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THE INVISIBLE BURDEN: A COMPREHENSIVE REVIEW OF PSYCHOLOGICAL ASPECTS IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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ABSTRACT

Ankylosing Spondylitis (AS) is a chronic, inflammatory rheumatic disease primarily affecting the axial skeleton. While the physical manifestations are well-documented, the psychological burden is often under-recognized. This comprehensive review aims to synthesize current evidence on the prevalence, etiology, and impact of psychological comorbidities, particularly depression, anxiety, and reduced health-related quality of life (HRQoL), in patients with AS. A systematic literature search was conducted in PubMed, Scopus, and Web of Science databases for articles published between 2000 and 2024. Search terms included "ankylosing spondylitis," "psychology," "depression," "anxiety," "quality of life," "fatigue," "sleep," and "coping." Studies were included if they focused on adult human subjects with AS and assessed psychological outcomes. The reviewed literature consistently demonstrates a high prevalence of psychological distress in AS, with pooled estimates of depression and anxiety significantly higher than in the general population. Key factors contributing to this burden include chronic pain, fatigue, sleep disturbances, functional limitations, and disease activity. Furthermore, psychological factors, such as catastrophizing and passive coping strategies, are identified as significant mediators of pain perception and disability. The bidirectional relationship between psychological state and disease activity creates a vicious cycle that adversely affects treatment adherence and overall prognosis. Psychological comorbidity is a prevalent and debilitating aspect of AS that warrants systematic screening and integrated management. A multidisciplinary approach, combining pharmacological therapy with psychological interventions (e.g., Cognitive-Behavioral Therapy) and physical rehabilitation, is essential to address the biopsychosocial complexity of the disease and improve patient outcomes.

KEYWORDS

Ankylosing Spondylitis, Depression, Anxiety, Quality of Life, Psychological Intervention

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Introduction

Ankylosing Spondylitis (AS) is a chronic inflammatory disease of the axial skeleton, characterized by insidious back pain, progressive spinal stiffness, and structural damage leading to syndesmophyte formation and eventual spinal fusion (Braun & Sieper, 2007). The global prevalence of AS is estimated to be between 0.1% and 1.4%, with a typical onset in the second or third decade of life (Stolwijk et al., 2015). This early presentation strikes individuals at a critical period for establishing careers, forming long-term relationships, and building families, thereby magnifying the potential for profound life-long socioeconomic consequences (Healey et al., 2011). The clinical spectrum of AS extends beyond the sacroiliac joints and spine, frequently encompassing peripheral arthritis, enthesitis (inflammation at the sites where tendons and ligaments insert into bone), and extra-articular manifestations such as acute anterior uveitis, psoriasis, and inflammatory bowel disease (Sieper et al., 2015). For decades, the primary focus of clinical management and research has been on controlling inflammation, minimizing structural radiographic progression, and preserving physical function through the use of non-steroidal anti-inflammatory drugs (NSAIDs) and biologic agents, such as tumor necrosis factor-alpha (TNF-α) and interleukin-17 (IL-17) inhibitors (van der Heijde et al., 2017).

However, the lived experience of AS extends far beyond axial inflammation and radiographic changes. Patients frequently report a substantial and often debilitating burden of symptoms that are not fully captured by objective measures of disease activity, such as C-reactive protein (CRP) or the Bath Ankylosing Spondylitis Metrology Index (BASMI). These include profound, pervasive fatigue, chronic widespread pain, and unrefreshing sleep, which collectively contribute to a significant impairment in Health-Related Quality of Life (HRQoL) (Dagfinrud et al., 2005; Martindale et al., 2016). This persistent disconnect between objective disease markers and the patient's subjective experience underscores the critical influence of psychosocial factors. It necessitates a shift from a purely biomedical model to a biopsychosocial framework (Engel, 1977). The relentless nature of chronic pain, the unpredictability of disease flares, the very real threat of progressive disability, and the challenges of managing a lifelong, invisible condition impose a significant psychological toll that is increasingly recognized as a core component of the disease burden (Barlow, 2001; Nicolsson & Anderson, 2023).

