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Behavioral Comorbidities in Rheumatoid Arthritis

A Psychoneuroimmunological Perspective

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CHECK POINTS

- Chronic stressors as well as traumatic loss can provoke depression; in turn, depression can increase sensitization to future events.
- Rheumatoid arthritis (RA) pain and depression tend to be predictive of each other and together lead to a downward spiral of functioning characterized by greater disability, increased sleep disturbance and fatigue, and heightened disease activity.
- Some studies suggest that factors other than pain may cause disordered sleep in patients with RA.

While tremendous therapeutic advancements have been made, patients with rheumatoid arthritis (RA) have a myriad of comorbidities, including fatigue, depression, and sleep disturbances. Data on the comorbidity of psychiatric disorders with arthritis are also striking: according to the NIMH Catchment Area program, the lifetime prevalence of psychiatric disorders among patients with RA is 63%. Indeed, approximately 20% of patients with RA are found to have current major depression with potential impact on RA symptoms. In this review, we discuss the biopsychosocial pathways linking stress to behavioral comorbidities with consideration of potential common underlying inflammatory mechanisms. We also describe behavioral treatment strategies that can improve the clinical management of these patients.

Psychological Stress and RA

A broad range of illnesses has been associated with stress, including a failure in regulation of autoimmune responses, which may give rise to inflammatory conditions such as RA. Psychological stress is also thought to aggravate disease activity in RA. Stress, defined as minor hassles and life events lasting hours or days, has been associated with subsequent increases in disease activity.[1]

Much social psychiatry research focuses on measuring the harmful effects of social stressors, separate from and in combination with dispositional variables such as psychopathology (eg, depression). Zautra and colleagues[2] found that stressful experiences led to increases in inflammatory markers in patients with RA, and the combination of stress and depressive symptoms predicted greater elevations of these markers of inflammation.[2] However, it is important to acknowledge the bidirectionality of these relationships as well. Chronic stressors as well as traumatic loss experiences can provoke depression; in turn, depression can increase sensitization to future events.

Influence of Depression on Pain and RA

Several longitudinal, prospective studies show that RA pain and depression tend to be predictive of each other and together lead to a downward spiral of functioning characterized by greater disability, increased sleep disturbance and fatigue, and heightened disease activity.[3,4] The combined burden of stress, pain, and depression increase vulnerability to illness and reduce capacity for successful adaptation.

Recent evidence also points to a significant influence of depression history on adaptation to illnesses such as RA. One study found that patients with RA who had had an episode of depression (but who were not currently depressed) had significantly greater pain than controls without a history of depression.[4] Moreover, Conner and colleagues[5] found that long-past episodes of major depression were associated with greater emotional reactivity to daily pain as well as less perceived control over pain episodes and their consequences.

Patients with RA who have had multiple depressive episodes fare the worst. Zautra and colleagues[6] found that recurrently depressed patients with RA reported higher levels of pain than patients who had never been depressed and those who had experienced only a single episode of depression.[6] Patients with RA who had a history of recurrent depression were also more stress-reactive; they reported more pain and affective reactivity following an experimentally induced interpersonal stressor than never- or once-depressed patients.

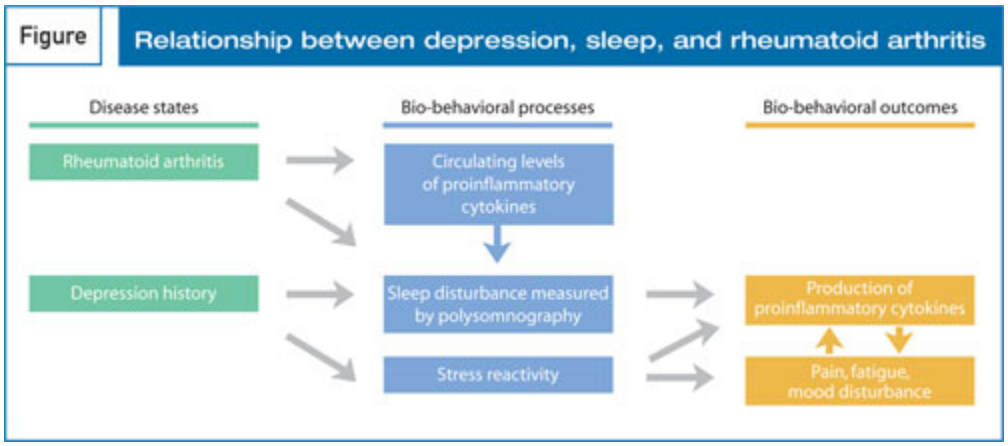
These findings indicate that a history of recurrent depression may serve as a hidden vulnerability, which leaves a “scar” that ultimately influences adaptation even after accounting for current mental health. Individuals who have had 2 or more depressive episodes report more stressful life events than their single-episode or never-depressed counterparts. Patients with recurrent depression also manifest greater sleep disturbance than those who had a single depressive episode.[7] Hence, it is possible that recurrent depression is associated with a more severe neurophysiological substrate and more social stressors than a single depressive episode.

