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Open-Label, Randomized, Parallel-Group Controlled Clinical Trial of Massage for Treatment of Depression in HIV-Infected Subjects

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Abstract

Objectives: The study objectives were to determine whether massage therapy reduces symptoms of depression in subjects with human immunodeficiency virus (HIV) disease.
Design: Subjects were randomized non-blinded into one of three parallel groups to receive Swedish massage or to one of two control groups, touch or no intervention for eight weeks.
Settings/location: The study was conducted at the Department of Psychiatry and Behavioral Neurosciences at Cedars-Sinai Medical Center in Los Angeles, California, which provided primary clinical care in an institutional setting.
Subjects: Study inclusion required being at least 16 years of age, HIV-seropositive, with a diagnosis of major depressive disorder. Subjects had to be on a stable neuropsychiatric, analgesic, and antiretroviral regimen for >30 days with no plans to modify therapy for the duration of the study. Approximately 40% of the subjects were currently taking antidepressants. All subjects were medically stable. Fifty-four (54) subjects were randomized, 50 completed at least 1 week (intent-to-treat; ITT), and 37 completed the study (completers).
Interventions: Swedish massage and touch subjects visited the massage therapist for 1 hour twice per week. The touch group had a massage therapist place both hands on the subject with slight pressure, but no massage, in a uniform distribution in the same pattern used for the massage subjects.
Outcome measures: The primary outcome measure was the Hamilton Rating Scale for Depression score, with the secondary outcome measure being the Beck Depression Inventory.
Results: For both the ITT and completers analyses, massage significantly reduced the severity of depression beginning at week 4 ($p \leq 0.04$) and continuing at weeks 6 ($p \leq 0.03$) and 8 ($p \leq 0.005$) compared to no intervention and/or touch.
Conclusions: The results indicate that massage therapy can reduce symptoms of depression in subjects with HIV disease. The durability of the response, optimal "dose" of massage, and mechanisms by which massage exerts its antidepressant effects remain to be determined.

Introduction

Depression is a common, often chronic and severe disorder. In the United States, approximately 10% of people suffer from major depression at any one time, and 20%–25% experience an episode of major depression at least once during their lifetimes. As with other serious illnesses, human immunodeficiency virus (HIV) infection often is accompanied by psychiatric complications, particularly depression.[1–8] It is estimated that as many as 1 in 3 HIV-infected persons suffer from depression.[9] Not only is depression itself a leading cause of disability, but the combination of depression and HIV disease is an even larger and growing contributor to the burden of disease worldwide.[10]

While pharmacologic intervention has been the mainstay for treatment of depression,[11] many people do not respond

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well to antidepressants. Since polypharmacy is common among those with HIV disease, the addition of another medication only increases the potential for serious drug–drug interactions and adverse events. Accordingly, new, safe, and efficacious nonpharmacologic treatments for depression, particularly in subjects infected with HIV, are needed. One such treatment modality that has received increasing attention is massage therapy.[12]

There have been several studies investigating the efficacy of massage therapy in psychiatric syndromes. As reviewed,[13–15] extant data indicate that massage therapy decreases symptoms of anxiety and depression in a wide array of childhood and adult neuropsychiatric disorders. However, many of these studies only compared massage to a nonintervention (NI) group, which does not adequately address the possibility of a "placebo" effect. Using a novel dual-control group design,[16] which included a light "touch" group to control for some of the nonspecific effects of massage and therapist–subject interaction, the efficacy of Swedish massage on the symptoms of depression was assessed in HIV-positive patients with comorbid major depression. The hypothesis was that massage therapy would reduce depression in subjects with HIV disease.

Materials and Methods

Subjects were recruited from the greater Los Angeles area by radio and newspaper advertisements, flyers and web postings, and screened on the telephone by study coordinators. The study was approved by the Institutional Review Boards at Cedars-Sinai Medical Center and the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center. Subjects signed an informed consent document prior to participation in the study. The study was registered with ClinicalTrials.gov (NCT00033852). All potential participants were assessed using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV[17] to identify major depressive disorder and comorbid conditions. Severity of depressive symptoms was determined by the Hamilton Depression Rating Scale (HAM-D)[18] and the Beck Depression Inventory (BDI).[19] The HAM-D is clinician-administered, whereas the BDI is a self-report instrument.

