For adult patients suffering from HIV/AIDS is Mindfulness Based Stress Reduction an effective adjuvant treatment option to improve immune function and psychological well-being?

A Review of the Literature

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June 2014
Preface and acknowledgement

This bachelor thesis is the final product of my studies at Fontys University of Applied Sciences, Eindhoven and represents the completion of my bachelor degree in Physiotherapy. Within the last years I have developed a great interest for holistic approaches, which lay in opposition to the modern medical model where the human body is seen as a collection of pieces, which are mostly analysed in isolation. Holistic medicine is known as an approach to life and health, which brings together the physical, mental and spiritual aspects of a person in order to create a total sense of well-being. Writing this paper gave me the opportunity to not only increase my knowledge about mind-body therapies but it also provided the chance to research a topic that will be gaining more and more public interest in future years due to the increasing development of lifestyle diseases such as HIV in western countries.

I would like to thank everybody who helped in the completion of this paper. I would like to express special thanks to my supervisor Anke Lahaie for her time, guidance and valuable tips throughout the last months as well as Tim van der Stam for his help with the topic preposition and my friends for their effort.

Thank you to my family and friends for being helpful and encouraging especially in moments of doubt. I would like to express my upmost gratitude and respect to my parents for their emotional and financial support, for their generosity and for making this enriching educational experience abroad possible. Without them my personal and education development would not have been the possible.

Valentine Senoner

Eindhoven, June 2014
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Acronyms and abbreviations

<table>
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<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral Therapy</td>
</tr>
<tr>
<td>CCT</td>
<td>Clinical Controlled Trial</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HPA</td>
<td>Hypothalamic-Pituitary-Adrenal</td>
</tr>
<tr>
<td>IES</td>
<td>Impact of Event Scale</td>
</tr>
<tr>
<td>M</td>
<td>Mean</td>
</tr>
<tr>
<td>MBSR</td>
<td>Mindfulness Based Stress Reduction</td>
</tr>
<tr>
<td>N</td>
<td>Number</td>
</tr>
<tr>
<td>NA</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>NK</td>
<td>Natural Killer Cell</td>
</tr>
<tr>
<td>NS</td>
<td>Not Significant</td>
</tr>
<tr>
<td>PANAS</td>
<td>Positive and Negative Affect Schedule</td>
</tr>
<tr>
<td>POMS</td>
<td>Profile of Mood State</td>
</tr>
<tr>
<td>PSS</td>
<td>Perceived Stress Scale</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>SCL-90R</td>
<td>Symptom Checklist-90-Revised</td>
</tr>
</tbody>
</table>
Abstract

Objective: Mindfulness Based Stress reduction has shown to provide benefits to patients suffering from chronic diseases. Since literature about its effects on HIV/AIDS patients is limited, the objective of the present review is to investigate whether Mindfulness Based Stress Reduction is an effective adjuvant treatment option to improve indices of immune function (CD4 and NK count) and psychological well-being of HIV/AIDS patients by summarizing the current literature on the topic.

Method: The electronic databases PubMed, the Cochrane Library and Medline were systematically searched for randomized controlled trials and clinical controlled trials. The included literature addressing the effects of Mindfulness Based Stress Reduction on immune function and psychological well-being underwent a methodological quality assessment by means of the PEDro scale. Moreover, a best evidence synthesis was performed in order to evaluate the evidence on the present topic.

Results: The search revealed three randomized controlled trials and one clinical controlled trial of good and fair quality. Two trials address the effects of Mindfulness Based Stress Reduction on immune function and on psychological well-being, while the remaining two analyse either the effects on immune function or on psychological well-being only. Outcomes reveal strong evidence for the effectiveness of Mindfulness Based Stress Reduction in the improvement of immune function and limited evidence for its effects on the enhancement of psychological well-being of HIV/AIDS patients.

Conclusion: There are promising results about the effects of Mindfulness Based Stress Reduction on immune function in HIV/AIDS patients. However, further and more extensive research is required to analyse its beneficial outcomes on psychological well-being and to substantiate the current findings.

Keywords: Mindfulness Based Stress Reduction, MBSR, Human Immunodeficiency Virus, HIV, Acquired Immunodeficiency Syndrome, AIDS, Stress, Tension, Pressure, Immune system, Immune function, CD4, Natural Killer Cell, NK, Psychological, Mental, Emotional
Introduction

Background information

Research in the field of psychoneuroimmunology has revealed an existing correlation between stress and immune function and claims that an exposure to stress affects the replication of the human immunodeficiency virus (HIV) and consequently its progression to the acquired immune deficiency syndrome (AIDS).\(^1\)

The human immunodeficiency virus is one of the world’s leading infectious diseases, which has claimed more than 25 million deaths in the last 30 years.\(^2\) Although it is largely widespread in African countries where two thirds of all HIV-infected individuals live,\(^2\) more and more people in the western world are yearly infected and faced with a disease that will lastly cost their lives. The human immunodeficiency virus is a retrovirus, which affects the cells of the immune system causing its gradual degradation. The progression of HIV leads to an immune deficiency which implies that the human body is no longer able to fight diseases leaving it susceptible to life threatening infections and cancer.\(^3,4\)

