Review

A Review of Treatment Studies of Depression in HIV

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Depression is a prevalent and interfering, yet potentially treatable illness commonly comorbid with HIV/AIDS. In HIV, symptoms and diagnoses of depression have been associated with poor adherence to antiretroviral medication regimens and to accelerated disease progression. This article is a review of the existing literature on the treatment of depression in the context of HIV, including: (1) psychosocial and behavioral health interventions that directly target Diagnostic and Statistical Manual of Mental Disorders *(DSM) unipolar depressive disorders, (2) psychosocial interventions that indirectly target depressive symptoms, and (3) psychopharmacologic treatment studies for DSM-IV unipolar depressive disorders. Psychosocial and psychopharmacologic treatments of depression appear to be effective for individuals with HIV. However, additional methodologically rigorous trials are needed for definitive inferences regarding treatment efficacy. Because of the high frequency of depression comorbid with HIV, and the association of depression with important self-care behaviors in this population, identification of efficacious treatments for depression has the potential to improve both overall quality of life and, potentially, health outcomes.*

Introduction

Depression is a highly prevalent and interfering illness, with lifetime prevalence between 4.9% and 17.9% and a 1-year point prevalence of 10%.[1,2] Symptoms of depression include persistent sadness, loss of interest, decreased appetite, low concentration, sleep problems, guilt/worthlessness feelings, decreased energy, psychomotor retardation, and suicidal ideation. In addition to significant distress, symptoms of depression can also cause other health-related functional and quality of life impairments.

Depression, for example, is associated with poor adherence to medical regimens.[3] Meta-analytic data also show that depressed patients are 3 times greater than nondepressed patients to be nonadherent to medical treatment recommendations,[4] which is largely consistent with the literature reporting that depression in those with HIV is related to diminished health status and health-related quality of life.[5,6]

Studies on the course of HIV suggest that anywhere from 20 to 37% of infected individuals may also have diagnosable depression,[7,8] rates that appear to be higher than the general population estimates (see also Dew et al, 1997[9]; Rabkin, 1996[10]). In a more recent study of 129 people living with HIV/AIDS, approximately one-third scored 14 or higher (≥ mild to moderate depression) on the Beck Depression Inventory (BDI)[11] and 27% met criteria for a current mood disorder.[12] Williams and colleagues[6] found that depression was widespread (54.2%) in a sample of individuals living with HIV even after controlling for demographic characteristics. Furthermore, a recent meta-analysis of data from 10 studies examining the prevalence of depression among HIV-infected individuals revealed a 2-fold increase in rates of depression compared with HIV-uninfected individuals.[13] The current estimates may represent an underestimation as there is evidence that depression may be under diagnosed in the context of HIV medical care.[14]

Various factors may contribute to heightened depression in HIV-infected individuals including the effects of HIV on the brain, stigma, occupational disability, isolation, body image changes, bereavement, and debilitation.[15] The elevated rates of depression among those living with HIV may also be partially attributable to stressors (ie, constant reminder of illness, daily stress, and interference) that accompany maintaining a strict HIV treatment regimen.

Thus, recognizing and treating depression is important because of its association with poor self-care and worse health outcomes in those with HIV.[16,17] Although earlier studies in HIV failed to find an effect for depression and HIV symptoms,[17,18] a subsequent meta-analysis found that depressive symptoms were directly related to symptoms of HIV infection.[19] Additionally, studies conducted over longer time intervals have found significant relationships between depressive symptoms and HIV disease progression (ie, Burack et al, 1993[20]).

Depression has been shown to be associated with declines in CD4+ cell counts over time.[20,21] Depression also predicts accelerated decline of CD4+

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cell numbers and significant increases in HIV viral load over 2 years when controlling for the effects of antiretroviral medication.[22] Finally, there is evidence from various cohorts that depression predicts worse survival rates in individuals with HIV.[23] These health-related findings offer some insight into studies that have also shown that depressed individuals with HIV use significantly more health care and related services (ie, Williams et al, 2005[6]).

The negative impact of depression on the course of HIV may manifest in maladaptive self-care behaviors. Indeed, depression has been shown to be associated with sexual risk taking,[24,25] substance abuse,[26] and poor treatment adherence.[16,27,28] Importantly, poor adherence is associated with poor medical outcome as measured by viral load or CD4+ cell count.[16,27,29-31] Poor adherence can also result in the development of viral mutations, which can lead to drug resistance.[29,32-37]

Individuals with HIV present with different types of stressors and various medical complications that could potentially account for the high rates of depression. Development and implementation of treatments that specifically target depression have the potential to improve overall quality of life and health outcomes in those with HIV.

For example, relief from depression could potentially increase medication adherence (see Fulk et al, 2004[38], Safren et al, 2004[39]), which would in turn affect illness severity and progression. The impact of depression on the course of HIV has initiated the application of specific psychosocial and pharmacologic treatments targeting individuals with HIV and comorbid depression.

This article reviews studies that have directly and indirectly examined the effects of specific psychosocial and psychopharmacologic interventions for the treatment of depression in HIV. Based on this qualitative review of the literature, recommendations for empirically informed treatment of depression in individuals with HIV are offered.

Psychosocial Interventions For Depression in HIV

A search of the literature was conducted using MEDLINE and PsychINFO by pairing the words, "depression" and "HIV" with various combinations of the following words: "treatment," "intervention," and "psychosocial." We located additional studies by screening the bibliographies of articles retrieved in the search. As outlined in Table 1, the literature search revealed 4 studies with psychosocial interventions that specifically targeted depression and had an indicator of depressed mood as an entry criterion, and 6 studies that did not have depression as an entry criterion, but reported on depression outcomes as part of a structured intervention. These 2 general types of studies are described separately.

Psychosocial Interventions Directly Targeting Depression

Kelly and colleagues[40] randomly assigned 68 men with HIV infection who scored over 23 on the Center for Epidemiologic Studies Depression Scale (CES-D)[41] to 1 of 3 conditions: 8 sessions of cognitive-behavioral group therapy (CBT), 8 sessions of social support group therapy (SSG), or a comparison control condition. The CES-D is a widely used 20-item self-report scale that is used to screen for depression and assess the level of one's depressive symptoms. A score of 16 is indicative of clinically significant depressive symptoms, although it does not constitute a clinical diagnosis of depression.