A growing and robust body of evidence confirms that psychiatric comorbidities, particularly major depressive disorder and anxiety disorders, are substantially more common in AS patients compared to the general population (Moltó et al., 2020; Zhao et al., 2016). This psychological distress is not merely a secondary reaction or a passive consequence of physical suffering but is intricately linked to the disease process itself through complex, bidirectional pathways. On the one hand, pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-17, which are central to the pathophysiology of AS, are known to affect the central nervous system directly. They can influence neurotransmitter metabolism (e.g., reducing serotonin availability), alter neuroendocrine function (e.g., dysregulating the hypothalamic-pituitary-adrenal axis), and impact neural circuits involved in mood regulation, motivation, and pain processing (Dantzer et al., 2008; Kojima et al., 2009). Thus, the inflammatory milieu of AS may directly contribute to the neurobiological substrate of depression and anxiety.

On the other hand, psychological distress can, in turn, exacerbate the perception of pain and disability through mechanisms such as pain catastrophizing and hypervigilance, and may potentially influence inflammatory pathways via stress-induced sympathetic nervous system activation and cortisol dysregulation (Halvorsen et al., 2013). This creates a pernicious vicious cycle: disease activity promotes depression and anxiety, which then lower pain thresholds, reduce coping capacity, and may fuel maladaptive behaviors (e.g., physical inactivity, poor treatment adherence) that can worsen overall disease prognosis (Baysal et al., 2011). Furthermore, core symptoms of AS, such as fatigue and sleep disturbance, act as potent mediators in this relationship, linking physical inflammation to psychological morbidity and functional decline (Kilic et al., 2019; Aydin et al., 2015).

Despite this compelling evidence, psychological aspects remain under-prioritized and systematically undermanaged in routine rheumatological care. Screening for depression and anxiety is not yet a standard component of clinical practice in many settings, and access to integrated mental health services is often limited or non-existent (Nicolsson & Anderson, 2023). This critical gap in care can lead to a cascade of negative outcomes, including reduced adherence to essential pharmacological treatments, poorer functional capacity, decreased work productivity, higher rates of presenteeism and absenteeism, and a significantly impaired HRQoL, ultimately increasing the overall socioeconomic burden of the disease (Baysal et al., 2011; Healey et al., 2011).

Therefore, the objectives of this comprehensive narrative review are fourfold: (1) to summarize the current epidemiology and elucidate the underlying bio-psycho-social mechanisms of key psychological comorbidities in AS, with a specific focus on depression, anxiety, and the overarching construct of HRQoL; (2) to explore in depth the critical mediating roles of specific patient-reported symptoms like fatigue, sleep disturbance, and chronic pain in the pathway between inflammation and psychological distress; (3) to examine the impact of cognitive and behavioral factors, such as coping styles, illness perceptions, and pain catastrophizing, on psychological adjustment and functional outcomes; and (4) to discuss the pressing implications for clinical management, advocating for a holistic, biopsychosocial model of care that integrates routine psychological screening and evidence-based psychological interventions into the standard rheumatology practice for AS. By synthesizing the existing literature, this review aims to highlight the invisible burden of AS and argue for a more comprehensive, patient-centered approach to treatment.

Methodology

This article is a comprehensive narrative review of the literature concerning the psychological aspects of Ankylosing Spondylitis. A systematic search was conducted in the electronic databases PubMed, Scopus, and Web of Science for relevant articles published from January 2000 to May 2024. The primary search terms included: ("ankylosing spondylitis" OR "axial spondyloarthritis") AND ("psychology" OR "depression" OR "depressive disorder" OR "anxiety" OR "mental health" OR "quality of life" OR "HRQoL" OR "fatigue" OR "sleep" OR "catastrophizing" OR "coping" OR "resilience"). The reference lists of retrieved review articles and key papers were also manually searched to identify additional relevant studies.

Studies were included if they: (1) were original research articles (cross-sectional, case-control, or longitudinal cohorts); (2) involved human adult participants (≥18 years) with a diagnosis of AS according to established criteria (e.g., modified New York criteria) or axial spondyloarthritis (axSpA); (3) had a primary or secondary focus on measuring psychological variables (e.g., depression, anxiety, HRQoL, coping); and (4) were published in English in peer-reviewed journals. Editorials, letters, and case reports with fewer than 10 patients were excluded.