According to information provided by the World Health Organization 35.3 million people were suffering from HIV worldwide in 2012 and alone that year 2.3 million individuals got newly infected.\(^4\) The human immunodeficiency virus is found in all body fluids including blood, saliva, nervous system fluid, breast milk and semen. However, the virus is only transmitted by blood, semen and breast milk through various ways including sexual transmission through oral, vaginal and anal sex, sharing of needles of infected individuals and through contaminated blood transfusions. Moreover, an infected mother can transmit the virus to the unborn child through pregnancy or by breastfeeding the new-born. Although there is no cure to this disease, the use of antiretroviral medication makes up a highly important part of HIV/AIDS management. The medication slows down the progression of the virus allowing the individuals to maintain a good state of health for extended periods.\(^3\)

Adults who receive an unexpected diagnosis of HIV may be exposed to high levels of emotional and psychological stress which might evoke feelings of helplessness, depression and hopelessness.\(^5\) Previous research in psychoneuroimmunology has found that psychosocial tension stimulates the endocrine system and causes an increased secretion of stress hormones which alter the function of the immune system affecting a person’s susceptibility to infections and other diseases as well as the progression of the human immunodeficiency virus.\(^5,6,7,8\)

Within the last few decades an increasing interest towards complementary treatments including mind-body therapies for the management of physical and psychological disorders has arisen in western health care. Mindfulness Based Stress Reduction (MBSR) is one of
many mind-body stress management therapies, which has gained a lot of attention since its development. MBSR is a structured program developed by John Kabat-Zinn in 1979 which helps individuals to improve their coping mechanism against stress by focusing on emotions, thoughts and sensations of the present moment through meditation and relaxation aiming at cultivating mindfulness. The eight-week MBSR program focuses on various exercises including breathing, body scan, hatha yoga and sitting meditation each learnt throughout the weeks and gradually combined. Moreover, the patients are required to practice the learnt skills at home daily in forty-five to one-hour sessions six times a week by means of a CD and a book.\(^9\)

In recent years various investigations have found promising results of MBSR practice on psychological aspects such as mood, quality of sleep and health related quality of life as well as physical aspects such as an increase in the number of lymphocytes and therefore a stronger immune system in patients suffering from cancer, fibromyalgia and other chronic illnesses.\(^{10,11,12,13}\)

According to SeyedAlinaghi et al.\(^6\) a HIV patient’s exposure to stress can be linked to alterations in the hypothalamic-pituitary-adrenocortical axis and sympathetic-adrenal-medullary immune mechanisms which are associated with a decreased antiviral defence and an increased HIV replication due to a reduction in the number of immune cells. This implies that psychological stress is a relevant factor, which requires great attention in the treatment of HIV/AIDS positive patients.

The aforementioned statement leads to the hypothesis that the performance of MBSR can strongly reduce the feeling of stress and emotional dissatisfaction and cause an improvement of the immune function by an increased replication of lymphocytes in HIV/AIDS patients. If a positive correlation between MBSR and immune function can be found, it may potentially imply that practicing MBSR can improve the coping mechanisms with stress factors and strengthen the immune system. Furthermore, if the intervention shows favourable effects it may provide a new and cost effective adjuvant treatment method to the conventional therapy often consisting of antiretroviral medication and psychological counselling in HIV/AIDS patients as well as a potential physiotherapeutic intervention for patients suffering from chronic illnesses.

Due to growing interest in MBSR and its proven effects in chronic illness such as cancer and fibromyalgia\(^{10,11}\) the objective of this paper is to summarize studies which investigate the effects of MBSR on the immune system and on psychological factors in HIV/AIDS patients and draw a conclusion on the current body of evidence.
Research question
For adult patients suffering from HIV/AIDS is Mindfulness Based Stress Reduction an effective adjuvant treatment option to improve immune function and psychological well-being?

Method

Search strategy
This review is based on a systematic literature search of the electronic databases PubMed, the Cochrane Library and Medline performed between the 1st of January and the 9th of April 2014 to identify studies analysing the effects of Mindfulness Based Stress Reduction on immune function and psychological well-being in HIV/AIDS patients.

A combination of the terms described in Table 1 and the use of Booleans (AND, OR) was applied to identify relevant studies. Moreover, reference lists of included articles were manually searched for additional literature. Figure 1 illustrates the adapted search string.

Table 1. Keywords, abbreviations and synonyms used in the search process

<table>
<thead>
<tr>
<th>Keyword</th>
<th>Abbreviation</th>
<th>Synonym / Associated term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mindfulness Based Stress Reduction</td>
<td>MBSR</td>
<td></td>
</tr>
<tr>
<td>Human Immunodeficiency Virus</td>
<td>HIV</td>
<td></td>
</tr>
<tr>
<td>Acquired Human Immunodeficiency Syndrome</td>
<td>AIDS</td>
<td></td>
</tr>
<tr>
<td>Stress</td>
<td></td>
<td>Tension</td>
</tr>
<tr>
<td>Immune system</td>
<td></td>
<td>Immune function</td>
</tr>
<tr>
<td>CD4</td>
<td></td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Natural Killer Cell</td>
<td>NK</td>
<td>Mental</td>
</tr>
<tr>
<td>Psychological</td>
<td></td>
<td>Emotional</td>
</tr>
</tbody>
</table>

Table 2. Search string adapted for search process

("Mindfulness Based Stress Reduction" OR "MBSR") AND ("HIV" OR "Human Immunodeficiency Virus" OR "AIDS" OR "Acquired Immunodeficiency Syndrome") AND ("Psychological" OR "Mental" OR "Emotional" OR "Immune function" OR "Immune system" OR "CD4" OR "Lymphocytes" OR "NK" OR "Natural Killer Cell" OR "Stress" OR "Tension" OR "Pressure")
Selection process

In order to obtain the latest evidence on the subject the present paper relies on randomized controlled trials and clinical controlled trials published between 2003-2013 written in the English language. Furthermore, studies were only included if full texts were available. The initial search was limited to randomized controlled trials only, since they are accepted as the gold standard delivering the highest evidence. However, due to the fact that only very few randomized trials have been performed on the current subject the search was extended to also include clinical controlled trials.