The CBT group intervention consisted primarily of skills training with regard to cognitive restructuring, progressive muscle relaxation, imaginal and cue-controlled relaxation, safe sex practice, and problem solving. The SSG group intervention was primarily based on teaching coping skills. Standardized assessment of depression was conducted with the CES-D and the depression subscale of the Symptom Checklist-90 (SCL-90-D).[42] Participants that completed the CBT and SSG group intervention showed significantly lower scores on the depression subscale of the SCL-90 than the control comparison group. There was also a trend for participants that completed the SSG to report less depression on the CES-D than the comparison group. Analyses of clinical significance of changes in depression at post-intervention and 3-month follow-up revealed that 59% of the CBT and 71% of the SSG participants were judged improved at post-intervention and 52% of the CBT and 50% of the SSG participants were judged improved at 3-month follow-up. The SSG also tended to reduce frequency of unprotected receptive anal intercourse, but the CBT group resulted in less frequent illicit drug use.

Markowitz and colleagues[43] randomly assigned 32 HIV-seropositive patients scoring at least 15 on the Hamilton Depression Rating Scale (HAM-D)[44], and with a clinical impression of a DSM-III-R mood disorder (major depression, dysthymia, or depression not otherwise specified) to interpersonal psychotherapy or supportive psychotherapy. Interpersonal therapy in this randomized clinical trial helped patients relate changes in mood to their environment and social roles. Supportive psychotherapy was a nonspecific client-centered intervention with an added psychoeducation component.

Last-observation-carried-forward analysis indicated that at midtreatment, interpersonal psychotherapy participants' scores on the HAM-D and the BDI were significantly lower than participants in the supportive psychotherapy condition. These significant differences were also observed at the end of treatment. Completer analysis also revealed differential improvement that favored interpersonal psychotherapy over supportive psychotherapy. Specifically, participants given interpersonal psychotherapy improved by a mean of almost 10 points on the HAM-D and nearly 17 points on the BDI by midtreatment. Participants undergoing supportive psychotherapy improved only 6 points in the HAM-D and 5 points on the BDI at midtreatment. Significant increases were observed in physical functioning for those in the interpersonal psy-

chotherapy condition, but no such improvements were observed for those in the supportive psychotherapy condition.

Another study by Markowitz and colleagues[45] involved randomly assigning 101 HIV-infected individuals scoring 15 or higher on the HAM-D and with a clinical judgment of significant depressive symptoms to interpersonal psychotherapy, CBT, supportive psychotherapy, or supportive psychotherapy with imipramine. Interpersonal psychotherapy included procedures to help patients relate changes in mood to events in their environment, CBT strategies consisted primarily of cognitive restructuring, and supportive psychotherapy consisted primarily of client-centered skills and psychoeducation.

Results revealed that participants in the interpersonal psychotherapy and supportive psychotherapy plus imipramine condition showed significantly greater decreases in depression on the HAM-D and BDI than both the CBT and supportive psychotherapy without imipramine groups. Participants in the interpersonal psychotherapy condition also performed significantly better than those in the supportive psychotherapy condition on the BDI. Among therapy completers, interpersonal psychotherapy was associated with significantly greater decreases in depression than both CBT and supportive psychotherapy. Furthermore, changes in physical functioning were significantly associated with changes in mood across conditions. CD4+ cell count did not change significantly by group or over time.

Lee and colleagues[46] evaluated the efficacy of a combination of a modified CBT group therapy and antidepressant medication for HIV patients diagnosed with major depressive disorder or dysthymia. The treatment consisted of 20 weekly (sample mean, 15 sessions completed), 2-hour sessions, which was done to permit more intensive work on dysfunctional core beliefs and relapse prevention. Outcome measures showed substantial reductions in symptoms of depression as assessed by the HAM-D (mean HAM-D scores declined from 26 at time of intake to 9 posttherapy; an improvement of more than 50% in HAM-D scores for each patient was observed at 6-month follow-up). Similar findings were observed on the BDI. Specifically, posttherapy, participants showed a mean decline of 24 at baseline assessment to 15. Improvement of more than 50% on BDI scores for each patient was also found at 6-month follow-up. Furthermore, significant improvements were also observed in general functioning as assessed by the Global Assessment Scale (scores increased from 57 at baseline assessment to 72 posttherapy, and then to 80 at 6-month follow-up).

Psychosocial Interventions Indirectly Targeting Depression

Treatment outcome studies that did not require depression as an inclusion criterion have also been conducted with patients with HIV. For example, Mulder and colleagues[47] randomized 39 asymptomatic HIV-seropositive patients to either a group CBT, experiential therapy, or a waiting list control condition. The CBT intervention included training in cognitive restructuring, behavior change strategies, assertiveness skills, and stress management (including relaxation training). In the beginning of the CBT program, an individually tailored behavioral activation plan was implemented that included increasing physical exercise or practicing relaxation exercises on a daily basis.

The experiential group psychotherapy intervention focused on enhancing the participants' personal awareness of their inner experiential process including incongruence between emotional, cognitive, and behavioral schemata. Therapists for this condition adopted a nondirective role and content themes emerged that included mastering of crises, importance of a social network, sexuality, bereavement, disease-related anxiety, and finding a purpose in life. CBT and experiential group psychotherapy both produced significant reductions in depression, as assessed by the BDI, compared with the waiting list control condition, although there were no statistically significant differences between the CBT and experiential group psychotherapy condition.

Lutgendorf and colleagues[48] examined the efficacy of a 10-week group cognitive-behavioral stress management (CBSM) intervention on dysphoric mood in 39 HIV-seropositive, symptomatic gay men. Men were randomized to either the CBSM or a modified waiting list control condition. The stress management modules included didactic components explaining physiological effects of stress, stress-immune relationships, cognitive-behavioral theory, identification of cognitive distortions, rational thought replacement, coping and assertiveness skill training, anger management, and identification of social supports. The relaxation component included training in a range of relaxation techniques from which participants were encouraged to select the method that worked best for them.

