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Mental Health Comorbidity in MS: Depression, Anxiety, and Bipolar Disorder

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Abstract Among individuals with multiple sclerosis (MS), mental health comorbidities play a significant role in contributing to secondary disability and detracting from quality of life. This review examines current evidence surrounding three mental health issues of particular relevance to MS: depression, anxiety, and bipolar disorder. We review what is known of the prevalence, correlates, screening mechanisms, and current treatment of each issue and provide recommendations for future areas of research.

Keywords Multiple sclerosis · Depression · Anxiety · Bipolar disorder

Introduction

Multiple sclerosis (MS) is a demyelinating and axonal disorder of the central nervous system that can result in an array of physical health challenges including impairments in sensation, motor function, and cognition. Clinicians and researchers alike have increasingly appreciated the impact of mental health conditions, including depression, anxiety, and bipolar disorder, which may also contribute to disease burden and detract from quality of life. Unfortunately, in many instances, these important disorders and symptoms go unrecognized and/or are undertreated.

The following review examines evidence on the prevalence and correlates, as well as screening and treatment, of these three disorders, with an emphasis on recent developments. There are considerable differences in the degree to which each condition has been the subject of scientific investigation. The literature on depression in MS is the most extensive and has matured to the point of offering initial guidance on assessment and management. Anxiety in MS has only recently emerged in the literature, but we offer insight into its risk factors, consequences, and future directions for treatment. The literature on bipolar disorder remains largely in its infancy, but underscores the frequency of the disorder and the impact on the lives of individuals with MS.

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Depression and MS

Depression: Incidence, Prevalence, and Course

Depressive disorders are highly prevalent among people with MS [1, 2]. Estimates of the specific incidence and prevalence of depressive disorders and symptoms have varied widely in the MS literature, due in part to the considerable heterogeneity of samples, measures, and methods, including how "depression" is defined. In one of the very few population-based studies, the annual prevalence of major depressive disorder (i.e., depressive symptoms consistent with a DSM depressive disorder diagnosis) was 15.7% [3]. In contrast, "depression" or "clinically significant depressive symptoms" (e.g.,

symptom severity levels observed on self-report measures to be highly correlated with depressive disorders) are reported to occur in 40–60% of individuals with MS [2, 4]. Recent meta-analyses and population-based studies suggest that adults living with MS have at least a one in four chance of developing depression over the course of their lifetime [1, 5•].

Given that the bulk of the epidemiologic research on depression has been based on depressive symptom severity rather than confirmed DSM-V depressive disorder diagnoses, additional research is needed to definitively determine the incidence and prevalence of depressive disorders, including dysthymia in MS. It may be that many of the "depression" cases in the literature represent subclinical depressive symptoms and/or dysthymia. Research is also needed to address important questions pertaining to the chronicity and duration of depressive disorders and symptoms, as well as the risk for future depressive episodes after remission of a depressive episode. Future estimates of depression prevalence should clearly operationalize caseness (i.e., how depression is defined). Use of standardized depression nomenclature and measures would further enhance cross-sample comparisons.

Depression: Relationship to MS Disease Characteristics and Symptoms

Inflammation in the periphery and within the central nervous system (CNS), alteration in the neuroendocrine system, as well as decreased neurotrophic factors are characteristics of both MS and depression [2]. Foley and colleagues observed that immunologic inflammatory changes, including lower $CD8^+$ percentages, a higher CD4/CD8 ratio, and increased $CD4^+$ cell counts and percentages, are associated with depressive episodes in MS [6]. Increased activation of the hypothalamic-pituitary-adrenal axis (HPA) is also associated with other CNS measures of inflammation, such as higher mean cerebrospinal (CSF) cell counts, higher concentration of CSF myelin basic protein, increased gadolinium enhancing lesions, and are associated with MS and depression [7]. Similarly, peripheral and CNS proinflammatory cytokines, such as tumor necrosis factor alpha (TNF *alpha*), interleukin (IL) 1B, and IL-6, are seen with depression [8, 9]. Low levels of brain-derived neurotrophic factor (BDNF) have been associated with depression in the general population in original studies and meta-analyses [10–12], though this has not always been replicated in MS [13]. In sum, there are complex interactions between the immune system and the neuroendocrine system that are associated with increased inflammation and depression in MS. These studies suggest that alteration of an immunological, inflammatory, or endocrine target, or a combination of targets may provide a promising intervention for depression in MS [2, 14].