Interrelationship Between Depression, Sleep, and RA

Sleep disturbance is thought to contribute to pain, fatigue, and depressed mood in patients with RA, and a number of studies show that subjective sleep complaints correlate with fatigue, functional disability, greater joint pain, and more depressive symptoms in these patients.[8] Indeed, sleep difficulties, pain, depressed mood, and fatigue appear to cluster in RA; depression is associated with greater pain, whereas sleep difficulties are associated with fatigue, depression, and pain.[3,9,10]

The relationship between sleep disturbance and other symptoms is complex (**Figure**). For example, sleep disturbance may be a symptom of depression or it may precipitate feelings of depression because it interferes with normal activities. Alternately, both sleep disturbance and depression may be manifestations of an underlying biological disturbance. To date, research on RA "sickness symptoms" has been primarily descriptive and cross-sectional, which has limited conclusions about how disordered sleep may influence and be influenced by other symptoms.

Prospective or experimental studies that simultaneously assess multiple symptoms using state-of-the-art measurement techniques are needed to advance our understanding of sleep and its association with other RA symptoms. Nevertheless, some data suggest that sleep disturbance makes a unique contribution to symptomatic pain in RA. One study showed that poor sleep is temporally associated with an overnight increase in tenderness in the peripheral joints in patients with RA who are experiencing an acute flare-up.[11]



On the other hand, noxious stimuli and pain are thought to interfere with sleep.[8] Indeed, Nicassio and colleagues[12] found that pain leads to subjective complaints of poor sleep, which, in turn, contributes to fatigue and depressive symptoms in patients with RA. However, Drewes and colleagues[10] report that sleep is similarly disrupted in patients with RA with and without an active pain flare-up, which suggests that factors other than pain may cause disordered sleep in patients with RA.

Proinflammatory Cytokines

Animal models, cell culture data, and anti-inflammatory cytokine antagonist treatments provide converging evidence that dysregulation of the proinflammatory cytokine network

underlies synovial inflammation in patients with RA.[13] Increases in monocyte production of interleukin (IL)-1 and tumor necrosis factor-α (TNF-α) correlate with destruction of cartilage and bone. In addition, plasma levels of IL-6 and TNF-α longitudinally predict increases of disease activity in patients with RA, and both IL-6 and TNF-α play key roles in the onset and pathogenesis of RA. Finally, proinflammatory cytokines show potent additive effects. TNF-α strongly induces production of IL-1 and IL-6, which, in turn, promotes a cascade of processes, such as leukocyte infiltration of synovial tissue, collagenase and prostaglandin E production, and bone resorption.