Study inclusion required being at least 16 years of age, HIV-seropositive, and having a diagnosis of major depressive disorder. Subjects had to have a score ≥ 15 on the HAM-D (21-item version) at screening. Subjects had to be on a stable neuropsychiatric, analgesic, and antiretroviral regimen for at least 4 weeks and planning to remain on the same regimen for the 8-week duration of the study. Approximately 40% of the subjects also were currently taking antidepressants. As with the antiretroviral regimens, subjects had been on a stable antidepressant regimen for >30 days and the regimen remained fixed for the duration of the study. All subjects were medically stable as determined by physical examinations, full chemistry panels, thyroid function tests, electrocardiograms, and urine drug screens, although they were not excluded for having a positive urine drug screen. Exclusion criteria included being unable to provide informed consent, an unstable medical condition (new opportunistic infection, malignancies, or acute hospitalizations during the past 30 days), active suicidal ideation or a recent suicide attempt, current or previous diagnosis of anorexia/bulimia nervosa, primary anxiety disorder, bipolar disorder or psychotic disorder, taking any growth hormone or adrenocorticoid preparations, massage therapy or new alternative medicine use in the preceding 30 days, and history of intolerance to or contraindication to massage.

Subjects were enrolled by the study coordinators and then randomized using a random numbers table by a nurse practitioner whose sole role in the study was to randomize subjects. Subjects were randomized 1:1:1 into one of three parallel groups—1 hour of Swedish massage or to one of two control groups: light touch (touch) twice per week (Monday/Thursday or Tuesday/Friday), or to NI for 8 weeks. Subjects were told that it was not known whether touch or massage was going to affect their depression and that some subjects, even those in the NI group, might feel better during the course of the study. Raters and subjects were asked not to discuss with each other as to what group the subjects were in. Blood and 24-hour urine were collected at baseline and week 8 for exploratory purposes, and findings will be presented in a subsequent report.

Sample size was based upon principles of statistical power analysis.[20] Based on existing data in the literature, the effect size was estimated to be large (≥ 0.5), resulting in the recruitment of 14–20/group at $p = 0.05$ and a power of 0.8. A total of 81 subjects were screened; 54 subjects were randomized into the study, 50 subjects completed at least 1 week of the protocol (intent-to-treat; ITT), and 37 subjects completed the entire study (completers). Of the 4 subjects who were randomized, but dropped out prior to week 1 (3 in the touch group and 1 in the massage group), 2 did not want to be in the touch group, another in the touch group had a change in neuropsychiatric regimen (thus excluding participation), and the 1 assigned to the massage group had a scheduling conflict. Of the 13 dropouts in the ITT group, 2 were in the NI group, 5 in the touch group, and 6 in the massage group, resulting in 12/14, 11/16, and 14/20 subjects completing the study, respectively. Reasons for ITT subjects not completing the study included 11 who were terminated due either to missing appointments, not returning or withdrawing for no stated reason or scheduling conflicts, plus one who had suicidal ideation and another who had an unstable medical condition after beginning the protocol. Recruitment was completed when at least 14 subjects met ITT criteria in each cell. Subjects were not followed after completion of the study. The last observation carried forward (LOCF) method was used for analyses of the ITT group. Since it was expected that some HIV-infected subjects might have abdominal discomfort, massage/touch was performed while subjects lay on their backs. The touch group had a massage therapist place both hands on the subject with slight pressure, but no massage, in a uniform distribution for 1 hour twice per week in the same pattern used for the massage subjects. Subjects were told that for study purposes, verbal communication between them and the therapist should be kept to a minimum and therapists were told to nicely reinforce this condition if needed. One (1) therapist performed more than 90% of the massage/touch procedures, with the secondary therapist substituting for the primary therapist only on rare occasions. No subject had more than two sessions with the secondary therapist. Ratings were performed on the NI group at the same intervals as those receiving massage or touch. The CONSORT Flow Diagram for the study is available as Supplementary material at www.liebertpub.com/acm

