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Optimizing the Effects of Stress Management Interventions in HIV

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Abstract

Scott-Sheldon, Kalichman, Carey, and Fiedler (2008) present a thoughtful, important, and timely meta-analysis of randomized controlled trials of stress management interventions in HIV. They differentiate controlled effect sizes across classes of acute outcomes including psychological distress, psychosocial processes, biological processes (immune status, viral, and hormonal) and fatigue. The authors join Scott-Sheldon et al., in considering future directions for this type of clinical psychosocial intervention research in HIV. Recommendations for addressing the high prevalence of psychosocial problems including diagnosable mental health disorders comorbid with HIV are presented. Suggestions for addressing medication adherence and accommodating interventions with concomitant substance use treatment are also considered. These recommendations are presented with an emphasis on expanding both the efficacy and effectiveness of psychosocial interventions in HIV. These recommendations are presented as realistic strategies for improving the modest treatment effect sizes for psychosocial outcomes and identifying meaningful effects on distal physiological outcomes associated with traditional stress management interventions in HIV.

Keywords

stress management interventions; HIV; immunity; psychopathology; psychoneuroimmunology

There is a large and growing body of literature identifying the deleterious health and immune consequences of disease-related and other stressors in people living with HIV (see Leserman, 2003, for a review). It is likely that stress contributes to poor disease outcomes by interfering with the adaptive management of HIV and through chronic activation of the hypothalamic-pituitary-adrenal and the sympathetic-adrenal-medullary systems with associated down-regulation of the immune system. Stress may compromise adaptive management of HIV through its association with increased rates of psychological distress and impaired execution of health behaviors. In light of the results of the meta-analysis presented by Scott-Sheldon, Kalichman, Carey, and Fiedler (2008), we consider these pathways with respect to future developments of stress management interventions in HIV that may assist with demonstrations of efficacy and effectiveness.

Stress Management and Psychopathology

Specifically, stress has been associated with higher levels of symptoms of depression (e.g., Catz, Gore-Felton, & McClure, 2002; Siegel, Schrimshaw, & Pretter, 2005; Sikkema, Kochman, DiFranceisco, Kelly, & Hoffman, 2003), high rates of clinical depression (e.g.,

Bing et al., 2001), high rates of posttraumatic stress disorder (see O'Cleirigh, Hart, & James, 2007, for a review) and severity of posttraumatic stress disorder (e.g., Kimerling et al., 1999) in people with HIV. This suggests the need to expand traditional stress management interventions in HIV to address psychopathological levels of distress. This is particularly indicated, as chronic depression (e.g., Ickovics et al., 2001) and lifetime trauma (e.g., Leserman et al., 2007) have both been related to worse survival in patients living with HIV. The modest effects of stress management interventions on symptoms of depression and anxiety identified by Scott-Sheldon et al., (2008) may also underscore the need to augment traditional stress management interventions in HIV so that they have sufficient potency to address comorbid psychopathology.

Generally, stress management interventions in patients living with HIV are not designed to treat clinically diagnostic levels of mood or anxiety disorders and several studies ruled out participants with psychiatric disorders. Although people living with HIV often have trauma histories and multiple stressful life events (e.g., Ironson, O'Cleirigh, Fletcher, et al., 2005; Leserman et al., 2005) and may derive particular benefit from stress management interventions, restrictive exclusion criteria may select participants with lower levels of stress/distress at study entry. This may contribute to floor effects and may restrict the ability of randomized controlled trials of cognitive-behavioral stress management to achieve larger effect sizes. In fact, moderation analysis conducted by Scott-Sheldon et al., (2008) identified larger treatment effects for anxiety among those who were more anxious at baseline, suggesting greater treatment effects are associated with higher levels of baseline distress.