In people with MS, depression is associated with gross, microscopic, and radiologic changes in the brain affecting specific structures and global brain volume [2]. Altered regional activity and decreased connectivity [15] within the limbic system [14, 16, 17], the forceps minor [18], the left medial frontal gyrus and right inferior frontal gyrus [18], decreased olfactory bulb volume, reduced right hippocampal volume, and increased lateral and third ventricle size have all been associated with depression in MS [15, 19, 20]. Feinstein and colleagues found that a pattern of lesions on T1 and diffusion tensor imaging was associated with depression and MS [2]. Increased lesion load is also independently associated with depression in MS [14, 21].

MS Disease Characteristics

No definitive picture has emerged regarding the relationship between depression and MS disease characteristics such as duration of illness, disability, and subtype. Studies have found conflicting information or no association between these phenomena and depression [22–25] for a variety of reasons, including the inter-correlation and competing influences of these variables, disease heterogeneity, and the fact that individual responses to the challenges of MS may vary considerably from person to person. However, several factors remain worthy of attention in clinical practice. Some studies suggest depression is more common earlier in the disease process as people come to terms with illness [4]. Interestingly, at the same time, depression has also been associated with the accumulation of greater global disability [4, 26] or impairment in ambulation [27] or self-care [28]. Depressive symptoms may also be elevated during periods of clinical relapse [29].

Cognition

Cognitive dysfunction is estimated to impact 40–60% of MS patients, with deficits typically observed in the domains of attention/concentration, information processing speed, memory, and executive function [30–33]. Given that both depression and cognitive dysfunction are among the most prevalent MS symptoms, it is not surprising that studies often identify a relationship between them [34, 35]. From a pathophysiological perspective, depression and cognitive dysfunction in MS may both arise directly from neurodegeneration. Neuroimaging studies have shown enlargements of the lateral and third ventricles to be associated with both depressive symptom severity and cognitive dysfunction [15, 36].

Compared to patients without depression, depressed individuals with MS have more cognitive dysfunction [37]. This has been shown using both objective neuropsychological assessment measures and self-report measures of perceived cognitive dysfunction [34, 35]. Several studies have demonstrated discrepancies between objective and perceived cognitive dysfunction, with depressive symptoms explaining the highest proportion of the variance in perceived cognitive dysfunction

[34, 35]. The relationship between depression and cognitive dysfunction appears to be stronger when tasks are more cognitively demanding [37, 38], suggesting that task difficulty moderates the impact of depression on cognitive function. Additionally, cognitive dysfunction is more likely to be associated with depression in patients who engage in maladaptive coping strategies in response to stress (e.g., avoidance) as opposed to more adaptive strategies (e.g., active planning) [39], highlighting that interventions focused on enhancing positive coping may reduce the adverse impact of depression on cognitive function.

Fatigue

Fatigue is reported in up to 90% of people with MS and is often identified as patients' most disabling symptom [40]. Comorbidity of depression and fatigue is particularly common, and together, these symptoms have been shown to significantly reduce patients' quality of life and reduce participation in daily activities [41–44]. Etiology of depression and fatigue in MS is believed to include a number of neurologic and behavioral factors. For example, recent neuroimaging studies have demonstrated that damage to lateral and medial tracts of the frontal lobes (e.g., forceps minor) and bilateral frontal lobe atrophy may be important factors contributing to both depression and fatigue in MS [18, 45]. Research has also identified production of cytokines by $CD8^+$ T cells as a mechanism underlying depression and fatigue symptoms.

Depression: Suicidal Ideation and Suicide

Individuals with MS are at elevated risk for both suicidal ideation and suicide. Roughly one quarter will endorse some form of suicidal ideation currently [46] or in the past 6 months [47]. Most epidemiologic studies have estimated the increased risk of eventual suicide to be between 1.6 and 2.3 times that of general population samples [48–52]. Not surprisingly, the most consistent predictor of suicidal ideation and completion is depression and other mental health difficulties including anxiety [46, 53–55]. Other risk factors for suicide include being younger and male [48, 49, 51, 55]. Individuals appear to be at greater risk in the first several years after diagnosis, after which risk subsides; however, it increases again over time with cumulative disability [48, 55]. Several studies have suggested that a high proportion of individuals with MS who present with suicidal ideation go untreated or undertreated [53]. As a result, specific screening for suicidality, as part of screening for depression, is recommended [46].