The selection process consisted of various phases and was initiated by screening the titles for keywords and relevancy. Subsequently, potentially relevant studies were analysed more closely by reading their abstracts and identifying the previously determined inclusion criteria. Accordingly, studies were only included if the trials were performed on adult subjects (>18 years) who suffered from HIV/AIDS and if the intervention consisted of a Mindfulness Based Stress Reduction program. Furthermore, for a study to be included pre- and post-intervention values for lymphocyte count had to be presented. Studies addressing the effects of other forms of meditation such as Mindfulness-Based Cognitive Therapy, Mantra, Zen or Qigong or the effects of Mindfulness Based Stress Reduction on pathologies other than HIV/AIDS were excluded. If studies did not meet the set inclusion and exclusion criteria, they were not considered eligible for full-text analysis. The selection process was concluded by screening reference lists of included articles for further relevant studies.

Outcome measures

For the present study the effects of MBSR on pre- and post-intervention lymphocyte counts (CD4 and natural killer cells) as well as psychological well-being were analyzed. Due to its multi-dimensional construct, in the current paper the term psychological well-being indicates a person’s state of mind dependent on various factors including perceived stress levels, levels of anxiety, depression and mood experienced through a diagnosis of HIV/AIDS and its related psychosocial tension which were measured by means of various questionnaires.

Methodological quality assessment

The reviewed literature, which was included based on inclusion and exclusion criteria underwent a methodological quality assessment in order to evaluate the quality of the studies. The adapted tool was the 11 Item Physiotherapy Evidence Base Database Scale provided by PEDro (Appendix I). The PEDro scale is a measurement tool based on the Delphi list developed by Verhagen et al. The scale was developed to determine the quality of randomized controlled trials but it is also applied in the quality assessment of clinical controlled trials to measure their internal validity (items 2-9) statistical analysis (items 10 and
11) and external validity (item 1). Item one is retained for completion purposes but not used to calculate the final score. Each item is scored with one or zero points based on fulfilling the criteria. A final score between zero and ten can be achieved. According to Eng et al. scores between nine and ten points were considered as 'excellent quality', scores between six and eight were of 'good quality', while studies with scores between four and five points were of 'fair quality'. Scores of four points or lower were classified as 'poor quality'. In order to perform a best evidence synthesis a study was considered of high methodological quality if it reached a score of 6 or higher, while it was classified as a low quality study if it scored 5 points or lower.

Data synthesis

Outcome measurements recorded for the changes in immune function and for the changes in psychological well-being of HIV/AIDS patients after the attendance of a MBSR program were retrieved from each study and depicted by means of detailed tables. Moreover, a brief description of the results was provided. Concluding, a best evidence synthesis was conducted based on study design, significance of results and the information obtained from the PEDro scale, whereas articles with a score of six and higher were considered as high quality literature. Thus, overall findings were evaluated according to the best evidence synthesis by Steultjens et al. as strong evidence, moderate evidence, limited evidence, indicative findings and no or conflicting evidence.

Results

Results search strategy and selection process

Using the adapted search string the search of the databases PubMed, the Cochrane Library and Medline identified 145 potentially relevant articles. Screening of titles resulted in the removal of 123 studies. Nine items were further identified as duplicates and therefore excluded. Subsequently, the abstracts of 13 articles were analysed for inclusion and exclusion criteria. After the removal of studies, which abstracts resulted irrelevant for the present review, six studies were considered eligible for full text analysis. Screening the reference list of so far eligible articles resulted in the addition of three items. After a full text analysis of so far eligible articles and an abstract screening of the added literature, five of the articles were excluded because they did not meet requirements set in the inclusion criteria or the exact topic of interest. Eventually, four studies were included in the present review. Figure 2 illustrates the search strategy applied.
Results data extraction

Design

The present study includes three randomized controlled trials\(^6,18,19\) and one clinical controlled trial\(^7\) which were published between 2003 and 2012. Of the included studies two studies examine the effects of MBSR on immune function and on psychological well-being,\(^6,7\) while the remaining two studies analyse the effects of MBSR on psychological well-being\(^18\) or on immune function\(^19\) only.
**Population**

A total of 370 HIV positive patients were included in the studies ranging from 56 to 173 participants per study at baseline. Of the 370 patients 310 were male (83.8%) and only 60 were female (16.2%). The average age of all participants ranged from 35.1 to 44.0 with a mean of 39.9 years. On average the patients were living with HIV since 9.6 years. Moreover, only the participants of two studies were receiving antiretroviral therapy at the time of the intervention period. Table 3 provides a detailed depiction of mean values of the population characteristics.