Blocking the action of TNF-α via antagonists is currently a major pharmacological strategy in the treatment of RA. For example, anti–TNF-α antibodies drop the bioactivity of IL-1 by 90% in synovial cultures. Moreover, clinical studies have shown that treatment with TNF-α receptor antagonists (eg, infusion of infliximab) rapidly binds TNF-α and induces decreases in plasma levels of IL-1 receptor antagonist (IL-ra) and IL-6 (within hours) after intravenous administration.[14] Along with the rapid (within hours) decline in circulating levels of proinflammatory cytokines, infliximab infusion induces acute (within hours) symptomatic effects, including alleviation of pain, morning stiffness, and fatigue.[15] Subsequently (within 2 to 4 weeks), infliximab infusion reduces joint tenderness and swelling.[13,14]

Finally, some data suggest that TNF-α antagonists may affect behavioral symptoms in patients with RA; in an open study, infliximab induced acute (within hours) improvements of sleep as measured by polysomnography, which raises the possibility that inflammatory responses may initiate and perpetuate behavioral complications in RA.[16]

Stress, Depression, and Sleep Disturbance

Among healthy adults, ongoing stressful circumstances are associated with elevations of in vivo markers of systemic inflammation, including increases in circulating levels of IL-6.[17] Even brief naturalistic stressors correlate with increases in stimulated IL-6 production.[18] Exposure to minor naturalistic stressors that may last from hours to weeks is associated with increases in circulating levels of IL-6, particularly in patients withRA who are depressed.[2,19] Moreover, chronic daily stress predicts greater stimulated monocyte production of IL-6 and impaired capacity of adrenocorticoids to suppress IL-6 production.[20] IL-6 production, in turn, is related to increased fatigue in patients with RA.[20]

Such stress-induced activation of inflammatory signaling is increasingly seen as having relevant clinical implications. Even short-term experimental psychological stress induces marked increases in monocyte production of TNF-α in patients with RA compared with healthy controls.[21] However, such increases in the expression of proinflammatory cytokines occur primarily in patients with RA who are not taking TNF-α antagonist medications.[21] Patients with RA who took TNF-α antagonists (infliximab, etanercept, or adalimumab) were protected from stress-related increases in TNF-α production, with unchanged production similar to responses in healthy controls.

The stress-induced increased TNF-α production that is seen in patients with RA who are not taking TNF-α antagonists may reflect altered TNF-α regulation at the cellular level. Infliximab, etanercept, and adalimumab work by binding to soluble TNF-α, which prevents it from attaching to its receptor, thus rendering the TNF-α biologically inactive. Finally, there is some evidence that these medications also block the activation of nuclear factor (NF)- κ, an intracellular transcription factor that initiates expression of genes specific to the production of TNF-α and other inflammatory cytokines. Acute psychological stress, as well as sleep deprivation, are known to induce the activation of NF- κ.[22,23]

Similar to the effects of psychological stress on inflammatory responses, disordered sleep also has key consequences for expression of proinflammatory cytokines. Sleep deprivation and disordered sleep lead to daytime elevations in circulating levels of IL-6 and TNF-α, along with increases in the cellular and genomic expression of markers of inflammation.[24-26] Moreover, sleep deprivation induces an exaggerated elevation of IL-6 and TNF-α in patients who show abnormal increases in resting levels of proinflammatory cytokine activity compared with controls.[27] In turn, elevated levels of IL-6 correlate with symptomatic reporting of fatigue with similar relationships between fatigue and other serum markers of proinflammatory activity (eg, IL-1ra, sTNF-RII, and neopterin).[28-30]

Increases of proinflammatory cytokine activity and disordered sleep are also implicated in reducing the pain threshold, which raises the testable hypothesis that disordered sleep and elevated proinflammatory cytokine activity mediate increased pain sensitivity in RA.[31,32] Basic studies show that proinflammatory cytokines contribute to hyperalgesia and pain sensitivity; pain neurons in the spinal cord secrete IL-1 and application of IL-1 into the dorsal horn provoking the increased firing of pain fibers.[33]

Similarly, in studies with healthy adults, experimental deprivation of sleep is associated with increased pain sensitivity during the morning.[32] Taken together, stress, depression, and sleep loss, and/or a failure to recover from it, may be associated with increased production of inflammatory markers in RA, which, in turn, amplifies symptomatic expression of pain and fatigue.