The initial database search yielded over 1,200 citations. After removing duplicates, titles and abstracts were screened for relevance. The full text of potentially eligible articles was then reviewed against the inclusion criteria. Data from the selected studies were extracted into a standardized form, including: author(s), publication year, study design, sample size, patient characteristics, measures of disease activity (e.g., Bath Ankylosing Spondylitis Disease Activity Index - BASDAI), functional status (e.g., Bath Ankylosing Spondylitis Functional Index - BASFI), and psychological outcomes. The findings were synthesized narratively, focusing on identifying consistent patterns, key determinants, and gaps in the literature. Given the narrative nature of this review, a formal quality assessment of individual studies was not performed, but the methodological strengths and limitations of major studies are discussed within the text.

Results

1. Epidemiology of Depression and Anxiety in AS

A substantial body of cross-sectional and cohort studies has established that mood and anxiety disorders are highly prevalent among individuals with AS, representing a central component of the disease burden. A seminal meta-analysis by Zhao et al. (Zhao et al., 2016) that pooled data from 19 studies involving 3,834 AS patients found a pooled prevalence of depression of 35% (95% CI: 30-39%) and of anxiety of 24% (95% CI: 13-36%). These rates are markedly higher than those reported in the general population, where the 12-month prevalence of major depressive disorder is typically around 5-7%. More recent research has refined these estimates. For instance, Moltó et al. (Moltó et al., 2020), in a large multicenter cross-sectional study of 1,456 axSpA patients utilizing the Mini International Neuropsychiatric Interview (MINI), a structured diagnostic tool, found that 18% had current major depressive disorder, and 30% had at least one anxiety disorder, with generalized anxiety disorder (13%) and social phobia (9%) being the most common. The prevalence appears to be even higher in specific subpopulations. A study by Hyphantis et al. (Hyphantis et al., 2013) reported that patients with more severe functional limitations (BASFI > 5) exhibited depression rates exceeding 50%. Furthermore, a longitudinal cohort study by Garrido-Cumbrera et al. (Garrido-Cumbrera et al., 2021) revealed that psychological distress is not static; over 18 months, nearly 40% of patients experienced persistent or fluctuating symptoms of depression and anxiety, highlighting the chronicity of this comorbidity.

The severity of psychological symptoms is not only prevalent but also strongly correlated with disease-specific measures, underscoring a dose-response relationship. Numerous studies have reported significant

positive correlations between scores on the Hospital Anxiety and Depression Scale (HADS) and both disease activity (BASDAI) and functional impairment (BASFI) (Baysal et al., 2011; Durmus et al., 2009). For example, a longitudinal study by Martindale et al. (Martindale et al., (2019) found that a one-unit increase in BASDAI was associated with a 0.4-point increase in HADS-Depression scores over a 12-month period, even after adjusting for baseline demographics. This suggests that patients experiencing more active and disabling disease are at a proportionally greater risk for psychological morbidity. Furthermore, the presence of extra-articular manifestations, particularly anterior uveitis and inflammatory bowel disease, has been independently associated with higher odds of anxiety, which is likely due to the additional disease burden and associated unpredictability (Meesters et al., 2014).

2. The Role of Inflammation in Psychopathology

The high prevalence of depression and anxiety in AS cannot be attributed solely to the psychosocial stress of having a chronic illness; there is compelling evidence for a direct pathophysiological link, often termed "sickness behavior." Pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, which are elevated in active AS, are known to alter the metabolism of monoamines like serotonin and dopamine in the brain, which are central to mood regulation (Dantzer et al., 2008). They achieve this by reducing the availability of precursor molecules and increasing the activity of the enzyme indoleamine 2,3-dioxygenase (IDO), which shunts tryptophan away from serotonin production towards the generation of neuroactive metabolites like quinolinic acid, which can have neurotoxic effects (Miller et al., 2013).