**Table 3. Population characteristics**

<table>
<thead>
<tr>
<th>Author</th>
<th>Gender</th>
<th>Mean age (years)</th>
<th>Time living with HIV (years)</th>
<th>Use of ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>SeyedAlinaghi et al. (2012)</td>
<td>Male 118, Female 53</td>
<td>35.1</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Robinson et al. (2003)</td>
<td>Male 32, Female 2</td>
<td>39.5</td>
<td>7.8</td>
<td>Yes</td>
</tr>
<tr>
<td>Creswell et al. (2009)</td>
<td>Male 43, Female 5</td>
<td>41.0</td>
<td>10.0</td>
<td>Yes (n=13)</td>
</tr>
<tr>
<td>Gayner et al. (2011)</td>
<td>Male 117, Female 0</td>
<td>44.0</td>
<td>11.0</td>
<td>NR</td>
</tr>
</tbody>
</table>

* numbers refer to individuals who concluded the study

**Intervention and control group**

MBSR represents the intervention of interest. All studies report adherence to the eight-week program principles set by John Kabat-Zinn in his publication *Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain and Illness*. The intervention consisted of weekly sessions, a day-long retreat in the seventh week, and daily home mindfulness meditation practice. The intervention principles comprised the following components: body scan exercises, yoga exercises, sitting meditation as well as other approaches to cultivate mindfulness in everyday living. All MBSR classes were delivered by trained individuals. The control intervention varied in each study from education and support condition to assessment only, treatment as usual and a one-day stress reduction education seminar. A brief overview of study characteristics is provided in Table 4.
Table 4. Study characteristic

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Study sample (MBSR/C)</th>
<th>Intervention</th>
<th>Variables immune function</th>
<th>Variables psychological well-being</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SeyyedAlinaghi et al. (2012)</td>
<td>RCT</td>
<td>173 (87/86)</td>
<td>MBSR</td>
<td>CD4 count</td>
<td>SCL-90R</td>
<td>3,6,9,12</td>
</tr>
<tr>
<td>Robinson et al. (2003)</td>
<td>CCT</td>
<td>56 (46/10)</td>
<td>MBSR</td>
<td>NK no. NK activity</td>
<td>PSS POMS</td>
<td>No</td>
</tr>
<tr>
<td>Creswell et al. (2009)</td>
<td>RCT</td>
<td>67 (41/27)</td>
<td>MBSR</td>
<td>CD4 count</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>Gayner et al. (2011)</td>
<td>RCT</td>
<td>117 (78/39)</td>
<td>MBSR</td>
<td>NA</td>
<td>IES intrusion IES avoidance PANAS Pos. affect PANAS Neg. affect HADS depression HADS anxiety</td>
<td>6</td>
</tr>
</tbody>
</table>

MBSR: Mindfulness Based Stress Reduction; C= control group; RCT= randomized controlled trial; CCT= clinical controlled trial; NK= natural killer cell; NA= not applicable; SCL-90= Symptom Checklist-90-Revised; IES= Impact of Event Scale; PANAS= Positive and Negative Affect Schedule; HADS= Hospital Anxiety and Depression Scale; PSS= Perceived Stress Scale; POMS= Profile of Mood States

* study sample refers to number of individuals at baseline assessment

Outcome measures

Two studies\(^6,19\) analysed the improvements of immune function by means of CD4 lymphocyte counts measured at pre- and post-intervention, while one study\(^7\) measured the effects of MBSR on immune function evaluating the number and activity of natural killer cells also at pre- and post-intervention.

Psychological well-being was measured on the basis of various questionnaires. Accordingly, authors applied the Symptom Checklist-90-Revised,\(^6\) the Perceived Stress Scale and the Profile of Mood States,\(^7\) as well as the Impact of Event Scale, the Positive and Negative Affect Schedule and the Hospital Anxiety and Depression Scale.\(^18\)

Results methodological quality assessment

Conducting the methodological quality assessment reveals that three articles\(^6,18,19\) are of high quality scoring six to seven points out of ten and one article\(^7\) is of low quality scoring four
points. Accordingly, the clinical controlled trial\(^7\) does not meet the scores set for randomization and concealed allocation as well as blinding and intent-to-treat analysis was not provided and consequently only scores four points. Due to small sample sizes and a relatively high dropout rate outcomes for more than 85% of individuals initially allocated to groups was only measured in one study.\(^6\) Baseline measurements do not show significant differences between groups which could have affected the later obtained outcome measurements. Statistical comparison as well as point measures and measures of variability for outcome measurements were described in all studies.

Table 5. Methodological quality assessment according to PEDro

<table>
<thead>
<tr>
<th>PEDro Item</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>Total</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SeyedAlinaghi et al. (2012)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>6 /10</td>
<td>High</td>
</tr>
<tr>
<td>Robinson et al. (2003)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4/10</td>
<td>Low</td>
</tr>
<tr>
<td>Creswell et al. (2009)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7/10</td>
<td>High</td>
</tr>
<tr>
<td>Gayner et al. (2011)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6 /10</td>
<td>High</td>
</tr>
</tbody>
</table>

*this item is not included in the calculation of the final score

Data summary and best evidence synthesis

**Immune function**

All three studies, which report outcome measurements for immune function, show an increase in outcome variables. SeyedAlinaghi et al.\(^6\), Creswell et al.\(^19\) and Robinson et al.\(^7\) provide a statistical significant difference from baseline to post-intervention values in the intervention group (p<0.001, p=0.02, p=0.05 and p=0.01 respectively), while values for the control group either decreased or remained fairly constant. Moreover, one study\(^6\) provides follow-up data at three, six, nine and twelve months, which reports high significance up to the ninth month follow-up assessment. These significant findings are illustrated in more detail in Table 6.