Depressive symptoms were assessed using the BDI. Pre- and post-intervention blood draws were conducted to obtain measures of herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) antibody titers, and measures of CD4+ (t-lymphocytes) and CD8+ (cytotoxic) cell counts. The intervention was associated with statistically significant decreases in depression. The intervention was also associated with greater immune control of latent HSV-2 virus, although no effect was observed for HSV-1 antibody titers, or CD4+ or CD8+ cell counts. Interestingly, lower levels of dysphoria were associated with lower HSV-2 antibody titers (indicating better immune control).

Antoni and colleagues[49] also evaluated the efficacy of CBSM relative to a waiting list control condition in symptomatic HIV-infected gay men. Results indicate that CBSM was associated with significant reductions in self-reported depressed affect, as assessed by the profile of mood states (POMS; McNair, Lorr, & Droppleman, 1981[50]) depression subscale for subjects in the intervention (n = 40) matched on questionnaire data to subjects in the control condition (n = 19). A subset of these

Table **1**. Psychosocial Treatments for Depressive Disorders and Symptoms in Patients with HIV

Reference and Study Design	Depression Entry Criteria	HIV Disease Stage	Enrolled/ Completed	Treatment Modality/ Duration/Type	Depression Measures	Significant Results and Health/Immune Outcomes
Kelly et al 1993[40] Randomized group CBT/SP, comparative trial	CES-D >16	HIV+ M= 24.1 months	77/44 experimental 38/27 control (men)	CBT, SP (8 sessions/group)	CES-D SCL-90-R	Results: Completers CES-D Change: CBT+SP = –8.0; Comp = –4.0 (P <.07) SCL-90-R (Dep) Change: CBT + SP = 0.8 (P < .05) Outcome: None
Markowitz et al 1995[43] Randomized IP/SP comparative trial	HAM-D ≥15 Clinical judgment of significant depressive symptoms	HIV+ > 6 months	IP: 19/14 SP: 17/16	IP/16 sessions (50 minutes)/ individual SP/8-16 sessions (30-50 minutes)/ individual	HAM-D BDI	Results: Completers HAM-D Change: IP = 10, SP = 6 BDI Change: IP = 17, SP = 5 Outcome: None
Markowitz et al 1998[45] Randomized IP/CBT/SP/SWI comparative trial	HAM-D ≥15 Clinical judgment of significant depressive symptoms	HIV+ > 6 months	101/69	IP, CBT, SP 8-16 sessions/ individual	HAM-D BDI	Results: Completers IP > CBT and SP CBT = SP IP=SWI Outcome: None
Mulder et al 1994[47] Randomized CBT/ET/WLC comparative trial	None	Asympto-matic HIV	11/8 12/7 15/12	CBT/15 sessions (2.5 hours)/ group ET/15 sessions (2.5 hours)/ group, WLC/4-month wait	BDI POMS-TMD	Results: Completers BDI Change: CBT+ET = –4.0, WLC = –0.2 (P <.01) POMS-TMD Change: CBT+ET= –6.0, WLC = 6.0 (P < .04) No significant difference between CBT and ET groups on mood outcomes. Outcome: None
Lutgendorf et al 1997[48] Randomized CBSM/WLC	None	HIV+ No AIDS diagno-sis, symp-tomatic	52/39 MSM	CBSM/10 sessions (135 minutes)/group	BDI POMS-DEP	Results: POMS-DEP Pre-Post Change: CBSM = –3.76 POMS-DEP Pre-Post Change: Control = +1.89 BDI Pre-Post Change: CBSM = –3.38 BDI Pre-Post Change: Control = +1.05 Outcome: Intervention-related reduction in HSV-2 antibody titers

(continued on page 116)

BDI indicates Beck depression inventory; CBSM, cognitive-behavioral stress management; CBT, cognitive-behavioral therapy; CES-D, Center for Epidemiologic Studies depression scale; ET, experiential group psychotherapy; HAM-D, Hamilton depression rating scale; HSV, herpes simplex virus; IP, interpersonal psychotherapy; M, mean; MDD, major depressive disorder; MSM, men who have sex with men; n/a, not available; POMS-DEP, profile of mood states depression subscale; POMS-TMD, profile of mood states total mood disturbance; SCL-90, symptom checklist-90; SLC-90-R (Dep), SCL-90 revised, depression scale; SP, supportive psychotherapy; SWI, imipramine and SP; WLC, wait-list control.

Table **1**. Psychosocial Treatments for Depressive Disorders and Symptoms in Patients with HIV (continued)

Reference and Study Design	Depression Entry Criteria	HIV Disease Stage	Enrolled/ Completed	Treatment Modality/ Duration/Type	Depression Measures	Significant Results and Health/Immune Outcomes
Lee et al 1999[46] Nonrandomized	DSM diagnosis of MDD or dysthymia	AIDS (category C) and HIV symptom (category B)	15/13	CBT w/ medication/ 20 sessions (2 hours)/group	HAM-D BDI	Results: HAM-D Pre-Post Change: –17 BDI Pre-Post Change: –9 Outcome: None
Antoni et al 2000[49] Randomized CBSM/WLC	None	HIV+ No AIDS diagnosis 200-700 CD4+ cells/μL or HIV symptom	59/n/a MSM	CBSM/10 sessions (135 minutes)/ group	POMS-DEP	Results: POMS-DEP Pre-Post Change: CBSM = –4.03 POMS-DEP Pre-Post Change: Control = +0.58 Outcome: Intervention-related reduction in urinary cortisol
Cruess et al 2000[51] Randomized CBSM/WLC	None	HIV+ No AIDS diagnosis 200-700 CD4+ cells/μL or HIV symptom	CBSM 42/37 WLC 23/20	CBSM/10 sessions (2.5 hours)/ group	POMS-TMD POMS-DEP	Results: POMS-TMD Pre-Post Change: CBSM = –11.2 POMS-TMD Pre-Post Change: Control = +3.78 POMS-DEP Pre-Post Change: CBSM = –2.32 POMS-DEP Pre-Post Change: Control = +0.84 Outcome: Intervention-related increases in testosterone CBSM: Significant pre-post decrease in HIV-related symptoms
Cruess et al 2002[52] Randomized CBSM/no treatment control trial	None	HIV symptomatic (category B only) or 200-700 CD4+ cells/μL	125/100 MSM	CBSM/10 sessions (2.5 hours)/group	BDI POMS-DEP POMS-TMD	Results: Completers BDI Change: CBSM = –3.31, Control = –1.1 (P <.10) Outcome: None
Blanch et al 2002[53] Open trial of group CBT	None	HIV infection for at least 3 months	49/39	CBT/16 weeks/ 1 session (2 hours)/week	BDI	Results: 74% had improved BDI scores Outcome: None