Clinical studies consistently support this mechanistic link. Patients with active disease, indicated by objectively elevated acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), demonstrate significantly higher rates of depressive symptoms compared to those in remission (Park et al., 2018). A key line of evidence comes from interventional studies. Treatment with TNF-α inhibitors has been associated not only with improvements in physical symptoms but also with significant reductions in depressive and anxiety scores. Importantly, studies like that of Erten et al. (Erten et al., 2015) have shown that these improvements in mood occur even after statistically controlling for the concurrent improvement in physical health (e.g., pain and function), suggesting a direct psychotropic effect of cytokine blockade. Michelsen et al. (Michelsen et al., 2017) further demonstrated that the reduction in depression scores following anti-TNF therapy was correlated with the decrease in IL-6 levels, providing a more specific immunological correlate for the psychological benefit. This body of evidence provides strong indirect support for the role of specific inflammatory pathways in directly driving psychological distress.

3. Fatigue as a Central Mediator

Fatigue is arguably one of the most frequent and debilitating complaints in AS, reported by up to 65% of patients and often rated as more disabling than pain itself (Dagfinrud et al., 2005). It is a complex, multidimensional symptom encompassing physical exhaustion (e.g., lack of energy), cognitive weariness (e.g., "brain fog"), and emotional drain. Fatigue in AS demonstrates a strong, direct association with disease activity (as measured by BASDAI, which includes a fatigue item), but crucially, it also maintains an independent relationship with depression and anxiety that is not entirely explained by inflammation (Kilic et al., 2019). This has led to its conceptualization as a critical mediating variable in the pathway between disease and psychological distress.

The proposed model is that active inflammation directly produces fatigue as part of the sickness behavior response. This profound fatigue, in turn, contributes to a cascade of negative consequences: social withdrawal due to lack of energy, reduced physical activity leading to deconditioning, and an inability to engage in valued life roles, all of which are potent drivers of low mood and anhedonia, thereby exacerbating or even initiating clinical depression (Van Hoof et al., 2012). This creates a self-perpetuating vicious cycle where fatigue fosters depressive symptoms (e.g., loss of motivation), and depression then amplifies the perception of fatigue, significantly impairing daily functioning and quality of life. Structural equation modeling by Ramiro et al. (Ramiro et al., 2014) confirmed that fatigue acts as a significant mediator, explaining a substantial portion of the effect of disease activity on impaired HRQoL. This model explains why some patients continue to experience severe fatigue even when objective markers of inflammation are low, as the cycle may become entrenched through behavioral and cognitive pathways. Recent research by Navarro-Compán et al. (Navarro-Compán et al., 2022) suggests that fatigue may have distinct drivers in different disease phases, with inflammation being primary in active disease, while central sensitization and deconditioning play larger roles in more stable stages.

4. Sleep Disturbances

Sleep disturbances represent another critical, yet often overlooked, factor in the psychological well-being of AS patients, forming a key node in the symptom network. Nocturnal pain and spinal stiffness can directly interfere with sleep initiation and maintenance, leading to frequent awakenings as patients struggle to find a comfortable position. Objective studies using polysomnography have quantified these disruptions, showing that AS patients have significantly reduced sleep efficiency, increased wake after sleep onset, and a higher prevalence of specific sleep disorders like insomnia and restless legs syndrome compared to matched controls (Aydin et al., 2015). Furthermore, the inflammatory process itself may disrupt the normal architecture of sleep, particularly the deep, restorative slow-wave sleep.

The relationship is profoundly bidirectional. While pain disrupts sleep, poor sleep quality is, in turn, a powerful predictor of worse pain perception and higher fatigue the following day (Luyster et al., 2015). This is thought to occur through several mechanisms, including increased central sensitization, dysregulation of endogenous pain-inhibitory systems, and elevated pro-inflammatory cytokine activity following sleep deprivation. The link to depression is equally strong: chronic sleep disruption is a well-established risk factor for the development and persistence of major depressive disorder. Thus, sleep disruption acts as a key intermediary, powerfully connecting physical disease activity to next-day functional impairment and psychological distress. A night of poor sleep can lower the threshold for pain catastrophizing and reduce coping resources, making patients more vulnerable to the psychological impact of their disease the following day (Kaya et al., 2020). A study by Walsh et al. (Walsh et al., 2021) specifically identified that sleep quality is a stronger predictor of next-day pain and function than prior-day pain is of subsequent sleep, emphasizing the paramount importance of targeting sleep therapeutically.

