteoarthritis: linkages with pain, disability, and depressive symptoms. Arthritis Care and Research (Hoboken). 2015;67(3):358-65. doi: 10.1002/acr.22459.
- [42] Kilinç H, Karahan S, Atilla B, Kinikli Gİ. Can fear of movement, depression and functional performance be a predictor of physical activity level in patients with knee osteoarthritis? Archives of Rheumatology. 2018;34(3):274-280. doi: 10.5606/ArchRheumatol.2019.7160.
- [43] Ahn H, Weaver M, Lyon D, Choi E, Fillingim RB. Depression and pain in Asian and White Americans with knee osteoarthritis. Journal of

- Pain. 2017;18(10):1229-1236. doi: 10.1016/j. jpain.2017.05.007.
- [44] Poon CL, Cheong P, Tan JW, Thumboo J, Woon EL, Clark RA, Cheok G, Pua YH. Associations of the modified STarT backtool and Hospital Anxiety and Depression Scale (HADS) with gait speed and knee pain in knee osteoarthritis: a retrospective cohort study. Disability and Rehabilitation. 2021:1-7. doi: 10.1080/09638288.2021.1883750.
- [45] Sayre EC, Esdaile JM, Kopec JA, Singer J, Wong H, Thorne A, Guermazi A, Nicolaou S, Cibere J. Specific manifestations of knee osteoarthritis predict depression and anxiety years in the future: Vancouver Longitudinal Study of Early Knee Osteoarthritis. BMC Musculoskeletal Disorders. 2020;21(1):467. doi: 10.1186/s12891-020-03496-8.
- [46] Billesberger LM, Fisher KM, Qadri YJ, Boortz-Marx RL. Procedural treatments for knee osteoarthritis: a review of current injectable therapies. Pain Research and Management. 2020;2020:3873098. doi: 10.1155/2020/3873098.
- [47] Ofori-Asenso R, Ackerman IN, Soh SE. Prevalence and correlates of falls in a middle-aged population with osteoarthritis: data from the Osteoarthritis Initiative. Health & Social Care in the Community. 2021;29(2):436-444. doi: 10.1111/hsc.13103.
- [48] Uckun AC, Donmez BK, Yurdakul FG, Garip Y, Bodur H. The role of pain catastrophizing and depression in the outcomes of physical therapy in a prospective osteoarthritis cohort. Pain Physician. 2020;23(2):209-218..
- [49] Jahanban-Esfahlan R, Mehrzadi S, Reiter RJ, Seidi K, Majidinia M, Baghi HB, Khatami N, Yousefi B, Sadeghpour A. Melatonin in regulation of inflammatory pathways in rheumatoid arthritis and osteoarthritis: involvement of circadian clock genes. British Journal of Pharmacology. 2018;175(16):3230-3238. doi: 10.1111/bph.13898.
- [50] Hosseinzadeh A, Kamrava SK, Joghataei MT, Darabi R, Shakeri-Zadeh A, Shahriari M, Reiter RJ, Ghaznavi H, Mehrzadi S. Apoptosis signaling pathways in osteoarthritis and possible protective

- role of melatonin. Journal of Pineal Research. 2016;61(4):411-425. doi: 10.1111/jpi.12362.
- [51] Zhang Y, Lin J, Zhou X, Chen X, Chen AC, Pi B, Pan G, Pei M, Yang H, Liu T, He F. Melatonin prevents osteoarthritis-induced cartilage degradation via targeting microRNA-140. Oxidative Medicine and Cell Longevity. 2019;2019:9705929. doi: 10.1155/2019/9705929. PMID: 31915516; PMCID: PMC6935446.
- [52] Hossain FM, Hong Y, Jin Y, Choi J, Hong Y. Physiological and pathological role of circadian hormones in osteoarthritis: dose-dependent or time-dependent? Journal of Clinical Medicine. 2019;8(9):1415. doi: 10.3390/jcm8091415.
- [53] Paulino Silva KM, de Sousa FL, Alves ACB, Rocha PA, da Costa HNAF, Ferreira WR, Reis TS, de Oliveira TKB, Cabral Batista SR, Lapa Neto CJC, Oliveira AG, de Lemos Jordão AJJM. Chondroprotective effect of melatonin and strontium ranelate in animal model of osteoarthritis. Heliyon. 2021;7(4):e06760. doi: 10.1016/j.heliyon.2021. e06760.
- [54] Hong Y, Kim H, Lee S, Jin Y, Choi J, Lee SR, Chang KT, Hong Y. Role of melatonin combined with exercise as a switch-like regulator for circadian behavior in advanced osteoarthritic knee. Oncotarget. 2017;8(57):97633-97647. doi: 10.18632/oncotarget.19276.
- [55] Stanford SC. Recent developments in research of melatonin and its potential therapeutic applications. British Journal of Pharmacology. 2018;175(16):3187-3189. doi: 10.1111/bph.14371.
- [56] Valdés-Tovar M, Estrada-Reyes R, Solís-Chagoyán H, Argueta J, Dorantes-Barrón AM, Quero-Chávez D, Cruz-Garduño R, Cercós MG, Trueta C, Oikawa-Sala J, Dubocovich ML, Benítez-King G. Circadian modulation of neuroplasticity by melatonin: a target in the treatment of depression. British Journal of Pharmacology. 2018;175(16):3200-3208. doi: 10.1111/bph.14197.
- [57] Satyanarayanan SK, Su H, Lin YW, Su KP. Circadian rhythm and melatonin in the treatment of depression. Current Pharmaceutical Design.