Depression and MS Disease-Modifying Therapies

There are mixed conclusions regarding the relationship between depression and disease-modifying therapies. Early studies on the interferon medications suggested a link with depression and suicide [56, 57], though most subsequent studies have failed to find this relationship [58–60]. No data specifically support a consistent association between worsening depression and other MS disease-modifying therapies.

Depression: Psychosocial Impact and Quality of Life

Quality of Life

Quality of life (QOL) is a multifactorial health-related outcome that is typically defined as an individual's satisfaction with his/her status in life, including aspects of physical and mental health functioning, happiness, and comfort [61]. A number of studies have identified depression as an important, and in some cases, the strongest, predictor of QOL in people with MS [41, 43, 62, 63]. In combination with fatigue, depression has been shown to independently predict QOL in MS, even after accounting for physical disability [64, 65]. Moreover, while physical disability is related to QOL, depression has been shown to significantly mediate this relationship [66]. In addition to depression predicting QOL in MS, a bidirectional relationship between these factors has also been proposed. A three-year longitudinal study demonstrated that poorer health-related QOL significantly predicted progression of depressive symptom severity [67].

Social Support

Personal relationships and social support may provider a buffer against depressive symptoms. In persons with MS, greater perceived social support, specifically positive social interactions, affective support, emotional support, and informational support, were associated with fewer depression symptoms [68, 69]. Conversely, depression symptoms may impact the use of available social relationships. During treatment for depression, one study found that perceived social support, and utilization of available supports, increased as depression symptoms were ameliorated [70].

Self-Care

In general, depression and self-care share an inverse relationship. Depressed individuals with MS are less likely to engage in positive activities such as exercise or adhering to medical recommendations, and are more likely to engage in negative behaviors such as alcohol and substance abuse [71–74]. There is an increase in non-adherence to disease-modifying medication among depressed individuals with MS [73, 74]. Depression has also been associated with patients deciding to withdraw from MS disease-modifying treatment [75].

Screening for Depression

Given the well-established negative impact of MS on mental health and quality of life, systematic screening and assessment of depressive symptomatology is recommended for all patients with MS [73, 76, 77]. However, due to the significant overlap of MS symptoms and the neurovegetative symptoms associated with depression (e.g., fatigue, difficulty concentrating, sleep disturbance), assessment of depression can be challenging. Recommendations for MS-specific cutoffs for screening of depression in MS have been developed for the BDI-Fast Screen and the Chicago Multiscale Depression Inventory [78]. Finally, use of the PHQ-2, which limits assessment to depressed mood and anhedonia symptoms, has been shown to be a useful screening tool for depression in MS [79, 80] due to its brevity, psychometric properties, and relative lack of confounding with MS symptoms (see Table 1).

Table 1 Screening to identify potential depression in MS

Instrument	Cut off value
Beck Depression Inventory (BDI-II) [78]	14
BDI Fast Screen (BDI-FS) [78]	4
Chicago Multiscale Depression Inventory (CMDI-Mood Scale) [78]	23
Patient Health Questionnaire Depression Module (PHQ-2) [79]	3

Treatment of Depression

Medication for Depression

There is limited evidence available regarding the use of pharmacologic interventions for depression in MS. A study of desipramine found that individuals receiving combined desipramine and psychotherapy had a greater reduction in depression than individuals receiving combined placebo and psychotherapy, although there was a high occurrence of anticholinergic side effects [81]. A study comparing psychotherapy modalities reported that sertraline was superior to supportive-expressive group therapy and comparable to individual cognitive behavioral therapy [82]. Finally, a study examining the efficacy of paroxetine relative to placebo for major depressive disorder (including dysthymia) had a null outcome, but among study completers, a greater proportion of individuals in the active treatment group (78.6 vs. 42.1%) were treatment responders (>50% reduction in symptoms) [83]. In all three studies, findings were limited by small sample sizes and potential bias from attrition. Very preliminary evidence suggests poorer pharmacotherapy outcomes for individuals with executive dysfunction, but this finding merits further investigation [84].