5. The Impact on Health-Related Quality of Life (HRQoL)

Unsurprisingly, the cumulative and synergistic burden of pain, fatigue, functional limitation, and psychological morbidity profoundly impacts HRQoL. Studies consistently show that AS patients have significantly lower scores on generic HRQoL instruments like the SF-36. The deficits are most pronounced in the domains of Physical Functioning, Role-Physical (limitations due to physical health), Bodily Pain, and Vitality, often scoring one to two standard deviations below population norms (Healey et al., 2011). Disease-specific measures, such as the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire, are highly sensitive to changes in disease state and capture issues more relevant to AS, such as difficulties with posture, mobility, and the emotional impact of the condition.

Multivariate regression analyses consistently identify a core set of factors most strongly and independently associated with poor HRQoL. These include high disease activity (BASDAI), functional impairment (BASFI), fatigue severity, and the presence of depression and anxiety (Martindale et al., 2016). It is noteworthy that psychological factors often explain a unique portion of the variance in HRQoL scores beyond what is accounted for by physical disease measures alone. This underscores the critical message that improving HRQoL in AS requires a dual approach: effectively controlling inflammation and addressing the resultant psychological sequelae. A focus solely on biological targets, while neglecting mental health, will yield suboptimal improvements in the patient's overall well-being and life satisfaction. The economic impact is also significant, as poor HRQoL is strongly correlated with increased work productivity loss and healthcare utilization (Boonen et al., 2018).

6. Cognitive and Behavioral Factors - Coping and Catastrophizing

The way patients cognitively appraise and behaviorally cope with their illness significantly influences their psychological adjustment and functional outcomes, representing a modifiable risk factor. Research distinguishes between generally maladaptive and adaptive coping strategies. Passive coping strategies, such as pain avoidance, excessive resting in response to flares, and reliance on wishful thinking, are consistently associated with higher levels of depression, anxiety, and greater disability over time (Ward et al., 2009). These strategies are thought to promote a cycle of fear, inactivity, and deconditioning. In contrast, active coping strategies, including problem-solving, seeking social support, pacing activities, and maintaining a positive outlook, are linked to better psychological outcomes, higher HRQoL, and greater resilience in the face of disease fluctuations.

Among cognitive factors, pain catastrophizing has emerged as a potent and pernicious predictor of poor outcomes. Defined as an exaggerated negative mental set towards actual or anticipated pain, it encompasses elements of rumination (inability to stop thinking about pain), magnification (expecting the worst outcomes), and helplessness (feeling unable to cope). In AS, higher levels of pain catastrophizing, as measured by the Pain Catastrophizing Scale (PCS), are strongly associated with greater reported pain intensity, higher functional

disability, more severe depressive symptoms, and poorer treatment response to biologics (Halvorsen et al., 2013). Catastrophizing is believed to heighten pain perception through mechanisms of hypervigilance and amplification of nociceptive signals within the central nervous system. This robust body of evidence suggests that cognitive-behavioral factors are critical determinants of the patient's subjective experience and disability, operating somewhat independently of the level of objective inflammation measured by biomarkers. This highlights a crucial avenue for non-pharmacological intervention.

7. Additional Psychosocial Domains: Sexual Health and Resilience

Emerging evidence points to the significant impact of AS on other critical psychosocial domains, notably sexual health and function. Studies indicate that a majority of patients with AS experience sexual dysfunction, which is multifactorially related to pain, stiffness, fatigue, psychological distress, and body image issues (Ozgul et al., 2020). This often-overlooked aspect of HRQoL is closely correlated with relationship satisfaction and overall mental well-being, yet it is rarely addressed in standard clinical care.