Table 1. Baseline Characteristics of the Three Study Groups

	No intervention	*Touch*	*Massage*
Sample sizes	14/12	16/11	20/14
Age	42.6 ± 4.9/43.1 ± 4.7	42.6 ± 5.1/42.6 ± 6.5	42.6 ± 6.5/44.0 ± 5.7
Male	14/12	15/10	17/11
Ethnicity (*n*)			
African American	0/0	4/3	2/2
White	9/8	8/5	9/6
Hispanic	2/2	3/2	3/1
Other	3/2	1/1	6/5
HAM-D	25.6 ± 5.8/26.1 ± 6.1	20.2 ± 3.8*/ 20.6 ± 3.5*	22.6 ± 5.9/22.4 ± 5.8
BDI	23.7 ± 7.8/22.8 ± 6.3	19.2 ± 5.2/18.5 ± 3.8	22.3 ± 9.7/21.2 ± 10.3
CD4+ T-cells/μL	256 ± 236/283 ± 245	289 ± 231/314 ± 229	397 ± 298/382 ± 313
Plasma HIV RNA copies/mL	558 ± 1081/599 ± 1173	35,459 ± 91,476/ 7304 ± 14,536	2491 ± 5338/ 3254 ± 6147
Number of subjects taking antidepressants	5/14 5/12	8/16 6/11	8/20 5/14

Study groups (no intervention [NI], touch, and massage) characterized as intent-to-treat (ITT) and completers; shown as (ITT/completers). For continuous variables, the mean ± standard deviation is shown; *$p \leq 0.05$ compared to NI.
HAM-D, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; HIV, human immunodeficiency virus.

The study was conducted in the Department of Psychiatry and Behavioral Neurosciences at Cedars-Sinai Medical Center, an academic research hospital located in Los Angeles, California. The primary outcome measure was HAM-D score measured at screen, baseline, and at weeks 1, 2, 4, 6, and 8. BDI score was used as a secondary outcome measure. Assessments were performed at the beginning of the week prior to the first massage/touch session of the week. To enhance enrollment and retention, all subjects were offered one additional massage for each week of participation in the study after completion of the controlled portion of the study.

Data were analyzed by two-way analysis of covariance with repeated measures (with baseline score as the covariate). Greenhouse-Geisser correction was performed when Mauchly's sphericity assumption was violated. If there was a group × time interaction ($\alpha \leq 0.05$), *post-hoc* contrasts were performed with one-way analysis of covariance to determine the location of significant differences. Significance levels were corrected for the number of *post-hoc* contrasts performed. Treatment response was defined by a reduction in HAM-D score ≥ 50% between baseline and week 8. Remission was defined as having a HAM-D score of ≤ 6 at the end of the study.

Results

Baseline measures

Baseline characteristics of the 50 ITT and the 37 completers are summarized in Table 1. There were no differences among the treatment groups except that the HAM-D score was lower in the touch versus NI group ($p \leq 0.05$).

Treatment effects

Figure 1 shows the effects of treatment on HAM-D scores over time in ITT (top) and completers (bottom). In ITT, there was an interaction between treatment and HAM-D scores over time ($F_{6,136} = 4.04$, $p \leq 0.002$). Additionally, there was a main effect of treatment ($F_{2,46} = 5.15$, $p \leq 0.01$). *Post-hoc* analyses showed that massage treatment was more effective in reducing HAM-D scores compared to both touch and NI, with the treatment effect emerging by week 4 ($F_{2,46} = 3.71$, $p \leq 0.04$) and maintained through weeks 6 ($F_{2,46} = 5.82$, $p \leq 0.01$) and 8 ($F_{2,46} = 7.76$, $p \leq 0.002$). No difference was found between NI and touch. The same pattern emerged when the analysis was performed in the completers ($F_{8,132} = 3.13$, $p \leq 0.005$). Compared to both other groups, HAM-D scores were significantly reduced in the massage group at week 4 ($F_{2,33} = 3.21$, $p \leq 0.04$), weeks 6 ($F_{2,33} = 4.36$, $p \leq 0.03$) and 8 ($F_{2,33} = 7.22$, $p \leq 0.005$). Similar results were obtained using the self-rated BDI for ITT ($F_{6,138} = 3.33$, $p \leq 0.005$) and for completers ($F_{8,132} = 3.00$, $p \leq 0.005$).

Response and remission (HAM-D)

Table 2 shows mean percent change in HAM-D (as calculated from baseline to week 8), the number and percent of treatment responders, and number and percent of treatment remitters for ITT and completers. For both, the percent reduction in HAM-D was significantly greater in the massage group as compared to both control groups ($p \leq 0.02$). Chi-square analyses indicated that that the number of responders was significantly greater in the massage group than in the two control groups (ITT group: $p \leq 0.05$; and completers: $p \leq 0.01$). There were no significant group differences in the proportion of remitters. As presented in Table 1, approximately 40% of the subjects were on a stable regimen of antidepressants. The percent change in HAM-D for those taking and not taking antidepressants for each group is shown in Table 3. Concurrent antidepressant treatment did not markedly affect the results.