Psychotherapy for Depression

Increasing evidence supports the use of psychotherapies to treat depression and depressive symptoms in MS. The most frequently studied and best supported therapy modality is individually delivered cognitive behavioral therapy (CBT). In a seminal comparative outcomes study, in-person individual CBT was shown to be superior to a modality of therapy emphasizing emotional expression and comparable to sertraline [82]. Other individual treatments emphasizing cognitive and behavioral skill building have also demonstrated improvements in depression and emotional distress [85, 86].

Psychotherapy for depression has also been effectively delivered in group format, with evidence supporting traditional cognitive behavioral therapy including behavioral activation (increasing personally rewarding activities) and identifying and challenging maladaptive thought patterns [87]; a six-session educational group focused on problem solving and goal setting, identifying and dealing with mood states, and managing relationships and the future [88]; and a five-session program including topics related to identity formation, identification and implementation of life goals, and managing negative emotions [89]. All three programs featured topics focusing on the experience of living with MS, but were also grounded in cognitive and behavioral skill building. The emphasis on developing a repertoire of skills appears to be particularly important as groups providing primarily peer support may have limited efficacy for improving depression [90].

Emerging Therapies: Telephone and Telehealth Interventions

Most recently, emerging evidence has supported the efficacy of telephone- and internet-based interventions. CBT delivered partially or completely via telephone has been shown to be effective in three randomized controlled trials [86, 91, 92]. Similarly, more broadly defined telephone-based self-management programs focusing on building skills and self-efficacy to address a range of MS-related symptoms have also demonstrated improvements in depression. For example, Ehde and colleagues examined an 8-week telephone-delivered program for fatigue, pain, and depressive symptoms [93]. Weekly sessions highlighted common principles of self-management (e.g., goal setting, problem solving) and CBT (e.g., challenging thoughts, managing emotions). Individuals in the treatment condition experienced significant decreases in depression. Session attendance was high. In a similar trial reflecting a hybrid of telephone and internet-based delivery, Moss-Morris and colleagues examined an eight-session online treatment for fatigue [94]. Intervention included eight modules reviewing topics such as rest and activity, sleep, examining thoughts and managing stress, as well as three telephone

support sessions. Individuals in the intervention experienced improvements in depression relative to controls. Fischer and colleagues examined a fully automated online program consisting of ten sequential 60-min modules highlighting specific CBT skills (e.g., behavioral activation, cognitive modification, problem solving) [95]. Individuals randomized to the program experienced improvement in depressive symptoms relative to controls at post treatment, although they varied considerably in their engagement with the internet content (range = 50 to 905 total minutes). Overall, telehealth interventions offer very significant benefits including flexibility and portability. They can overcome barriers of distance and geography and improve both access to, and ongoing participation in, treatment. These pros should be weighed against difficulties ensuring an adequate "dose" of treatment, particularly in web-based intervention, and the evidence from the broader literature that treatment gains may be better sustained over time in face-to-face treatment [96].

Physical Activity for Depression

A variety of physical activity interventions have been found to improve depression in MS. Structured programs involving supervised, in-person activities including resistance training [97] and cycling [98] have had beneficial effects on mood. More recently, telephone counseling and web-based education and monitoring have been used to support individuals in the establishment and maintenance of self-selected physical activity goals, which in turn have produced significant improvements in depression [99–101]. Physical activity counseling brings similar trade-offs to psychotherapy. In-person, structured programs provide better opportunities to control exposure to an adequate "dose" of exercise, but telehealth-based programs provide much greater access to care, an issue of considerable importance to individuals with MS who may experience an increase in physical disability over time.

Future Directions

Overall, evidence guiding treatment for depression in MS is in an early stage of development. Many newer psychotherapies such as Behavioral Activation, Acceptance and Commitment Therapy and Mindfulness Based Cognitive Therapy, as well as most newer antidepressant medications remain untested in rigorous trials. There is no specific evidence examining combination therapies (e.g., psychotherapy and psychopharmacology) for either treatment response or maintenance. Moderators of treatment outcome (what works for whom and under what circumstances) remain largely unknown and are also important targets of future investigation. Given that depression remains undertreated, future efforts also need to address the implementation gap between available evidence-based treatments and their use in clinical practice.