According to the PEDro scale two studies\(^6,19\) are of high quality and one\(^7\) of low quality. Using a best evidence synthesis shows that there is strong evidence for the effectiveness of MBSR in the improvement of immune function of HIV/AIDS patients.
Table 6. Mean changes and corresponding significance based on baseline and post-intervention measurements for immune function

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Control</th>
<th>Variable</th>
<th>M Δ*</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sayed-Alinaghi et al. (2012)</td>
<td>MBSR</td>
<td>Education and support group</td>
<td>CD4 count</td>
<td>+25.44</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Robinson et al. (2003)</td>
<td>MBSR</td>
<td>Assessment only</td>
<td>NK cells count %</td>
<td>+17.25</td>
<td>p=0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NK cell activity at 20 % lysis</td>
<td></td>
<td>p=0.05</td>
</tr>
<tr>
<td>Creswell et al. (2009)</td>
<td>MBSR</td>
<td>1-day stress reduction education seminar</td>
<td>CD4 count</td>
<td>+10</td>
<td>p=0.02</td>
</tr>
</tbody>
</table>

MBSR= Mindfulness Based Stress Reduction; C= control group; NK= natural killer cell
* M Δ indicates differences measured between pre-test and first post-test assessment

Table 7. Mean changes and corresponding significance based on baseline and post-intervention measurements for psychological well-being

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Control</th>
<th>Variable</th>
<th>M Δ***</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sayed-Alinaghi et al. (2012)</td>
<td>MBSR</td>
<td>Education and support group</td>
<td>SCL-90R*</td>
<td>- 11.86</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Robinson et al. (2003)</td>
<td>MBSR</td>
<td>Assessment only</td>
<td>PSS*</td>
<td>+ 0.12</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POMS*</td>
<td>- 8.66</td>
<td>NS</td>
</tr>
<tr>
<td>Gayner et al. (2011)</td>
<td>MBSR</td>
<td>1-day stress reduction education seminar</td>
<td>IES intrusion*</td>
<td>- 4.7</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IES avoidance*</td>
<td>- 5.8</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PANAS</td>
<td>+ 3.5</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pos. affect*</td>
<td>- 5.7</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neg. affect*</td>
<td>- 1.4</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HADS depression*</td>
<td>- 2.2</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HADS anxiety*</td>
<td>- 1.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

MBSR= Mindfulness Based Stress Reduction; C= control group; SCL-90= Symptom Check List-90-Revised; IES= Impact of Event Scale; PANAS= Positive and Negative Affect Schedule; HADS= Hospital Anxiety and Depression Scale; PSS= Perceived Stress Scale; POMS= Profile of Mood States; NS= not significant
* negative outcome number indicates an improvement
** positive outcome number indicates an improvement
*** M Δ indicates differences measured between pre-test and first post-test assessment
Psychological well-being

As illustrated in Table 7 the study conducted by Robinson et al.\textsuperscript{7} reports no significant differences at post-intervention between the intervention and control group, while the study by Gayner et al.\textsuperscript{18} shows significant findings only in two (p<0.05, p<0.05) out of six recorded items. SeyedAlinaghi et al.\textsuperscript{6} found a significant change (p<0.001) in outcome measures for the improvement of psychological well-being after the attendance of a MBSR program. Two of the above analysed studies\textsuperscript{6,18} result to be of high methodological quality and one\textsuperscript{7} of low quality according to the PEDro scale. Conducting the best evidence synthesis indications are found that the present data is of limited evidence.

Discussion

Based on data provided in randomized controlled trials\textsuperscript{6,18,19} and one clinical controlled trial\textsuperscript{7} of good and fair quality according to the PEDro scale, strong evidence has been found that attendance to an eight-week MBSR program yields significant improvements in the indices of immune function of HIV/AIDS patients measured by means of lymphocyte counts (CD4 and natural killer cell).\textsuperscript{6,7,19} However, only limited evidence could be deduced from self-reported questionnaires for its effectiveness on improving indices of psychological well-being such as levels of anxiety and depression.\textsuperscript{6,7,18}