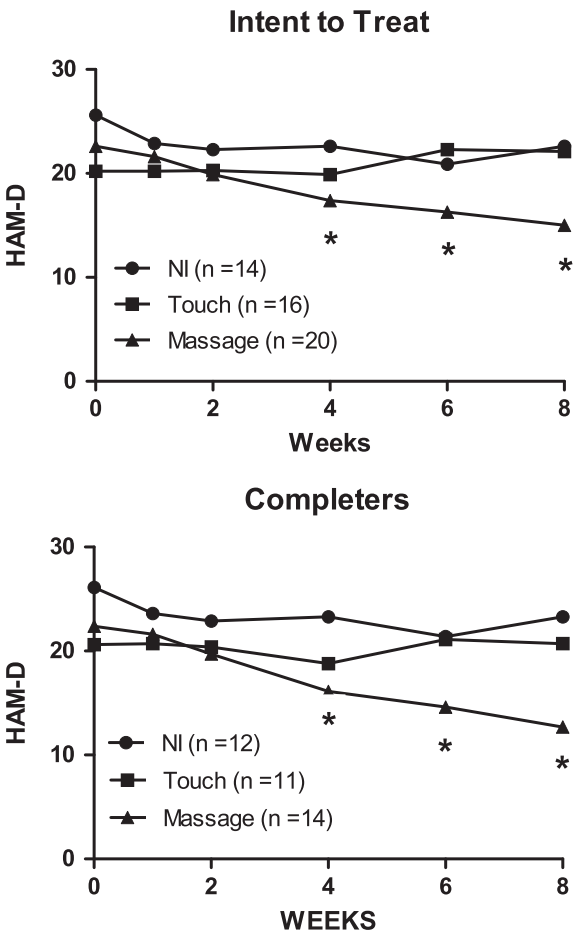

FIG. 1. Hamilton Depression Rating Scale (HAM-D) scores in the three study groups [no intervention (NI), touch, and massage] over the 8 weeks of the study. Intent-to-treat (ITT) subjects are shown in the top graph and completers in the bottom graph. *Asterisks signify location of significant differences. In ITT, HAM-D scores were significantly lower in the massage group at weeks 4, 6, and 8 ($p \leq 0.03$, $p \leq 0.006$, and $p \leq 0.001$, respectively). Similarly, in completers, HAM-D scores were significantly lower in the massage group at weeks 4, 6, and 8 ($p \leq 0.03$, $p \leq 0.02$, and $p \leq 0.003$, respectively). See Results section for further details.

Response (BDI)

The percent change in BDI from baseline to week 8 for the NI, touch, and massage groups was −22.0%, −6.4%, and −31.7% ($F_{2,49} = 3.7$, $p \leq 0.03$), respectively, for the ITT, and, −21.8, −9.7, and −38.6% ($F_{2,36} = 3.4$, $p \leq 0.05$), respectively, for the completers. For the ITT, percent reduction in BDI was significantly greater in massage versus touch ($p \leq 0.01$), but not between NI and massage or NI and touch (both $p \leq 0.2$). For completers, there was a significant difference between touch and massage ($p \leq 0.02$), but not between NI and massage ($p \leq 0.3$) or between NI and touch ($p \leq 0.4$).

Discussion

Major depression and dysthymic disorders are particularly problematic among HIV-infected patients.[9] Although antidepressant therapy has been shown to be at least partially effective in the HIV-infected population, many subjects have a limited response or are refractory to treatment, with some studies showing up to 50% being unresponsive to therapy.[7,11] Moreover, drug therapy in these subjects can result in toxicity and important drug–drug interactions with other medications used to manage HIV or its complications. Because these complications can be particularly troublesome for those in the advanced stages of HIV disease, many individuals are utilizing complementary and alternative medicine (CAM) therapies for a variety of reasons, including the treatment of depression.[21]

This trial showed highly significant improvements in relief of depression in those receiving massage versus touch or NI. In general, there was little difference between the ITT and completer analyses for the NI and touch groups. However, the effect of massage was more robust in the completers. This is not surprising since 5 of the 6 subjects in the massage group dropped out after only 1 week of treatment, and the sixth subject dropped out after 2 weeks of treatment. Since the effects of massage were essentially nil at weeks 1 and 2, their inclusion by the LOCF method in the ITT group weakened the magnitude of effect of massage.