BDI indicates Beck depression inventory; CBSM, cognitive-behavioral stress management; CBT, cognitive-behavioral therapy; CES-D, Center for Epidemiologic Studies depression scale; ET, experiential group psychotherapy; HAM-D, Hamilton depression rating scale; HSV, herpes simplex virus; IP, interpersonal psychotherapy; M, mean; MDD, major depressive disorder; MSM, men who have sex with men; n/a, not available; POMS-DEP, profile of mood states depression subscale; POMS-TMD, profile of mood states total mood disturbance; SCL-90, symptom checklist-90; SLC-90-R (Dep), SCL-90 revised, depression scale; SP, supportive psychotherapy; SWI, imipramine and SP; WLC, wait-list control.

participants (34 CBSM, 13 wait-list controls) provided 24-hour urinary samples pre- and post-intervention, which yielded a measure of urinary free cortisol output. Those assigned to the CBSM intervention had significantly less cortisol output at the completion of the study compared with controls. In addition, greater decreases in depressed mood were related to greater decreases in urinary cortisol over the intervention period.

Cruess and colleagues[51] examined the efficacy of CBSM for psychological distress in 65 HIV-seropositive men. Participants were randomized to either a CBSM intervention or a wait-list control condition. Significant reductions were observed in depression, as assessed by the POMS depression subscale, for those in the CBSM condition. However, those randomized to the wait-list control condition showed no significant changes in depression. Furthermore, participants in the CBSM condition showed significant increases in testosterone whereas control participants showed significant decreases. Further, changes in depression were inversely related to changes in testosterone and post-intervention mean testosterone levels for the CBSM group were approaching that of healthy men of similar age.

Cruess and colleagues[52] also examined the efficacy of a 10-week CBSM intervention with 125 HIV-infected gay men. Participants were randomized to either the group CBSM intervention or a no treatment control condition. They report results for 100 participants who completed the intervention. The CBSM intervention was associated with significant reductions in depressive symptoms as measured by the BDI and the depression subscale of the POMS. However, little change on the BDI and the depression subscale of the POMS was observed in the no treatment control condition. Furthermore, increases in cognitive coping strategies (acceptance) and self-efficacy, and decreases in dysfunctional attitudes significantly predicted greater reductions in depressive symptoms.

Blanch and colleagues[53] evaluated the efficacy of a CBT group intervention for 39 patients having HIV infection for at least 3 months. The intervention program lasted for 16 weeks with 1 weekly session for 2 hours. The group intervention consisted of psychoeducation, problem solving, relaxation training, cognitive modification, and a behavioral activation component. Results revealed significant reductions in depression as assessed by the BDI. At 3 months of follow–up, 74% of the patients showed an improvement on the BDI scores. Of all patient characteristics at baseline, only transmission of the HIV infection by sexual intercourse and transmission by intravenous drug use predicted change in depression.

Summary: Psychosocial Treatment Studies of Depression in HIV

A review of the literature suggests that psychosocial interventions derived from a wide variety of theoretical orientations are effective in treating depression among individuals infected with HIV. Significant reductions were found in depression outcome studies in which psychosocial interventions either directly or indirectly targeted depression. Specifically, psychological interventions for depression in individuals with HIV appear to be significantly better than no treatment. However, less definitive inferences can be made regarding the relative efficacy of various psychosocial interventions for depression in HIV-infected individuals.

Although some studies seem to indicate that social support interventions have incremental (ie, better than other credible treatments) efficacy for the treatment of depression in HIV-infected individuals (ie, Kelly et al, 1993[40]), other studies offer evidence for the incremental efficacy of interpersonal psychotherapy (ie, Markowitz et al, 1995[43]). Very few studies have compared CBT-based treatments with other interventions in the treatment of depression in HIV-infected individuals. The limited available evidence does seem to suggest that CBT is equally as effective as other treatments (ie, Mulder et al, 1994[47]).

Psychopharmacologic Interventions: Depression in HIV

As outlined in Table 2, the literature search on pharmacologic interventions for depression in patients with HIV infection revealed 3 studies using selective serotonin reuptake inhibitors (SSRIs),[15,54,55] 2 studies examined the relative effects of SSRIs and tricyclic antidepressants (TCAs),[56,57] and 2 studies examined the effects of psychostimulants.[58,59]

Selective Serotonin Reuptake Inhibitors (SSRIs)

Zisook and colleagues[15] randomized 47 HIV-seropositive patients meeting diagnostic criteria for major depressive disorder and had a current depressed episode of at least 4 weeks duration and were at category A or B for HIV disease stage to receive either fluoxetine or a placebo. Patients were initially instructed to take 1 capsule (fluoxetine 20 mg or placebo) increasing to 2 and 3 capsules by the 4th and 5th weeks respectively. All patients attended a minimum of 7 weeks of supportive and psychoeducational group therapy.

No significant differences were found between patients receiving fluoxetine or a placebo on the clinical global impressions improvement scale (CGI-I). However, patients receiving fluoxetine demonstrated significant reductions in depression as assessed by the BDI and the HAM-D compared with those in the placebo condition. Furthermore, there were significantly more responders in the treatment group (64%) than in the placebo group (23%). Most prominent side effects reported by patients in the fluoxetine condition included nausea (48%), headaches (32%), dry mouth (32%), and diarrhea (24%). Patients in the placebo group were more likely to endorse effects of headaches (36%), nausea (23%), loss of appetite (18%), and insomnia (18%).