On a related point, results of the meta-analysis found nonsignificant treatment effects for coping and social support outcomes (Scott-Sheldon et al., 2008). Clinically significant behavioral withdrawal and anxious avoidance are core features of diagnosable mood and anxiety disorders. The presence of untreated or undertreated diagnostic levels of depression or anxiety disorders in participants with HIV may compromise the full efficacy of stress management interventions. Although stress management interventions can produce modest reductions in depressive or anxious symptoms, they are not designed to remediate major depressive disorder or treat specific anxiety disorders. This enduring depression-related withdrawal or anxiety-related avoidance may render stress management interventions targeting coping or social support ineffective, notwithstanding modest effects on depressed and anxious mood. Expanding traditional stress management interventions that would allow for triage of patients into interventions that target clinically significant anxiety/avoidance or withdrawal/isolation because of a diagnosable psychiatric disorder may well result in significant intervention-related increases in adaptive coping or social support utilization.

Stress Management and Health Behaviors

Adherence—Adherence to antiretroviral medications is critical for the effective management of HIV (e.g., Hammer, Saag, & Schecter, 2006; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2006, 2008) and poorer adherence has been repeatedly associated with more rapid HIV disease progression (e.g., Bangsberg et al., 2000; Castillo et al., 2004; Catz, Kelly, Bogart, Benotsch, & McAuliffe, 2000; Kitahata et al., 2004). The relationship between stress and suboptimal medication adherence in HIV is also demonstrated (e.g., Chesney et al., 2000; Mugavero et al., 2006; O'Cleirigh, Ironson, & Smits, 2007; Vanable, Carey, Blair, & Littlewood, 2006). These findings provide a strong rationale for the incorporation of adherence-training components in stress management interventions in HIV. Of the 47 interventions reviewed by Scott-Sheldon et al., (2008), only 6 included intervention components to address medication adherence. However, 4 of those were reported within the past 5 years, suggesting that adherence-training components may be more common among more recent interventions. Some of our earlier work developed

brief evidence-based adherence interventions for HIV (e.g., Safren, Hendriksen, Mayer, Pickard, & Otto, 2003; Safren, Otto, Worth, et al., 2001) that could be accommodated into stress management interventions, and we are currently working on an ongoing program of research to integrate the treatment of depression with adherence counseling in HIV (Safren, Hendriksen, Mayer, Pickard, & Otto, 2003; Safren, O'Cleirigh, Tan, et al., in press) that may be associated with clinically meaningful reductions in viral load.

Substance use—Substance use is a significant health risk behavior and higher levels of stress have been associated with increased substance use in people living with HIV (Ibanez, Purcell, Stall, Parsons, & Gomez, 2005; Pence, Miller, Whetten, Eron, & Gaynes, 2006). Specifically targeting substance abuse disorders may be beyond the scope of stress management interventions, and substance dependence is a common exclusion criterion in stress management efficacy testing in HIV. However, there are developing models of cognitive-behavioral interventions that can accommodate participants with substance use disorders. One strategy currently being explored in our ongoing work includes providing cognitive-behavioral treatment for depression and adherence in the context of substance abuse treatment programs (Soroudi et al., in press). Another idea is to proactively provide case management as a part of stress management interventions in HIV to actively link participants to needed substance abuse and/or mental health treatment (see also O'Cleirigh & Safren, 2007).

Design and Assessment Issues in Establishing the Efficacy of Stress Management in HIV

The aforementioned outlined recommendations (to incorporate intervention components addressing comorbid mental health and health behavior issues into traditional stress management treatments) are consistent with the recommendations suggested by Scott-Sheldon et al., (2008) and would likely have a favorable effect on stress management effectiveness by accommodating real-world comorbidities and generating interventions with broader applicability. These suggestions are also in line with the recommendations of Carroll and Rounsaville (2003), who suggested a hybrid model of intervention testing that incorporates design elements that support both efficacy and effectiveness. This hybrid approach may be particularly suited to the complex issues that face many people living with HIV.