Reciprocal Influence of Inflammation

Although there is much speculation about the role of biological factors in RA-related sleep complaints and associated "sickness symptoms" of fatigue, pain, and affective disturbance, empirical research has been extremely limited. Basic research on neural-immune signaling has shown that peripheral proinflammatory cytokines exert potent effects on neural processes that lead to a constellation of behavior changes, including abnormal sleep, depressed mood, and social withdrawal.[34-36] Experimentally induced immune activation is associated with depressed mood, fatigue, and difficulty concentrating.[37]

Acute administration of IL-6 also leads to fatigue and early night decreases of delta sleep,

although some data show that endotoxin challenge and release of cytokines enhances non-REM sleep.[38,39] We have further found that nocturnal elevations of IL-6 before sleep onset correlate with prolonged sleep latency and that this effect is independent of the contribution of IL-6 levels later in the night or confounding factors (eg, body mass index, age).[27]

Finally, a recent study has examined the effect of a single dose of the TNF receptor antagonist, infliximab (3 mg/kg) on sleep as measured by polysomnography.[16] In 6 women with RA, infliximab infusion induced acute (within hours) improvements in sleep latency and sleep efficiency, and this improvement in sleep occurred before the amelioration of joint pain.

One reciprocal model that encompasses the association between inflammation and behavioral symptoms in RA would posit that stress and sleep loss induce increases in the production of inflammatory markers, which then promotes the manifestation of clinical symptoms such as pain, fatigue, and affective disturbance. In turn, nocturnal elevations of proinflammatory cytokines and pain recursively initiate further difficulties with stress and sleep in patients with RA. In other words, stress, sleep, and proinflammatory cytokines show a bidirectional relationship that develops into a feed-forward, vicious circle in patients with RA and contributes to a progressive deterioration in clinical outcomes as measured by disease severity and associated psychiatric comorbidities.

Clinical Impact of Treatment

Pharmacological treatments for RA have been effective in controlling pain, inflammation, and swelling, but they may not address key psychosocial vulnerabilities that contribute to adaptation. The gold standard of behavioral approaches, cognitive-behavioral therapy (CBT), attempts to change maladaptive ways of thinking and feeling in response to illness. The specific techniques have encompassed an extensive range of strategies, including biofeedback and relaxation training, cognitive restructuring and distraction, and activity pacing. The majority of studies have focused on the management of pain, but some CBT trials have also emphasized the management of stress and the development of more general life management skills.

A recent review of 25 randomized clinical trials that tested psychosocial treatments for RA underscores the effectiveness of these approaches in increasing patients' ability to cope with pain and reduce pain, physical disability, and depressive symptoms.[40] Yet the findings show substantial variability across outcome measures. The effects were strongest for active coping outcomes and relatively more modest for pain and affective disturbance, a pattern that was also evident in a review of behavioral treatments for RA and osteoarthritis.[41] The findings invite speculation about the general effectiveness of behavioral interventions for RA and the role of individual differences in the response to treatment based on patients' history and clinical needs.

Recent evidence highlights the adaptive value of positive emotional resources, particularly in those who are vulnerable because of social stressors and/or a history of

depression. More attention to this and other potential "resilience" factors may provide greater specificity about the nature of the relationship between depression and pain and offer new targets for therapeutic and preventive treatments for those with chronic pain.

A study by Matsuzaki and colleagues[42] revealed that mirthful laughter lowered circulating levels of plasma IL-6, which suggests the potential treatment effectiveness of mood change for disease severity. Unique difficulties in patients with RA also may point the way to successful interventions tailored to address problems in affective regulation that underlie inflammatory processes in RA and other illnesses.

We have found that interventions that focus on mindfulness and emotional regulation generally are more successful in reducing pain and elevating well-being among patients with RA with recurrent depression than standard treatment, such as CBT.[43] Thus, vulnerabilities due to depression history may be offset for those who learn ways to weather the storms of negative emotions that accompany pain and distress and sustain positive affect in spite of their chronic difficulties.

There is qualified support for mindfulness meditation in addition to the pain management skills training in standard CBT for the treatment of pain in patients with RA. In addition, data highlight the importance of recognizing and managing depression in patients with RA because those with a history of depression appear to have a differential response to intervention approaches that emphasize self-management strategies compared with those that do not.

Drugs Mentioned in This Article
Adalimumab (Humira)
Etanercept (Enbrel)
Infliximab (Remicade)

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