Rabkin and colleagues[54] randomized 120 HIV-seropositive patients meeting diagnostic criteria for major depressive or dysthymic disorder with no recent HIV-related opportunistic

Table **2**. Psychopharmacologic Treatment for Depression in Patients with HIV

Reference	Design	Depression Entry Criteria	HIV Disease Stage	Enrolled/ Completed	Antidepressant/ Dosage/Duration	Depression Measures	Significant Results
Selective serotonin reuptake inhibitors (SSRIs)							
Targ et al 1994[55]	Randomized, blind, placebo (with group psychotherapy control) trial	MDD or adjustment disorder with 24 item HAM-D >16	Asymptomatic HIV+ taking zidovudine	20/18 (MSM)	Fluoxetine/20 mg/ 12 weeks	HAM-D POMS POMS-DEP	No significant group differences
Zisook et al 1998[15]	Randomized, double-blind, placebo (with group psychotherapy control) trial	MDD (DSM-III-R) with current episode of 4 weeks duration	HIV disease category A or B	47/37 (men)	Fluoxetine/20-60 mg/6.4 weeks	HAM-D BDI-13 CGI-I	HAM-D mean change: fluoxetine, 12.1; placebo, 6.6 (P <.05). HAM-D ≥ 50% decrease: fluoxetine, 64%; placebo, 23% (P <.01). BDI mean change: fluoxetine, 5.9; placebo, 1.2 (P <.05)
Rabkin et al 1999[54]	Randomized, double blind, placebo-controlled trial	MDD or dysthymic disorder (DSM-IV)	HIV+ with no current opportunistic infection	120/87 (> 90% men)	Fluoxetine/20-40 mg/8 weeks/18-week follow-up	HAM-D CGI SCL-90-D BHS	CGI responders: fluoxetine, 74% (n=42); placebo 47%, (n=14). HAM-D mean change: fluoxetine, 13.1; placebo, 10.4
SSRIs and tricyclic antidepressants (TCAs)							
Elliott et al 1998[57]	Randomized, placebo-controlled, comparative trial	MDD (DSM-III-R) and 21-item HAM-D ≥18	HIV+	25/11 (> 90% male) 25/10 25/13	Paroxetine/33.9 mg/12 weeks Imipramine/162.5 mg/12 weeks Placebo/12 weeks	HAM-D CGI	HAM-D full responders: paroxetine, 55% (n=6); imipramine, 80% (n=8); placebo, 23% (n=3) CGI Responders: paroxetine, 46% (n=5); imipramine, 90%
Schwartz et al 1999[56]	Randomized, placebo-controlled, comparative trial	MDD (DSM-III-R) and 17-item HAM-D ≥14	HIV+ with no current opportunistic infection	8/8 (women) 6/4 (women)	Fluoxetine/20-40 mg/6 weeks Desipramine/75-100 mg/6 weeks	HAM-D CGI	HAM-D mean change: fluoxetine, 9.0; desipramine, 7.17 CGI responders: fluoxetine, 75% (n=6); desipramine, 50% (n=3)
Psychostimulants							
Fernandez et al 1995[58]	Randomized, double-blind comparative trial	MDD (DSM-III-R), and 24-item HAM-D ≥15	HIV+	12/9 8/6 (MSM)	Desipramine/150 mg/6 weeks Methylphenidate/30 mg/6 weeks	HAM-D MMPI-D BSI-D POM-D	No significant differences in pre-post change scores at 6 weeks between the groups. Significant one-tailed (P < .05) experiment-wise pre-post changes on all measures of depressed mood
Wagner et al 2000[59]	Randomized, double-blind, placebo controlled trial	MDD (DSM-IV) and debilitating fatigue	HIV+	23/22 (men)	Dextroamphetamine (dextro) 10-40 mg/2 weeks	HAM-D BSI-D BHS VAS	Responders: dextro, 73%; placebo, 25% (P < .05) *HAM-D mean change: dextro, 7.6; placebo, 5. *BSI-D mean change: dextro, 1.02; placebo, 1.05 *VAS mean change: dextro, −2.1; placebo, 0.9 (* not significant)

BDI indicates Beck depression inventory; BHS, Beck hopelessness scale; BSI-D, brief symptom inventory depression scale; CGI, clinical global impression; CGI-I, CGI-Improvement; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; HAM-D, Hamilton depression rating scale; MDD, major depressive disorder; MMPI-D, Minnesota multiphasic personality inventory depression scale; MSM, men who have sex with men; POMS, profile of mood states; POMS-DEP, profile of mood states depression subscale; POMS-TMD, profile of mood states total mood disturbance; SCL-90, symptom checklist-90; SCL-90-D, SCL-90 depression scale; VAS, visual analogue scale.

infection to 8 weeks of fluoxetine or a placebo. Fluoxetine dosage was fixed at 20 mg for the first 4 weeks and increased by 20 mg/day as indicated by the absence of clinical improvement and significant side effects. Patients were followed up for 18 weeks to assess the impact of treatment on immune markers. In an intent-to-treat analysis, 57% of fluoxetine patients and 41% of placebo patients were identified as responders on the HAM-D, but this difference was not statistically significant. Among patients who completed the study, however, significantly more patients responded to fluoxetine (74%) than to placebo (47%). However, fluoxetine treatment was not significantly related to CD4+ cell change over time. Six patients, all taking fluoxetine, discontinued treatment because of side effects (sleepiness, diarrhea, insomnia, upset stomach, overstimulation, rash) and 50% of patients taking placebo and 50% taking fluoxetine reported at least 1 treatment-related side effect during the trial.

Targ and colleagues[55] randomly assigned 20 participants with HIV infection scoring a 16 or higher on the HAM-D and who also met DSM-IV diagnostic criteria for either major depressive disorder or adjustment disorder with depressed mood to either structured weekly group therapy, focused on active skills in behavioral coping, in addition to fluoxetine (20 mg/day) or identical group therapy with placebo. Participants were enrolled for 12 weeks, and met with a study physician weekly to have questions answered relating to medication adherence and side effects. Among those who completed the study, patients in the fluoxetine treatment plus therapy group as well as the placebo plus therapy group reported significant reductions in depression. However, there was no statistical difference between the 2 treatment conditions.