Anxiety and MS

Anxiety: Incidence, Prevalence, and Course

Anxiety symptoms and disorders are highly prevalent among individuals with MS, although the quantity of literature focused on anxiety pales in comparison to depressive disorders. The most rigorous study on anxiety disorders in MS suggests that the lifetime prevalence of any anxiety disorder was 35.7% [102]. The most commonly identified disorders were generalized anxiety disorder (18.6%), panic disorder (10%), and obsessive compulsive disorder (8.6%).

As summarized in the following subsections, there is a variety of research on the association of anxiety symptoms with MS, MS symptoms, comorbidities, and quality of life, although the literature is complicated by the varying definitions of anxiety, ranging from specific anxiety disorders to more general anxiety symptoms.

Anxiety: Relationship to MS Disease Characteristics and Symptoms

Relationship Between Anxiety and MS Disease Course, Duration, and Disease Characteristics

A handful of studies have explored associations of anxiety with MS, noting that higher levels of anxiety symptoms may be associated with longer disease duration [103] (although others disagree) [104]; may be more common among individuals with secondary progressive MS [105, 106] and/or women with relapsing-remitting MS [24]; and may worsen with exacerbations and pseudoexacerbations [107, 108].

Relationship with Patient Demographics and Symptoms

Anxiety is more prevalent among women [24, 102, 109] and individuals of younger age [110, 111]. It often co-occurs with other mental health conditions, particularly depression [44, 105, 112, 113], and the two conditions may be predictive of each other [114]. Anxiety co-occurs with a variety of symptoms often attributed directly to MS, including wobbliness and unsteadiness [115], fatigue [44, 116], pain [117], and both objective and subjective cognitive dysfunction [118–121]. The relationship between anxiety and MS-related disability is unclear, such that some believe worse anxiety is associated with greater MS-related disability, while others disagree. Finally, anxiety may be associated with maladaptive health behaviors, such that it is associated with a higher likelihood of being a smoker [122] and, in the case of specific anxieties (e.g., injection phobia), may impact medication adherence [123, 124].

Anxiety: Psychosocial Impact and Quality of Life

Anxiety is often found to be negatively associated with quality of life [125]. For example, both health anxiety [126] and social anxiety [127] are associated with poorer quality of life, regardless of level of disability. Furthermore, anxiety may strengthen the relationship of disability with quality of life [66]. Beyond objective functioning, anxiety is also associated with outlook on future wheelchair dependence, with individuals with higher levels of anxiety more likely to predict future wheelchair dependence [128]. Functionally, anxiety is associated with decreased productivity at work [129].

Screening for Anxiety

There is a limited body of literature establishing the validity and reliability of anxiety screening measures for use with people with MS. Two measures have a modest level of support: The Hospital Anxiety and Depression Scale (HADS) [105], an oft-used measure of common anxiety and depression symptoms, and the Generalized Anxiety Disorder-7 (GAD-7) [105], a brief assessment of anxiety symptoms consistent with the diagnosis of Generalized Anxiety Disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [130].

Treatment for Anxiety Disorders

Unfortunately, there is a distinct absence of anxiety-focused treatment literature in MS. For example, in a systematic review of depression and anxiety treatments for individuals with MS, only a single anxiety intervention study was included, with the intervention focused on injection phobia [131•, 132]. A number of recent intervention studies have noted direct or indirect effects on anxiety through the use of mindfulness-based stress reduction [133], biofeedback [134], an Internet-delivered behavioral intervention [101], and relaxation training [135]. There is a need for increased research in this area, including using traditional psychotherapies (e.g., cognitive behavioral therapy), as well as newer therapies (e.g., acceptance and commitment therapy), that have been successful in the treatment of anxiety in other settings.

Bipolar Disorder and MS

Bipolar Disorder: Incidence, Prevalence, and Course

Bipolar disorder (BPD) is a serious chronic mood disorder characterized by recurrent episodes of depression, mania, hypomania, or mixed states. The disorder is associated with reduced quality of life, greater medical utilization, loss of employment, and increased risk of suicide. Prevalence rates in the general population for bipolar I range from 1 to 2%. If the definition includes other forms of the disorder, such as bipolar II, prevalence may be as high as 4% [136].