MBSR is increasingly being used in clinical settings for patients with chronic diseases including infectious and psychological disorders, yielding successful outcomes. However, positive results need to be interpreted with caution since the ability of MBSR to combat diseases is still far from proven.\textsuperscript{9} Nonetheless, a drop in symptoms of psychological dissatisfaction found by SeyedAlinaghi et al.\textsuperscript{6} might indicate a strengthening of well-being. Similarly, the increase of immune cells recorded after the attendance of a MBSR program indicates that a slight improvement in the immune functioning of HIV/AIDS patients can be noted.\textsuperscript{6,7,19} These findings are consistent with those reported by Carlson et al.\textsuperscript{20} and by Witek-Janusek et al.,\textsuperscript{21} who found improved immune patterns in cancer patients up to one year following the attendance of a MBSR program. Since average values of CD4 lymphocytes in healthy individuals amount up to 500 – 1600 cells/mm\textsuperscript{3} and a number below 200 cells/mm\textsuperscript{3} in infected individuals indicates that the virus has progressed to AIDS,\textsuperscript{22} it remains questionable whether an increase of just 25 CD4 lymphocyte cells after the intervention as reported by SeyedAlinaghi et al.\textsuperscript{6} is enough to be considered clinically relevant for the course of HIV progression. Nonetheless, an increase of immune cells can be considered as a corroborative for the initiation of antiretroviral therapy, as a higher number of CD4 lymphocytes at starting point yields better outcomes of antiretroviral therapy in the long run regarding the progression to AIDS and death rates.\textsuperscript{23}
Given the late development of MBSR in 1979 and the increasing trend of mind-body therapies, research on the effects of MBSR on various disorders became more popular only in recent years. The literature search of the present review proves this by identifying only four relevant studies, which address MBSR on HIV/AIDS patients. This leads to the assumption that although positive outcomes are reported, analysing them from a more critical point of view they should be understood as indications and analysed with care.

This particularly applies to the study performed by Robinson et al. Analyzing both outcomes, immune functioning and psychological well-being of HIV/AIDS patients, Robinson et al. found a statistical significant change of immune function characterized by an increase in natural killer cell number and natural killer cell activity by 116% and 110% respectively, yet missing statistically relevant values for indicators of psychological well-being. This pre- to post-test clinical controlled trial, however, is characterized by several pitfalls detected in the way of trial conduction, which also explains the low score achieved on the PEDro scale and the associated fair quality of the study. Accordingly, a rather small sample size of patients (intervention n=46, control n=10), was specifically recruited based on one single inclusion criterion of a self-reported HIV diagnosis and non-randomly allocated to intervention or control group depending on whether subjects were interested or 'not interested in participating in MBSR'. The nature of patient allocation performed in this study leads to a population bias since personal interest and enthusiasm for the intervention increases the likelihood of success in trials. Furthermore, a high drop out rate was reported in the intervention group and values for only 24 subjects could be provided lacking an intent-to-treat analysis. The main reason for stopping the trial was 'a loss of interest in the study or the techniques being learnt,' which indicates that the patient's initial expectations of a MBSR program could not be met. Consequently, although significant results were reported their validity remains questionable.

Although other studies reached a better PEDro score and can therefore be considered to be of good quality, two studies are characterized by small sample sizes and high drop out rates and only one study was able to retrieve results from more than 85% of subjects. The high attrition rate possibly indicates a lack of dedication or time required for daily practice. As compared to pharmacological trials, which mostly require subjects to ingest an oral medication, behavioural interventions such as MBSR are much more sophisticated and need adherence to program requirements. For patients who are already suffering from higher levels of stress making time for daily practice and group meetings by rearranging personal schedules may lead to an additional stress factor and increase levels of stress in the short term explaining high drop out rates and losses for follow up. Moreover, the decision of withdrawal from the intervention can also depend on the quality of the given class. The ability
of the therapist to convey enthusiasm and motivation to patients is one key to successfully complete a behavioural intervention.\textsuperscript{24}

Studies which analysed the effects of MBSR on immune function show common outcome measures all indicating an improvement.\textsuperscript{6,7,19} However, when it comes to analysing the effects of MBSR on psychological well-being of HIV/AIDS patients the results of the present study are limited. For this outcome measure only one study\textsuperscript{6} found significant changes in the recorded variable. Although other studies also provide improvements in psychological well-being no or only limited significance was found.\textsuperscript{7,18} Therefore, findings on this parameter do not fully support previous research performed on cancer patients using the same measurement tools.\textsuperscript{25,26} However, it can be presumed that a change in trial characteristics by implementing a different control intervention could have yielded more significant changes in the study by Gayner et al.\textsuperscript{18} The results show slight improvements in all outcomes but statistically significant changes only in two out of six measured indices. More interestingly, together with the minor changes in the intervention group, which were recorded over time, improvements were also measured in the control group, which received 'treatment as usual'.\textsuperscript{18}(p 272) The study does not report whether subjects were receiving antiretroviral therapy at the time of intervention, but if that was the case a spontaneous improvement of psychological aspects could be associated to a general improvement of one's bodily condition. Yet, taking a closer look at the study design reveals that 'treatment as usual'\textsuperscript{18}(p 272) included psychotherapy or counselling. This control intervention is not ideal in regards of the variable being tested and leads to the assumption that significant outcomes could have been reported if the nature of the intervention applied to the control group did not consist of psychological or social procedures.