Comparison of Tricyclic Antidepressants (TCAs) and SSRIs

Elliott and colleagues[57] randomly assigned 75 HIV-seropositive patients with major depressive disorder to receive paroxetine (an SSRI), imipramine (a TCA), or a placebo in a 12-week trial. Paroxetine treatment was initiated at 10 mg/day and subsequently increased to 20 mg/day and then 40 mg/day, in the first and second weeks, respectively. Imipramine treatment was initiated at 50 mg/day and subsequently increased to 100 mg/day and then 200 mg/day, in the first and second weeks, respectively. After the second week, neither the imipramine nor the paroxetine treatment groups had increased doses; decreased doses were only in relation to medical illness or serious drug complications. Forty-five percent (n = 34) of the study participants completed the entire 12-week trial. Intent-to-treat analysis revealed that both active drugs yielded significant reductions in depression, as assessed by the HAM-D, compared with placebo at week 6, week 8, and at week 12.

For participants who completed the treatment, both active drugs produced significant reductions in depression at week 8. However, only imipramine was superior to placebo at week 12. Intent-to-treat analysis showed significantly higher full response rates for paroxetine (38.9%) and imipramine (68.8%) than for placebo (13.6%) after 12 weeks. Common side effects reported in the paroxetine group included dry mouth (52%), nausea (24%), and headache (24%). Dry mouth (56%), heat palpitations (36%), and nausea (32%) were commonly reported in the imipramine group. Patients in the placebo condition were more likely to report concerns of anxiety (60%), nausea (36%), and dry mouth (28%). Treatment drop-out due to side effects was significantly greater among those in the imipramine treatment group compared to both other groups.

Schwartz and colleagues[56] examined the efficacy of 20 to 40 mg/day of fluoxetine (an SSRI) compared with 75 to 100 mg/day of desipramine (a TCA) in a group of 14 HIV-infected women with major depression. Because of insufficient power to detect statistical differences between groups, results were presented with descriptive statistics only. At baseline, participants receiving fluoxetine reported reductions in depressive symptoms, as assessed by the HAM-D, from baseline (20.88) to 6-week post assessment (11.88). Similar reductions in depression were observed for participants receiving desipramine from baseline (22.00) to 6-week post assessment (14.83). Sixty-three percent of patients receiving fluoxetine met criteria for a partial to full response and 50% of patients receiving desipramine met criteria for a partial to full response. Common side effects reported by patients in the fluoxetine group include dry mouth (25%), headache (25%), and nausea (25%). Those in the TCA group generally reported concerns of dry mouth (50%), headache (50%), and insomnia (50%).

Psychostimulants

Fernandez and colleagues[58] randomized 20 HIV-seropositive participants with depression to receive either desipramine or methylphenidate (a psychomotor stimulant) for a 6-week observational study. Subjects randomized to either the desipramine or methylphenidate treatment group had a mean daily drug dose of 150 mg or 30 mg, respectively. Significant reductions in depression as assessed by the HAM-D and the POMS depression subscale were observed for both medications at week 6 of treatment over baseline for both groups. However, there were no significant differences in pre-post change scores at 6 weeks between the groups. Treatment responder analysis revealed that 40% of all patients receiving desipramine showed greater than 50% reduction in HAM-D scores. Forty-three percent of all methylphenidate-treated patients demonstrated a greater than 50% reduction in HAM-D scores. Significant side effects were reported by 22% (ie, dry mouth) of the desipramine-treated patients versus 16% (ie, restlessness) of the methylphenidate-treated patients.

Wagner and colleagues[59] randomly assigned 23 HIV-seropositive men with depression to dextroamphetamine or placebo for a 2-week trial. Seventy-three percent assigned to dextroamphetamine responded to treatment

with significant reductions in mood and increases in energy level, compared with 25% improvement observed in participants assigned to placebo. Among completers in the dextroamphetamine group, significant improvement in depressive symptoms as measured by both the clinician-rated HAM-D and self-reported BSI depression subscale were found at week 2. The most common treatment-related side effects (reported by 22% of the sample) were overstimulation, insomnia, and loss of appetite or weight, or both, with each reported at some point during the treatment.

Summary: Pharmacologic Treatment Studies of Depression in HIV

A review of the literature suggests that a wide range of pharmacologic agents appear to be effective in the treatment of depression in HIV-infected individuals. Such agents included SSRIs, TCAs, and psychostimulants. Overall, the various pharmacologic agents appear to be better than placebo. However, there is no definitive evidence in the literature suggesting that any one pharmacologic agent is more efficacious than another in the treatment of depression in HIV-infected individuals. In fact, there is some evidence to suggest that some of the observed effects of active drug treatment may be partially attributable to high response to placebo.[57] Although active drug treatments generally demonstrate a statistically significant advantage over placebo, these differences tend to be relatively modest. These modest effects for active drug treatment could be a reflection of both dose and duration of treatment. Arguably the doses used in many of the pharmacologic trials are low (ie, with TCAs, paroxetine). Furthermore, the duration of treatment in many of the trials is approximately 6 weeks, which may be short for an efficacy assessment.

An important consideration in evaluating the effectiveness of pharmacologic treatment of depression in HIV-infected individuals is treatment drop-out. High attrition rates were very common, with estimates of drop-out rates at approximately 27%.[54] Although various reasons for treatment drop-out may be considered, side effects attributable to active drug treatment were not uncommon. For example, Rabkin and colleagues[54] found that 50% of patients taking fluoxetine reported at least 1 treatment-emergent side effect during the trial. The most frequent side effects reported were gastrointestinal symptoms including upset stomach and diarrhea (26%), nervousness (18%), sleepiness and appetite and weight loss (13% each), dry mouth (11%), and sexual dysfunction (10%). Thus, it appears that pharmacologic treatment of depression in HIV-infected individuals is more effective than placebo for patients who are able to tolerate it. However, a substantial portion of patients experience intolerable side effects, and this group may require consideration of alternative effective treatment.