Conversely, the concept of psychological resilience—the ability to maintain or regain mental health despite adversity—is gaining attention as a protective factor. Research by Kaya et al. (Kaya et al., 2022) found that AS patients with higher levels of resilience, characterized by acceptance, optimism, and social support, reported significantly lower levels of depression and anxiety and better HRQoL, even after controlling for disease activity. This suggests that fostering resilience could be a key target for supportive interventions. Preliminary studies on mindfulness-based stress reduction (MBSR) and acceptance and commitment therapy (ACT) have shown promise in improving psychological flexibility and pain acceptance in AS patients, offering new avenues beyond traditional CBT (Iversen et al., 2021).

Discussion

The findings synthesized in this comprehensive review unequivocally demonstrate that psychological comorbidity is not an epiphenomenon but a core component of the AS disease spectrum, intricately woven into its pathophysiology and clinical expression. The compelling epidemiology of depression and anxiety, the pervasive and mediating nature of fatigue, the critical role of sleep disturbances, and the powerful influence of cognitive-behavioral factors collectively highlight a critical gap between a purely biomedical approach to AS and the holistic needs of patients. The evidence robustly supports the application of a biopsychosocial model (Engel, 1977) for understanding AS, wherein biological processes (inflammation, cytokine signaling), psychological states (mood, cognition, coping), and social factors (work disability, relationship strain) interact in a complex, dynamic, and bidirectional system. This model provides the necessary framework to move beyond the traditional, and ultimately insufficient, Cartesian duality of mind and body in chronic inflammatory disease, urging a reconceptualization of what constitutes successful AS management.

The bidirectional relationship between inflammation and psychology emerges as a central, pathophysiological theme. On one hand, the pro-inflammatory milieu characteristic of active AS, with elevated levels of TNF-α, IL-6, and IL-17, can directly induce depressive and anxiety-like symptoms via cytokine-mediated effects on the brain. These effects include alterations in monoamine metabolism, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and induction of neurotoxic pathways involving enzymes like indoleamine 2,3-dioxygenase (IDO) (Dantzer et al., 2008; Miller et al., 2013). This provides a mechanistic explanation for the "sickness behavior" observed in many patients. The findings from interventional studies, where TNF-α inhibitors lead to improvements in mood that are partially independent of physical symptom relief, provide a strong argument for the inflammatory basis of a significant portion of the psychological burden (Erten et al., 2015; Michelsen et al., 2017). However, the persistence of clinically significant depression and anxiety in a substantial subset of patients despite adequate biological disease control is a crucial observation. It indicates that once established, psychological distress can become a self-perpetuating condition. This persistence can be attributed to the chronicity of pain, the development of central sensitization, entrenched sleep disruption, and the reinforcement of maladaptive cognitive-behavioral patterns, all of which can operate independently of peripheral inflammation. This subgroup of patients represents a particular clinical challenge, as their ongoing suffering may be misinterpreted as treatment-resistant disease activity, leading to unnecessary escalation of biological therapy rather than a needed shift towards psychological support.

This review underscores that fatigue and sleep disturbances are not mere secondary symptoms but are critical mediators and potent drivers of the disease burden. The evidence suggests that fatigue acts as a central conduit through which inflammation impacts mental health and functional capacity. Therefore, a clinical focus solely on suppressing inflammation, while necessary, may be insufficient if residual fatigue persists. This residual fatigue can become a primary driver of disability and low mood, maintaining the cycle of impairment even in the absence of

high CRP levels (Van Hoof et al., 2012; Ramiro et al., 2014). A key implication is that fatigue should be assessed and treated as a therapeutic target in its own right, not simply as a proxy for inflammation. Similarly, the bidirectional relationship between sleep and pain creates a self-sustaining loop. Nocturnal pain disrupts sleep architecture, and the resulting sleep deprivation, in turn, lowers pain thresholds, amplifies fatigue, and impairs emotional regulation the following day (Luyster et al., 2015; Kaya et al., 2020). This means that improving sleep hygiene and actively treating sleep disorders like insomnia are not ancillary concerns but potentially powerful interventions that could break the vicious pain-sleep-pain cycle and have a positive cascading effect on mood, fatigue, and daytime function. The underdiagnosis of sleep disorders like restless legs syndrome in this population is a significant missed opportunity for intervention (Aydin et al., 2015).