Analysing the results of the present study, however, evokes scepticism about the validity of the statement regarding the intimate connection between immune system and psychological well-being which was provided by ample research in the field of mind-body therapy and psychoneuroimmunology (PNI).\textsuperscript{11,20,27} Accordingly, the exposure to stressful events causes alterations in the immune function acting on the hypothalamic-pituitary-adrenal axis (HPA) and thereby influences the severity of infectious diseases.\textsuperscript{8} As a consequence to this stress the HPA provokes the release of stress hormones such as adrenaline, noradrenaline and cortisol which bind to receptors on immune cells causing a modification in their function and an altered immune response associated with a decreased antibody production, decreased macrophages and lymphocytes.\textsuperscript{5,8,28} Since HIV/AIDS is characterized by immune suppression, the previous explanation is particularly important for patients suffering from this disease who are exposed to high levels of stress and negative affect evoked by fears of the future, doubts and regrets of behaviour and actions of the past and the threat of lifelong illness eventually leading to death. One might assume that a damping of stress levels would enhance psychological well-being which in turn allows the immune system to thrive as the
number of stress hormones acting on it will decrease. Although both studies\textsuperscript{6,7} analysing the effects of MBSR on immune function and psychological well-being yielded positive outcomes in the indices of immune function, only one\textsuperscript{6} was able to find improvements of immune function and psychological well-being possibly indicating the close connection of psychological well-being and immune functioning mentioned above. More interestingly, the psychological improvements lasted up to the sixth month post-intervention showing an overlap with the amelioration of immune function, which was recorded up to the ninth month follow-up assessment. However, it remains unclear if the recorded outcomes are due to a causal dose-response relationship or just a random finding. Since declining numbers of CD4 lymphocytes represent an important prognostic indicator for HIV progressions to AIDS as well as a hallmark for the initiation or alteration of antiretroviral therapy\textsuperscript{29,30} the findings of this study\textsuperscript{6} could be of high relevancy indicating that an eight-week MBSR program aids delaying HIV progression and the onset of AIDS. However, more extensive research is required in order to validate this statement.

Consequently, the hypothesis that the performance of MBSR can strongly reduce the feeling of stress and emotional dissatisfaction and cause an improvement of the immune function by an increased replication of lymphocytes in HIV/AIDS patients can only partly be confirmed, since results referring to an enhancement of psychological well-being were equivocal.

Several limitations of the present study need to be acknowledged. The number of relevant trials performed on HIV/AIDS patients is limited. Although added value was given to randomized controlled trials due to their higher quality as compared to clinical controlled trials and their ability to better re-produce results, the author was compelled to include clinical controlled trials in order to draw a more comprehensive conclusion. Moreover, two studies were characterized by small sample sizes and a correspondingly high attrition rate.\textsuperscript{7,19} Additionally, follow up data was only reported in two studies.\textsuperscript{6,19} Since progression of HIV occurs at a slow pace,\textsuperscript{31} studies providing outcome changes over several years might shed some more light on the beneficial effects of MBSR. A further limitation consists in the multi-dimensional construct of the term ‘psychological well-being’. Since the term does not have a specific definition and is characterized by a subjective interpretation, studies analysing symptoms associated to the term were included, despite the fact that different questionnaires were used. This leads to the assumption, that although various aspects of psychological functioning were assessed, an improvement on the measured parameters indicates an enhancement of psychological well-being, yet lacking same outcome measures in all studies. Furthermore, the author came to the conclusion to state the evidence for psychological well-being as limited since one\textsuperscript{18} study failed to show significant findings for at least 50% of measured items. Although previous research has shown that the applied questionnaires have a value of $\alpha > 0.40$ indicating sufficient reliability\textsuperscript{32,33,34,35} one should remain critical in the evaluation of psychological questionnaires, for most because they are self-reported and
results therefore relay on subjective evaluation of patients. Although plenty of research has been performed on the effects of MBSR on various diseases the present paper is the first review addressing the correlation between MBSR and HIV/AIDS and indicates a lack of knowledge and research performed in this field. Consequently, this study offers the most recent data and the associated body of evidence regarding the effects of MBSR on immune function and psychological well-being in HIV/AIDS patients. MBSR is currently gaining popularity and the results obtained in the present and previous studies show that MBSR could play a relevant role also for physio- and psychosomatic therapists and represents a new treatment option for patients suffering from musculoskeletal and chronic disorders as well as from psychosomatic diseases.

Considering the fact that strong evidence has been found for the improvements of immune function following a MBSR program it can be assumed that it represents a successful adjuvant treatment option for HIV/AIDS patients. Although the limited evidence found for its effects on psychological well-being weakens the aforementioned statement it does not make it invalid. Therefore, the implementation of MBSR should be considered in the treatment of HIV/AIDS patients.

To conclude, it is recommended that further research about the effects of MBSR in HIV/AIDS be undertaken. Especially the correlation and a possible overlap of immune function and psychological well-being should be analysed in randomized controlled trials with larger sample sizes and follow-up assessments in order to gain information about the long-term effects of MBSR. Only then a more precise conclusion can be drawn about the effectiveness of MBSR as an adjuvant treatment option in HIV/AIDS patients. Nonetheless it can be stated on this occasion that the so far performed research indicates promising results.