Treatment Of Depression in HIV: A Methodological Critique

Defining Depression

Although there is evidence from clinical trials that psychosocial and pharmacologic treatments are effective for the treatment of depression in HIV-infected individuals, additional methodologic issues must be addressed in future clinical trials before more definitive inferences regarding efficacy can be made. One such issue is the marked variability in the operational definition of depression in HIV treatment studies.

For example, all participants evaluated by Markowitz and colleagues[45] were judged to have clinically significant depressive symptoms. However, only 53% met DSM-III-R criteria for a current mood disorder. Meaningful comparisons of treatment studies should be based on the notion that the condition being treated is reliably similar. However, there is some inconsistency in the classification of depression between and within psychosocial and pharmacologic HIV outcome studies. Depression is often identified in such studies as a disorder, a symptom, a syndrome, or a complaint. The consideration of "depression" as either the self-report of depression, major depression, or dysthymia could have implications for the generalizability of the treatment outcome findings.

For example, HIV patients with major depression may clinically differ from those who are more chronically depressed (ie, dysthymia). HIV patients with major depression or dysthymia may also clinically differ from those with just symptoms of depression as a result of a life stressor. Although the broad definition of depression does highlight the importance of defining outcome in the broadest possible fashion in terms of addressing the external validity of the findings obtained, the differences in the entry criteria for depression may limit comparisons between and within psychosocial and pharmacological treatment modalities.

This qualitative review of treatment studies of HIV seems to suggest that pharmacologic trials are generally more stringent in their definition of depression than psychosocial treatment studies. Pharmacologic trials typically infer the presence of depression in HIV-infected individuals based on structured diagnostic interview (major depression). However, the presence of depression in psychosocial treatment studies is often inferred based on cut of scores on self-report measures (depressive symptoms).

Thus, HIV patients in pharmacologic trials may present with more severe depression than those recruited in psychosocial treatment studies. The cut of scores used to infer depression in psychosocial treatment studies not only limits meaningful comparisons with pharmacologic trials, it also allows for limited comparison with other psychosocial treatment studies as different measures of depression (ie, BDI, CGI, POMS, HAM-D, CES-D, SCL-90) are often used. The use of different measures of depression in HIV-infected individuals makes comparisons across studies difficult as some measures emphasize the physical symptoms of depression and others focus exclusively on the affective aspects of depression.

Depending on the assessment

modality, depression may also be confounded with symptoms of HIV, as there is considerable overlap between the physical symptoms of depression and symptoms of HIV progression. The overlap between symptoms of depression and HIV becomes more important given that both psychosocial and pharmacologic treatment studies recruit patients across the whole range of disease stages. Importantly, patients at the later stages of HIV disease will appear more depressed because of the overlay of HIV-related disturbances of appetite, sleep, libido, weight, and energy, on symptom measures of depression and presumably will create difficulties assessing treatment impact (particularly on studies using the BDI for example). The overlap between symptoms of depression and HIV is an important issue for assessment and treatment outcome that has not been adequately addressed in the literature. The selection of the appropriate measures to diagnose and assess change in depression in HIV-infected individuals will surely need to account for these assessment considerations in future treatment trials.

Determining Treatment Efficacy

The evidence that psychosocial and pharmacologic treatments are efficacious for the treatment of depression in HIV must be considered in the context of the limitations of the clinical studies. Studies on the efficacy of psychosocial treatments for depression in HIV were largely consistent with the use of control conditions to rule out nonspecific treatment factors (ie, treatment credibility, expectation for improvement, experimental demand). These studies were also largely consistent in the direct comparison of validated techniques (ie, CBT vs SSG). However, the internal consistency of the clinical trials must be considered.

For example, the outcome of treatment studies utilizing different medication doses and duration of treatments across different treatment conditions[43,53] must be interpreted with caution. In addition to consistency in the delivery of treatment for depression in HIV, the presence of clearly defined target symptoms, reliable and valid measures, blind evaluators, appropriate assessor training, manualized treatment procedures, unbiased assignment to treatment conditions, and ratings of treatment adherence should be a prerequisite before inferences can be made regarding the efficacy of psychosocial and pharmacologic treatments of depression in HIV treatment outcome studies.

Future demonstrations of efficacy may well be aided by the consideration of dismantling designs to help identify the functional significance of specific aspects of multifaceted psychosocial treatment procedures. Similar methodologic considerations may be applied to pharmacologic treatment outcome studies in which random assignment may be used to assess the relative effects of a given pharmacologic treatment (eg, SSRI), no treatment (eg, wait-list), nonspecific factors (placebo), and credible pharmacologic alternatives (eg, TCA). Such design considerations in treatment outcome studies examining the efficacy of psychosocial and pharmacologic interventions for depression in patients with HIV would be consistent with a cost-effective agenda in which treatment delivery consists of only necessary and sufficient empirically based interventions.

Discussion

As the HIV epidemic grows, with 40,000 new infections per year[60], and with individuals living indefinitely on highly active antiretroviral therapy, so will the number of individuals with comorbid depression. However, established guidelines for treating depression in HIV are lacking. With the advent of studies identifying the consequences of depression in HIV infected individuals; the identification of effective treatments for depression should be a focus of further research. This qualitative review of the literature does suggest that a wide range of psychosocial and psychopharmacologic interventions are effective in the treatment of depression for individuals with HIV. However, continued research is needed to identify which treatments for depression are better for which patients with HIV under which set of circumstances. By matching specific treatments for depression to specific patients with HIV treatment, gains may be maximized.

Significant improvement in symptoms of depression was found in treatment outcome studies directly and indirectly targeting depression in HIV. Furthermore, it appears that CBT, interpersonal psychotherapy, and supportive therapy can be helpful in the treatment of depression in individuals with HIV. Identification of the treatment component that is common across these diverse psychosocial interventions that may account for the equivalent reductions in depression may be informed by consideration of predictors of treatment outcome.