In addition to adapting behavioral science intervention technology and the parameters around its delivery, deliberate use of appropriate study design can help to establish the efficacy of stress management interventions. The results of the meta-analysis presented by Scott-Sheldon et al., (2008) raise some issues concerning assessment and analysis that may affect the ability to demonstrate the efficacy of stress management interventions. First, the authors report that the treatment effects for anxiety were heterogeneous and that this heterogeneity may be accounted for by the incorporation of adherence training components. The detailed presentation by the authors of the weighted effect sizes associated with the differing anxiety outcomes suggests the hypothesis that interventions that assess current anxious affect (e.g., Profile of Mood States) are less likely to favor the intervention than interventions that assess more enduring physical, cognitive and affective symptoms of anxiety (e.g., Hamilton Anxiety Measure; State-Trait Anxiety Inventory; Mental Health Inventory; Medical Outcomes Study 36-Item Short Form Health Survey). This use of differing anxiety outcome measures used across the reviewed studies may provide a competing explanation for the heterogeneous effects. Differing methods of anxiety assessment may account for inconsistent relationships in outcomes important in HIV (O'Cleirigh, Hart, & James, 2007). Standardizing outcome assessment and relating measured outcomes to the theoretical assumptions supporting the intervention (e.g., treatment impact on current effect vs. effect on broader symptoms) may allow for a

demonstration of stronger outcomes. When possible, the use of diagnostic measures of specific anxiety disorders may provide a useful standard, particularly when examining the effect of anxiety reduction on medication adherence. The relationship between anxiety and adherence in HIV is complex and may be best informed by an assessment of the presence or absence of particular anxiety disorders.

Second, Scott-Sheldon et al., (2008) suggested that incorporating follow-up assessment over time may be important to demonstrate the significant effects of stress management interventions on important biological outcomes. This is particularly relevant for stress management effects that are hypothesized to be mediated by intervention-related changes in distress or endocrine function and will be most appropriately assessed at sufficiently distal follow-up to allow time for these mediated effects to emerge. For example, significant mediated stress management treatment effects relating to immune reconstitution and changes in HIV viral load have been identified at 6 to 15 months of follow-up (e.g., Antoni, Carrico, Duran, et al, 2006; Antoni, Cruess, Klimas, et al, 2002). Whereas stress management intervention effects on neuroendocrine and antibody liter outcomes, for example, may well be more appropriately evaluated posttreatment (e.g., Cruess, Antoni, Cruess, et al., 2000; Lutgendorf, Antoni, Ironson, et al., 1997). The ability to demonstrate immune and health benefits of stress management interventions in HIV will likely increase estimates of the cost-effectiveness of these interventions. Accordingly, we recommend the inclusion of biological and health outcomes, with sufficiently distal follow-up assessments to realistically assess their effects. This recommendation will likely benefit the assessment of both intervention efficacy and effectiveness. The incorporation of follow-up assessments to support efficacy testing could also provide the opportunity to include distal booster or intervention sessions of targeted treatment components. This treatment delivery strategy could enhance the effectiveness of stress management interventions by supporting relapse prevention and maintenance of treatment effects.

Third, Scott-Sheldon et al., (2008) suggest that difficulty accounting for the complex effects of antiretroviral medications on biological outcomes, particularly on CD4 cells and HIV viral load, may interfere with the assessment of intervention effects on these outcomes. Several recent studies (Ironson, Balbin, Stuetzler, et al., 2005; Ironson, O'Cleirigh, Fletcher, et al., 2005; Ironson, O'Cleirigh, Weiss, Schneiderman, & Costa, 2008) have demonstrated the ability to model reliable changes in both CD4 and viral load over time, accounting for the differential effects of antiretroviral medications (ART) using mixed-level modeling. This technique allows for a consideration of antiretroviral medication as a time-dependent covariate (accommodating changes in ART over time) and allows for an estimation of the effects of ART on CD4 and viral load at each assessment time point. The same modeling procedures can also be used to account for the effects of adherence to ART on HIV biological markers (Ironson, O'Cleirigh, Fletcher, et al., 2005). Perhaps most encouragingly mixed level modeling has been used to separate the effects of adherence to ART from the effects of stress management intervention decreases in depressed mood with reductions in HIV viral load, controlling for adherence. (Antoni, Carrico, Durán, et al., 2006).