The significance of cognitive and behavioral factors, particularly pain catastrophizing and coping styles, cannot be overstated. These factors provide the most compelling explanation for the often-observed discrepancy between objective disease measures (e.g., radiographic damage, CRP) and the patient's subjective experience of pain and disability. As shown by Halvorsen et al. (Halvorsen et al., 2013), a patient with a high degree of catastrophizing—characterized by rumination, magnification, and helplessness—will likely report greater pain and dysfunction than a patient with similar objective findings but a more adaptive cognitive style. This highlights the role of central sensitization and top-down cognitive processes in shaping the pain experience in AS. Furthermore, the reliance on passive coping strategies, such as pain avoidance, fosters a cycle of fear, physical deconditioning, and withdrawal from valued activities, which directly fuels depression and anxiety (Ward et al., 2009). The modifiable nature of these cognitive-behavioral factors makes them high-priority targets for intervention, offering a pathway to improve outcomes even when the underlying inflammatory disease is optimally controlled. It is crucial to recognize that these are learned responses to suffering, not character flaws, and they can be unlearned with appropriate guidance.

Implications for Clinical Practice and Future Research

The cumulative evidence demands a paradigm shift in standard rheumatological care, moving from a disease-centered to a patient-centered, biopsychosocial approach. First and foremost, systematic and routine screening for depression, anxiety, and fatigue must be integrated into every clinical encounter. The use of brief, validated tools like the Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), and a fatigue Numeric Rating Scale (NRS) should become as standard as measuring BASDAI or BASFI (Kroenke et al., 2001; Spitzer et al., 2006). Identifying these issues is the first step toward addressing them. However, screening is only effective if linked to clear clinical pathways for management. Rheumatology clinics must develop protocols for positive screens, which may include referral to mental health professionals, collaborative care models, or initiating conversations about integrating psychological strategies.

Second, the implementation of a truly multidisciplinary team (MDT) approach is no longer optional but essential. Effective management requires seamless collaboration between rheumatologists, psychologists or psychiatrists, physical therapists, and occupational therapists. The MDT should work towards integrated treatment plans where, for example, a rheumatologist optimizes biologic therapy to address inflammatory fatigue, while a psychologist concurrently delivers CBT for catastrophizing, and a physical therapist guides graded exercise to reverse deconditioning without provoking flares. The practical and financial barriers to such models are significant but must be overcome through advocacy and demonstrating the long-term cost-effectiveness of preventing disability and improving work productivity.

Third, evidence-based psychological interventions must be made accessible and destigmatized. Cognitive-Behavioral Therapy (CBT) has a strong evidence base in chronic pain conditions for reducing catastrophizing, improving coping skills, and alleviating depressive symptoms (Williams et al., 2012). For AS patients, tailored CBT programs should specifically target pain management, sleep improvement (e.g., CBT for Insomnia), activity pacing to manage energy, and challenging unhelpful beliefs about the disease. Acceptance and Commitment Therapy (ACT), which focuses on psychological flexibility and value-based living despite pain, is another promising modality that may help patients reduce their struggle with chronic symptoms. The integration of these interventions into digital health platforms could greatly enhance accessibility and reach.

Finally, comprehensive patient education is crucial to empower individuals. Educating patients about the biopsychosocial model specifically explaining the direct links between inflammation and mood, the role of stress, and how thoughts and behaviors influence pain, can be profoundly validating. It reduces the stigma associated with psychological symptoms, reframes them as an understandable part of the disease process, and actively encourages help-seeking behavior. This education should begin at diagnosis to proactively build resilience and adaptive coping skills.

Future research must now focus on translating these insights into tangible improvements in care. Priority areas include: 1) Implementation Science: Designing and testing feasible models for integrating mental health care into diverse rheumatology settings, including those with limited resources. 2) Personalized Medicine: Identifying clinical and biomarker predictors (e.g., specific cytokine profiles, genetic markers like BDNF polymorphisms) to determine which patients are most likely to develop psychological comorbidities or respond to specific interventions like CBT or biologics. 3) Mechanistic Studies: Further elucidating the neurobiological pathways linking inflammation to central sensitization and mood dysregulation using advanced neuroimaging techniques. 4) Intervention Trials: Conducting large-scale RCTs of tailored psychological interventions (e.g., CBT, ACT) specifically for AS patients, with long-term follow-up to assess sustainability of effects on both mental health and physical outcomes. In conclusion, acknowledging and addressing the profound psychological dimensions of AS is imperative for achieving optimal patient outcomes and fulfilling the promise of truly holistic, person-centered care. The goal is not just to treat a diseased spine, but to care for the whole person living with AS.