The results from this study are consistent with other studies indicating that Swedish massage might be useful for the treatment of depression in HIV-uninfected individuals.[13–15] However, rigorous trials of many CAM interventions including massage are somewhat limited and difficult to interpret because participants in the study are usually not "blind" to the interventions.[22] Accordingly, we incorporated two control groups into the design of this study, a touch group and an NI group.[16] The touch group was utilized, along with an NI arm, to account for the potential effects associated with human contact independent of massage therapy. Severity of depression was also assessed using two rating scales: the HAM-D (clinician-administered) and the BDI (self-report), and general concordance was found between the results from the two instruments, which further bolstered these findings. When the study was designed, it was hypothesized that the effects of touch would fall in between those produced by NI and massage. However, touch had very little effect over time, particularly in comparison to massage. It has been reported that moderate pressure might be necessary in order to observe meaningful effects of touch or massage.[23] In this study, only minimal (light) pressure was applied in the touch regimen, which could account for its lack of effect on depression scores.

Although subjects received massage for 1 hour twice weekly, the optimal frequency has not yet been defined. Studies in the literature have used daily to weekly massage with evidence of a clinical response.[13–15] Based on the available literature, an intermediate frequency was chosen. An additional rationale for this frequency was that if massage was effective, it might prove more translatable to real-world conditions than daily treatments. The duration of 8 weeks of treatment was selected based upon previous studies that demonstrated a clinical effect in as little as 4 weeks and that pharmacologic studies of depression typically last at least 8 weeks. The results showed that the effects of massage were observed at 4 weeks. However, depression scores in the massage group were on a downward trajectory between weeks 6 and 8, suggesting that further treatment might be even more effective. Extending the massage

Table 2. Comparison of Baseline and Final HAM-D Scores in the Three Study Groups

Treatment	*Baseline HAM-D*	*Week 8 HAM-D*	*% Change HAM-D*	*#/% Responders*	*#/% Remitters*
NI					
ITT ($n=14$)	25.6 ± 5.8	22.6 ± 8.0	−11.7	2/14	0/0
Completers ($n=12$)	26.1 ± 6.1	23.3 ± 7.8	−10.7	1/8.3	0/0
Touch					
ITT ($n=16$)	20.2 ± 3.8[a]	22.1 ± 8.2	9.4	1/6.3	0/0
Completers ($n=11$)	20.6 ± 3.5	20.7 ± 8.0	0.5	1/9.1	0/0
Massage					
ITT ($n=20$)	22.6 ± 5.9	15.0 ± 9.1[b,c]	−33.6[d]	8/40.0[e]	3/15
Completers ($n=14$)	22.4 ± 5.8	12.7 ± 8.9[b,c]	−43.3[d]	8/57.1[f]	3/21.4

Mean (± standard deviation) baseline and week 8 Hamilton Depression Rating Scale (HAM-D) scores, % change in HAM-D (baseline to week 8), number (#) of treatment responders (% change in HAM-D ≥ 50%), number (#) of treatment remitters (week 8 HAM-D ≤ 6) in the intent to treat (ITT) and completer groups.

[a]Compared to No Intervention (NI) at baseline ($p \le 0.03$).

[b]Compared to baseline HAM-D ($p \le 0.01$).

[c]Compared to both NI and touch at week 8 ($p \le 0.02$).

[d]Significantly reduced as compared to NI and touch groups for ITT ($p \le 0.02$) and completers ($p \le 0.01$).

Significantly different compared to NI and touch in both [e]ITT ($p \le 0.04$) and [f]completers ($p \le 0.006$) by χ^2 analysis.

treatments, as well as determining the optimal frequency for the intervention, would be worthwhile explorations.

The response profile in the massage group is not unlike that observed in pharmacologic treatment trials of antidepressants, where it frequently can take weeks before a significant antidepressant effect emerges.[24,25] Thus, it might be inferred that the antidepressant effects of massage might be mediated by mechanisms similar to those of more traditional pharmacologic agents. The profile of response in the massage group also argues against (but does not disprove) a nonspecific or placebo effect. Although subjects were not told that the antidepressant response to massage might take weeks, this is what was observed. Since massage can produce a number of positive subjective effects acutely (e.g., reduced anxiety, peripheral vasodilation, muscle relaxation), one might expect an antidepressant effect earlier, but this did not occur.