Finally, Scott-Sheldon et al., (2008) consider that, in the presence of advanced disease, severely compromised immunity may overwhelm the potential effects of stress management interventions on biological outcomes. They suggest that this may account for the absence of significant treatment effects on immune and hormonal outcomes assessed immediately postintervention. In the case of HIV-infected patients managing the onset of Category C (AIDS-defining) symptoms or those coping with the challenges of salvage therapy in the face of severely depleted CD4+ cell counts and uncontrolled viremia, the ability of stress management interventions to affect underlying biology may well be limited. However there is an encouraging body of research identifying the ability of stress management

interventions to positively affect immune and neuroendocrine outcomes in patients with symptomatic disease. Among people managing symptomatic HIV disease, stress management interventions have been associated with better immune system reconstitution, improved control over latent herpes viruses, and increase in CD4 cell counts (Antoni, Cruess, Klimas, et al., 2002; Cruess, Antoni, Cruess, et al., 2000; Lutgendorf et al., 1997; Petrie, Fontanilla, Thomas, Booth, and Pennebaker, 2004) and favorable changes in HIV viral load for those with detectable viral load at study entry (Antoni, Carrico, et al., 2006). In addition, beneficial stress management intervention-related changes in hormonal outcomes have been reported for patients with advanced HIV infection for cortisol and DHEA-S/cortisol ratios (Antoni, Cruess, Klimas, et al., 2005; Antoni, Wagner, Cruess, et al., 2000), testosterone (Cruess, Antoni, Schneiderman, et al., 2000), and norepinephrine (Antoni, Cruess, Cruess et al., 2000). The results of these studies suggest some optimism for the ability of stress management intervention to affect underlying pathophysiological processes in patients with advanced HIV infection. Furthermore, it is likely that those with advanced disease are also managing higher levels of HIV-related stress (e.g., medication adherence, symptom onset, job loss) and may be well placed to derive particular psychosocial benefit from stress management interventions. Establishing the efficacy of these procedures across patients at all stages of HIV infection progression will strengthen the demonstration of program effectiveness, and demonstrating intervention effects across a variety psychosocial and biological outcomes will support the cost-effectiveness of stress management interventions.

Summary and Conclusions

The meta-analysis of stress management intervention effects in people living with HIV (Scott-Sheldon et al., 2008) provides encouraging evidence that supports the efficacy of these interventions in reducing symptoms of anxiety, depression, and distress. However, the nonsignificant effects, assessed immediately posttreatment for social support and coping are sobering. We support the recommendations of Scott-Sheldon et al., (2008) to expand traditional stress management interventions to address diagnostic levels of depressive and anxiety disorders. Specifically, we recommend the adaptation of stress management procedures to address clinical levels of depression and posttraumatic stress disorder. The high prevalence of these disorders in people with HIV and their association with increased substance use and poorer adherence identifies them as priority targets for treatment. The treatment of substance use may be beyond the scope of stress management interventions. However, the delivery of these interventions in the context of substance use treatment facilities, or the use of case management referral and other procedures to enhance usual standard of care, may expand the traditional reach of stress management programs.

ART adherence is critical for effective management of HIV. Comorbid mood, anxiety, and substance use disorders interfere substantially with adherence. More interventions are needed that fully integrate adherence training into stress management procedures. To support a full examination of the intervention effects on underlying pathophysiological processes, we also recommend the incorporation of sufficiently distal follow-up assessment based on a hypothesized mechanism of action and realistic time frame for the effects to occur. Follow-up assessments may also provide a useful mechanism to incorporate additional treatment sessions to support relapse prevention and maintenance of treatment effects.

Generally, we believe that the next generation of interventions targeting health behavior change in HIV in general, and stress management interventions in particular, should address clinical levels of mental health comorbidities. This may allow for a demonstration of even greater efficacy on distress and distress-mediated endocrine and immune outcomes. Treating

psychopathological levels of distress may also support the maintenance of treatment effects. The development of these interventions will help greatly in ensuring that behavioral science intervention technology can meet the complex needs of people living with HIV.

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