- 2018;24(22):2549-2555. doi: 10.2174/1381612 824666180803112304.
- [58] Cardinali DP, Srinivasan V, Brzezinski A, Brown GM. Melatonin and its analogs in insomnia and depression. Journal of Pineal Research. 2012;52(4):365-375. doi: 10.1111/j.1600-079X.2011.00962.x.
- [59] Mendoza J. Circadian insights into the biology of depression: Symptoms, treatments and animal models. Behavior Brain Research. 2019;376:112186. doi: 10.1016/j. bbr.2019.112186.
- [60] Vega-Rivera NM, Ortiz-López L, Granados-Juárez A, Estrada-Camarena EM, Ramírez-Rodríguez GB. Melatonin reverses the depression-associated behaviour and regulates microglia, fractalkine expression and neurogenesis in adult mice exposed to chronic mild stress. Neuroscience. 2020;440:316-336. doi:10.1016/j. neuroscience. 2020.05.014.
- [61] Smagula SF, Ancoli-Israel S, Blackwell T, Boudreau R, Stefanick ML, Paudel ML, Stone KL, Cauley JA, Osteoporotic Fractures in Men (MrOS) Research Group. Circadian rest–activity rhythms predict future increases in depressive symptoms among community-dwelling older men. The American Journal of Geriatric Psychiatry. 2015;23(5):495-505.
- [62] Xie S, Fan W, He H, Huang F. Role of melatonin in the regulation of pain. Journal of Pain Research. 2020 Feb 7;13:331-343. doi: 10.2147/JPR. S228577.
- [63] Hemati K, Amini Kadijani A, Sayehmiri F, Mehrzadi S, Zabihiyeganeh M, Hosseinzadeh A, Mirzaei A. Melatonin in the treatment of fibromyalgia symptoms: A systematic review. Complementary Therapy in Clinical Practice. 2020;38:101072. doi: 10.1016/j.ctcp.2019.101072.
- [64] Quera Salva MA, Hartley S, Barbot F, Alvarez JC, Lofaso F, Guilleminault C. Circadian rhythms, melatonin and depression. Current Pharmaceutical Design. 2011;17(15):1459-70. doi: 10.2174/138161211796197188.

- [65] Penders TM, Stanciu CN, Schoemann AM, Ninan PT, Bloch R, Saeed SA. Bright Light therapy as augmentation of pharmacotherapy for treatment of depression: a systematic review and meta-analysis. Primary Care Companion CNS Disorders. 2016;18(5). doi: 10.4088/PCC.15r01906.
- [66] Tsai YF, Wong TK, Juang YY, Tsai HH. The effects of light therapy on depressed elders. International Journal Of Geriatric Psychiatry. 2004;19(6):545-548.
- [67] Zhao X, Ma J, Wu S, Chi I, Bai Z. Light therapy for older patients with non-seasonal depression: a systematic review and meta-analysis. Journal of Affective Disorders.2018;232:291-299. doi: 10.1016/j.jad.2018.02.041.
- [68] Tao L, Jiang R, Zhang K, Qian Z, Chen P, Lv Y, Yao Y. Light therapy in non-seasonal depression: an update meta-analysis. Psychiatry Research. 2020;291:113247. doi: 10.1016/j. psychres.2020.113247.
- [69] Ibrahim MM, Patwardhan A, Gilbraith KB, Moutal A, Yang X, Chew LA, Largent-Milnes T, Malan TP, Vanderah TW, Porreca F, Khanna R. Long-lasting antinociceptive effects of green light in acute and chronic pain in rats. Pain. 2017;158(2):347-360. doi: 10.1097/j.pain.00000000000000767.
- [70] Wu MC, Sung HC, Lee WL, Smith GD. The effects of light therapy on depression and sleep disruption in older adults in a long-term care facility. International Journal of Nursing Practice. 2015;21(5):653-659.
- [71] Henderson TA, Morries LD. Multi-watt nearinfrared phototherapy for the treatment of comorbid depression: an open-label single-arm study. Frontiers in Psychiatry. 2017;8:187.
- [72] Salehpour F, Mahmoudi J, Kamari F, Sadigh-Eteghad S, Rasta SH, Hamblin MR.Brain Photobiomodulation therapy: a narrative review. Molecular Neurobiology. 2018;55(8):6601-6636. doi: 10.1007/s12035-017-0852-4.
- [73] Caldieraro MA, Cassano P. Transcranial and systemic photobiomodulation for major depressive disorder: a systematic review of efficacy, tolerability and biological mechanisms. Journal of Affective Disorders. 2019;243:262-273.

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- [74] Hennessy M, Hamblin MR. Photobiomodulation and the brain: a new paradigm. Journal of Optics. 2016;19(1):013003.
- [75] Taglietti M, Facci LM, Trelha CS, de Melo FC, da Silva DW, Sawczuk G, Ruivo TM, de Souza TB, Sforza C, Cardoso JR. Effectiveness of aquatic exercises compared to patient-education on health status in individuals with knee osteoarthritis: a randomized controlled trial. Clinical Rehabilitation. 2018;32(6):766-776. doi: 10.1177/0269215517754240.
- [76] Watanabe T, Fujiwara Y, Chan FKL. Current knowledge on non-steroidal anti-inflammatory drug-induced small-bowel damage: a comprehensive review. Journal of Gastroenterology. 2020;55(5):481-495. doi: 10.1007/s00535-019-01657-8.
- [77] Jung JH, Seok H, Kim JH, Song GG, Cho, SJ. Association between osteoarthritis and mental health in a Korean population: a nationwide study. International Journal of Rheumatic Diseases. 2018:21(3):611-619.

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