Incidence and Prevalence in Multiple Sclerosis

The prevalence and incidence of bipolar disorder has been evaluated in multiple sclerosis as a whole, at the time of diagnosis, and across time. Overall estimates of prevalence range from 0 to 16% [5•]. Most recent studies suggest that BPD is roughly twice as common in MS, both at the time of diagnosis (3.15% in MS, as compared to 1.69% in matched controls) [137] and in the MS population more broadly (4.7% in MS vs. 2.3% in matched controls) [5•]. One population-based study found bipolar disorders in 5.83% of persons with MS [1]. These studies have generally found that bipolar disorders are more common in women with MS [5•, 137].

Bipolar Disorder: Psychosocial Impact and Quality of Life

Not surprisingly, BPD impacts quality of life (QOL). A recent study of individuals with MS examined QOL in those with BPD, depression, or no mood disorder. Both depression and BPD were associated with worse QOL, and BPD had the greatest impact [138].

In the general population, suicidal ideation and suicide attempt are more common in persons with BPD than most other psychiatric or medical conditions. Up to 50% of patients with BPD in the general population reported at least one suicide attempt, with approximately 35% resulting in hospitalization [136]. Approximately one fifth of patients with BPD die from completed suicide [136]. Although there is little specific data on the relationship between BPD and suicide in MS, the elevated risk of suicide in both populations raise special concern for individuals who may be burdened with both illnesses [138].

Bipolar Disorder: Relationship to MS Disease Characteristics and Symptoms

The pathogenesis of increased risk of BPD in MS is still under investigation. The analysis of a nationwide Swedish cohort sought to examine factors such as genetic or familial liability, psychological trauma, and biological mechanisms [139]. There was no increased risk of MS in siblings with BPD, or BPD in siblings with MS, thus they concluded that the increased prevalence of BPD in MS was likely not due to familial factors. Temporal analysis of MS and BPD also argued against the development of BPD due to emotional distress from being diagnosed or living with a chronic medical condition, suggesting risk was likely due to a biological, possibly inflammatory, mechanism.

Screening for Bipolar Disorder

Information on the utility of screening tools for identifying BPD in MS is limited. The Mood Disorder Questionnaire [140] represents one option of a standardized measure that can be incorporated into clinical practice for the assessment of individuals for whom there is some initial suspicion of BPD. The measure consists of 13 yes/no items screening for a lifetime history of manic and hypomanic symptoms and has been utilized successfully in individuals with MS [138]. This instrument has displayed a high false positive rate in some community samples, and a follow-up clinical interview and/or mental health referral is warranted [141].

Treatment for Bipolar Disorder

Treatment of BPD has not been explicitly examined in MS; however, case studies provide preliminary information for future investigation. Consistent with the inflammatory theory above, one case study examined a patient with three new T2 gadolinium-enhancing lesions on MRI admitted for manic episode with psychotic features [142]. She was successfully treated with intravenous methylprednisolone and risperidone. As always, the risk of precipitating mania with steroids should be considered.

Conclusion

Depressive disorders and symptoms are extremely common among individuals with MS. They contribute to overall disease burden and detract from quality of life. Although MS providers often experience significant and competing demands for their time during a clinical encounter, routine screening for depression, including suicidality, should be part of ongoing management of this chronic illness. A minimal knowledge base neither refutes nor supports the use of pharmacotherapy as treatment of depression specifically in MS. Emerging evidence supports the use of individual psychotherapy, particularly CBT, as a first line treatment. In particular, telephone-administered CBT currently provides the best evidence of efficacy to date [143]. This treatment modality is particularly relevant as it has the potential to provide improved access to services for individuals who may experience barriers to care related to distance and disability [144]. Programs that focus on self-management and goal setting, whether focused on symptom management or on a health behavior, such as exercise, represent promising new areas of investigation.

Anxiety disorders and symptoms occur at a lesser frequency than depression in MS, but similarly add to disease burden and detract from quality of life. They have received comparatively lesser attention, particularly with respect to treatment, and merit further investigation. Similarly, though relatively rare, providers should be cognizant of the increased risk of bipolar disorder in MS and the potential need for additional psychiatric assessment and follow-up.

Compliance with Ethical Standards

Conflict of Interest Aaron P. Turner, Kevin N. Alschuler, Abbey J. Hughes, Meghan Beier, Jodie K. Haselkorn, Alicia P. Sloan, and Dawn M. Ehde declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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