For example, Cruess and colleagues[52] found that increases in coping strategies significantly predicted greater reductions in depression in HIV-infected individuals. Importantly, the coping technique examined emphasized acceptance, suggesting that perhaps coming to terms with HIV illness may have important implications for facilitating positive gains during treatment for depression. It is also possible that different psychosocial interventions utilize different techniques (ie, problem solving; psychoeducation) that may help maximize adaptive coping to illness. Maximizing adaptive coping in individuals with HIV and depression appears to be a useful strategy, given the multiple stressors that are involved in living with and maintaining a medication treatment regimen.[61,62]

This review of the treatment outcome literature suggests that pharmacotherapy is also effective for the treatment of depression in patients infected with HIV. Pharmacologic agents such as SSRIs, TCAs, and psychostimulants appear to be generally better than placebo. However, patients with HIV treated with placebo also often demonstrated substantial improvement in depressive symptoms.[15] Thus, it is unclear the percentage of variance in the efficacy of pharmacotherapy for depression in HIV that may be

accounted for by the "placebo effect," In fact, a recent meta-analysis of double-blinded, randomized controlled trials (7 studies that included 494 subjects) examining the efficacy of antidepressant treatment among HIV-seropositive depressed individuals found that the pooled effect size from the random effects model was 0.57.[63] However, placebo response explained nearly 62% of the variance in effect sizes across the studies.

It is also unclear in the treatment outcome literature if one pharmacologic agent has any incremental efficacy (over and above a placebo and the next best drug treatment) over another drug treatment. Furthermore, the determination of the utility of pharmacotherapy for depression in HIV should be partially dependent on how many patients can tolerate the treatment in its entirety. Indeed, adverse side effects are common in pharmacologic treatment trials for depression in HIV.[54] Furthermore, patients with HIV and comorbid depression often suffer from multiple physical complications and often receive many toxic medications. Thus, receiving more medication that potentially produces additional adverse effects may not be optimal.

Although both psychosocial and pharmacologic interventions seem to be effective for the treatment of depression in HIV, there is very little research suggesting if patients with HIV may receive more benefit from psychosocial or pharmacologic treatments. This is largely due to a paucity of rigorous treatment outcome studies directly comparing a psychosocial intervention with a pharmacologic intervention for depression in HIV. This qualitative review seems to suggest that psychosocial interventions are largely equivalent to pharmacologic interventions for the treatment of depression in HIV. However, the absence of a difference between psychosocial and pharmacologic interventions may be a result of the loose diagnostic criteria for depression in psychosocial treatment studies.

There is some evidence in the general depression treatment literature suggesting that the selection of psychosocial interventions over pharmacologic interventions may maximize treatment gains after treatment discontinuation. For example, Hollon and colleagues[64] found that depressed patients withdrawn from cognitive therapy were significantly less likely to relapse during continuation than patients withdrawn from medications (30.8% vs 76.2), and no more likely to relapse than patients who kept taking continuation medication (30.8% vs 47.2%). Consideration of potential treatment complications seems to suggest that psychosocial treatments may also offer an advantage as pharmacologic treatment of depression will likely be complicated by HIV illness, adverse drug effects, drug interactions, and potential for abuse. These considerations would support a model in which validated psychosocial interventions, when available, are considered first line treatments for depression in individuals with HIV.

Treatment of depression could result in substantial improvement in quality of life for patients with HIV. However, further research is greatly needed to determine if treating depression increases self-care behaviors such as adherence and if treating depression results in improvements in HIV-specific markers of disease severity or progression such as viral load or CD4+ count. Cook and colleagues[65] report a recent study examining the effects of treated and untreated depressive symptoms on the likelihood of utilization of antiretroviral therapy among a cohort of HIV-infected women who screened positive for probable depression. Regression analysis was used to estimate the impact of psychosocial mental health treatment on the probability of antiretroviral utilization, controlling for clinical indicators (CD4+ count, viral load), demographic features (race or ethnicity, income), and behavioral factors (recent crack, cocaine, or heroin use). Results showed that use of antidepressants plus psychosocial treatment, or psychosocial treatment alone significantly increased the probability of antiretroviral utilization, compared with receiving no depression treatment. Use of antidepressants alone did not differ significantly from receiving no depression treatment. These findings suggest that efforts to enhance access to psychopharmacologic and psychosocial treatments (or psychosocial treatment alone) may increase use of the most effective HIV therapies.

Ideally, an effective treatment of depression in HIV should also translate to changes in illness progression and increases in self-care behaviors. Preliminary work has begun to develop and evaluate treatments that specifically target HIV medication adherence and depression that has shown promising results in a case series[39] and is being tested by our group in 2 randomized controlled trials. Additionally, some studies have shown that effective psychosocial treatment of depression in HIV translates into improvements in immune outcomes of central importance for people managing HIV disease.

For example, Lutgendorf and colleagues[48] found that psychosocial treatment of depression in symptomatic HIV-seropositive gay men was associated with greater immune control of latent HSV-2 virus and lower levels of dysphoria were associated with lower HSV-2 antibody titers. Studies have also shown that psychosocial treatment of depression in symptomatic HIV-infected gay men is related to greater decreases in urinary cortisol and significant increases in testosterone.[49,51] These studies suggest that psychosocial treatment for depression may have important implications for HIV-specific markers of disease severity. However, much less is known of the effects of pharmacologic treatment for depression on similar HIV markers.

The current literature does support the utility of both psychosocial and pharmacologic strategies for the treatment of depression in HIV-infected individuals. However, there are several methodologic limitations of psychosocial and pharmacologic treatment outcome studies including high levels of attrition, variable stages of infection, variability in treatment duration, and more studies that target gay men than other risk groups such as injection drug

users, that limit strong inferences regarding treatment efficacy.[66] Indeed, the vast majority of the depression outcome studies are undertaken predominantly with HIV-infected men. Future treatment studies will need to focus on women, particularly given that minority women are now at substantial risk for HIV. The presence of systematic differences in depression entry criteria and outcome assessment based on these entry criteria is also an important limitation of current psychosocial and pharmacologic HIV treatment outcome studies. Indeed, differences in the operational definition of depression limits meaningful comparisons across treatment modalities and greatly impacts conclusions about the generalizability of the interventions. Future research addressing these and other methodological limitations may facilitate the development of more effective treatments of depression in HIV-infected individuals.

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