There have been a number of studies on the efficacy of antidepressant pharmacologic therapy in subjects with HIV disease.[11] Both tricyclic antidepressants and selective serotonin reuptake inhibitors are efficacious in this population.[7] In general, response rates in this population can range from 43% to 87%. However, these treatments require that patients take additional medications at a time when they are already on many drugs, often resulting in drug–drug interactions[23] and in subsequent development of adverse events.[7] Thus, while pharmacologic treatment for depression in HIV-infected patients is at least partially effective, there remains a need for additional treatment modalities in those who fail to satisfactorily respond, or are intolerant to these medications. In the present study, about half of the subjects showed a response to massage, defined as a reduction in HAM-D ≥ 50%. The data also indicated that concurrent treatment with antidepressants did not significantly alter the response, although there was a trend for the response to touch and massage to be somewhat greater in those subjects on antidepressants. It remains to be determined whether massage actually works better as a first-line treatment to produce sustained remission, or is better utilized as an augmenting agent.

Table 3. Percent Change in HAM-D from Baseline to Week 8 for Those Taking and Those Not Taking AD

Treatment	*ITT*	*Completers*
NI + AD	−10.7%	−10.6%
NI − AD	−12.6%	−10.4%
Touch + AD	+9.4%	+12.4%
Touch − AD	+6.4%	−14.4%
Massage + AD	−36.6%	−47.0%
Massage − AD	−31.6%	−41.0%

Within each group, subjects are divided into those on a stable AD regimen and those not on any AD, and further separated into ITT and completer groups.

HAM-D, Hamilton Depression Rating Scale; AD, antidepressants; ITT, intent-to-treat; NI, nonintervention.

Swedish massage is the most widely practiced type of massage in the United States. Massage has a number of complex physiologic and psychologic effects, not least of which is relaxation of both the musculature and the mind.[12] Although the mechanism(s) of action of massage have not been elucidated, massage therapy is thought to stimulate large nerve fibers, resulting in alterations in the secretion of endorphins, oxytocin, and other hormones.[26,27] Massage also has been shown to enhance parasympathetic and reduce inflammatory activity.[28,29] The use of massage for treatment of depression might be a useful paradigm to study the underlying changes that occur from depression to remission without the added complexity of nonspecific drug effects.

There are some limitations that warrant mention. Most of the subjects in this study were males. There is no *a priori* reason to believe that there would be sex differences in response, as none of the previous studies of massage described females as being less responsive. In the current study, 3 women were randomized to massage, and all 3 showed a marked drop in HAM-D from baseline to week 8. For these women, HAM-D scores were 18, 23, and 19 at baseline, and 4, 9, and 12 at week 8, respectively. In contrast, the 1 female

subject in the touch group showed an increase in HAM-D from 20 at baseline to 33 at week 8. Although this issue needs to be empirically tested, this study's preliminary data suggest that women respond to massage in a fashion comparable to men. This issue deserves further attention, as depression is not only more prevalent in women than men in general, but also within the HIV population. After controlling for clinical status, treatment, and other factors, HIV-infected women with chronic depressive symptoms were twice as likely to die of AIDS as those without such symptoms.[30,31] Some other limitations are the relatively modest sample size and the differences, albeit small, in baseline HAM-D between the NI and touch groups. There was an attempt to control for other extraneous variables that are part of the study procedures (e.g., degree of verbal interaction between the therapist and subject), but such variables are not easily controlled or monitored and could have somehow influenced the results. Finally, since the study required subjects to be able to come to the facility twice a week, it is not clear how selection bias might have impacted the results.

Conclusions

The results suggest a potential benefit of massage for HIV-infected individuals with depression. Whether the effects of massage are generalizable to other types of depression, as well as to non-HIV subjects with depression, remain to be determined.

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Disclosure Statement

Dr. Poland reports that at the time of the study (but not at present) he owned <$5000 in Pfizer stock and had research funding from GlaxoSmithKline. Dr. Gertsik's employer (Parexel International) is a contract research organization focusing on pharmaceutical research consulting, although Dr. Gertsik does not receive any direct support or compensation from any pharmaceutical company. Ms. Smith is the founder of The Heart Touch Project, a nonprofit educational organization dedicated to the training and delivery of compassionate and healing touch to homebound or hospitalized, men, women, and children. Dr. Daar reports receiving research support from Abbott Laboratories, Merck Laboratories, Pfizer, and ViiV and being an advisor or consultant for Bristol Myers Squibb, Gilead Sciences, Pfizer, Merck Laboratories, and Tibotec. All other authors reported no competing financial interests exist.

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