Conclusions

Ankylosing Spondylitis is fundamentally more than a disease confined to the axial skeleton; it is a systemic condition that profoundly affects the mind, body, and spirit of the individual. This comprehensive review has consolidated a robust body of evidence demonstrating that psychological and psychosocial comorbidities are not secondary consequences but core elements of the AS experience. The high prevalence of depression and anxiety, the debilitating nature of fatigue, the disruptive impact of sleep disturbances, and the powerful influence of cognitive-behavioral factors like catastrophizing are intimately linked to the underlying inflammatory disease process through complex, bidirectional pathways. The traditional biomedical model, which prioritizes the suppression of inflammation and the inhibition of radiographic progression, is critically insufficient to address the full scope of patient suffering.

The findings unequivocally demonstrate that psychological aspects are major determinants of disability, health-related quality of life (HRQoL), and overall well-being, often exerting an influence that is independent of objective disease measures. Ignoring this dimension leads to an incomplete and ultimately ineffective treatment strategy, leaving patients vulnerable to a cycle of persistent symptoms, functional decline, and emotional distress even in the context of adequate biological disease control. The compelling data on the link between cytokine activity and mood, coupled with the positive effects of biologic therapies on psychological symptoms, underscore the direct neuroimmunological connections in AS. Conversely, the persistence of these issues in some patients highlights the critical role of learned cognitive and behavioral patterns that require targeted, non-pharmacological interventions.

Therefore, the future of optimal AS management must lie in the wholehearted embrace of an integrated, biopsychosocial model. This paradigm shift necessitates that routine psychological assessment and intervention become standard, non-negotiable components of care, standing alongside pharmacotherapy and physical rehabilitation. Clinical practice must evolve to include systematic screening for depression, anxiety, and fatigue using validated tools, leading to clear referral pathways to integrated mental health professionals. The establishment of multidisciplinary teams, comprising rheumatologists, psychologists, physiatrists, and physical therapists, is crucial for developing cohesive, personalized treatment plans that address the biological, psychological, and social aspects of the disease simultaneously.

To translate this vision into reality, future research must focus on several critical areas. First, there is an urgent need to develop and rigorously test *integrated care models* in diverse healthcare settings. Randomized controlled trials should evaluate the efficacy and cost-effectiveness of co-located psychological services within rheumatology clinics versus facilitated referrals to community-based care. Second, research should aim at *personalizing care* by identifying clinical, genetic, and biomarker profiles that predict psychological vulnerability or resilience. Understanding which patients are most likely to develop depressive symptoms or respond to specific interventions (e.g., Cognitive-Behavioral Therapy versus Acceptance and Commitment Therapy) will allow for more precise and effective treatment matching. Third, the *efficacy of targeted psychological interventions* must be established in large, well-designed RCTs specifically for the AS population. These trials should move beyond simply assessing mood changes to include outcomes such as pain catastrophizing, fatigue impact, sleep quality, functional capacity, and treatment adherence. Furthermore, mechanistic studies utilizing advanced neuroimaging techniques could elucidate how psychological interventions modulate brain networks involved in pain processing and emotional regulation in patients with AS.

In conclusion, achieving truly patient-centered care for individuals with Ankylosing Spondylitis requires a fundamental reconceptualization of the disease. By acknowledging and actively addressing the profound interplay between inflammation, psychology, and social well-being, clinicians and researchers can move beyond merely treating a diseased spine to empowering the whole person living with AS. The ultimate goal is to transform the clinical approach from one of passive symptom management to one of active enablement, fostering not just physical health but also mental resilience and a restored sense of quality of life.

Conflicts of Interest: The authors declare no conflicts of interest.

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