**Conclusion**

Analysing the effects of MBSR on immune function and psychological well-being of HIV/AIDS patients by summarizing the current literature on the present topic revealed that the attendance of an eight-week MBSR program yields significant improvements in the immune function of HIV/AIDS patients. However, the results obtained for psychological well-being resulted to be limited indicating that more research is required in this this field. Yet, the evidence found shows that the implementation of MBSR as an adjuvant treatment option for HIV/AIDS patient could provide a new method to buffer immune cell declines in this particular patient population.
References


PEDro scale

1. eligibility criteria were specified
   no [ ] yes [ ] where:

2. subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)
   no [ ] yes [ ] where:

3. allocation was concealed
   no [ ] yes [ ] where:

4. the groups were similar at baseline regarding the most important prognostic indicators
   no [ ] yes [ ] where:

5. there was blinding of all subjects
   no [ ] yes [ ] where:

6. there was blinding of all therapists who administered the therapy
   no [ ] yes [ ] where:

7. there was blinding of all assessors who measured at least one key outcome
   no [ ] yes [ ] where:

8. measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups
   no [ ] yes [ ] where:

9. all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by “intention to treat”
   no [ ] yes [ ] where:

10. the results of between-group statistical comparisons are reported for at least one key outcome
    no [ ] yes [ ] where:

11. the study provides both point measures and measures of variability for at least one key outcome
    no [ ] yes [ ] where:

The PEDro scale is based on the Delphi list developed by Verhagen and colleagues at the Department of Epidemiology, University of Maastricht (Verhagen AP et al 1998). The Delphi list: a criteria list for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus. Journal of Clinical Epidemiology, 51(12):1235-41. The list is based on "expert consensus" not, for the most part, on empirical data. Two additional items not on the Delphi list (PEDro scale items 8 and 10) have been included in the PEDro scale. As more empirical data comes to hand it may become possible to "weight" scale items so that the PEDro score reflects the importance of individual scale items.

The purpose of the PEDro scale is to help the users of the PEDro database rapidly identify which of the known or suspected randomised clinical trials (ie RCTs or CCTs) archived on the PEDro database are likely to be internally valid (criteria 2-9), and could have sufficient statistical information to make their results interpretable (criteria 10-11). An additional criterion (criterion 1) that relates to the external validity (or “generalisability” or “applicability” of the trial) has been retained so that the Delphi list is complete, but this criterion will not be used to calculate the PEDro score reported on the PEDro web site.

The PEDro scale should not be used as a measure of the “validity” of a study’s conclusions. In particular, we caution users of the PEDro scale that studies which show significant treatment effects and which score highly on the PEDro scale do not necessarily provide evidence that the treatment is clinically useful. Additional considerations include whether the treatment effect was big enough to be clinically worthwhile, whether the positive effects of the treatment outweigh its negative effects, and the cost-effectiveness of the treatment. The scale should not be used to compare the “quality” of trials performed in different areas of therapy, primarily because it is not possible to satisfy all scale items in some areas of physiotherapy practice.
Notes on administration of the PEDro scale:

All criteria **Points are only awarded when a criterion is clearly satisfied.** If on a literal reading of the trial report it is possible that a criterion was not satisfied, a point should not be awarded for that criterion.

**Criterion 1** This criterion is satisfied if the report describes the source of subjects and a list of criteria used to determine who was eligible to participate in the study.

**Criterion 2** A study is considered to have used random allocation if the report states that allocation was random. The precise method of randomisation need not be specified. Procedures such as coin-tossing and dice-rolling should be considered random. Quasi-randomisation allocation procedures such as allocation by hospital record number or birth date, or alternation, do not satisfy this criterion.

**Criterion 3** Concealed allocation means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to. A point is awarded for this criteria, even if it is not stated that allocation was concealed, when the report states that allocation was by sealed opaque envelopes or that allocation involved contacting the holder of the allocation schedule who was “off-site”.

**Criterion 4** At a minimum, in studies of therapeutic interventions, the report must describe at least one measure of the severity of the condition being treated and at least one (different) key outcome measure at baseline. The rater must be satisfied that the groups’ outcomes would not be expected to differ, on the basis of baseline differences in prognostic variables alone, by a clinically significant amount. This criterion is satisfied even if only baseline data of study completers are presented.

**Criteria 4, 7-11** **Key outcomes** are those outcomes which provide the primary measure of the effectiveness (or lack of effectiveness) of the therapy. In most studies, more than one variable is used as an outcome measure.

**Criterion 5-7** Blinding means the person in question (subject, therapist or assessor) did not know which group the subject had been allocated to. In addition, subjects and therapists are only considered to be “blind” if it could be expected that they would have been unable to distinguish between the treatments applied to different groups. In trials in which key outcomes are self-reported (eg, visual analogue scale, pain diary), the assessor is considered to be blind if the subject was blind.

**Criterion 8** This criterion is only satisfied if the report explicitly states **both** the number of subjects initially allocated to groups and the number of subjects from whom key outcome measures were obtained. In trials in which outcomes are measured at several points in time, a key outcome must have been measured in more than 85% of subjects at one of those points in time.

**Criterion 9** An intention to treat analysis means that, where subjects did not receive treatment (or the control condition) as allocated, and where measures of outcomes were available, the analysis was performed as if subjects received the treatment (or control condition) they were allocated to. This criterion is satisfied, even if there is no mention of analysis by intention to treat, if the report explicitly states that all subjects received treatment or control conditions as allocated.

**Criterion 10** A between-group statistical comparison involves statistical comparison of one group with another. Depending on the design of the study, this may involve comparison of two or more treatments, or comparison of treatment with a control condition. The analysis may be a simple comparison of outcomes measured after the treatment was administered, or a comparison of the change in one group with the change in another (when a factorial analysis of variance has been used to analyse the data, the latter is often reported as a group × time interaction). The comparison may be in the form hypothesis testing (which provides a “p” value, describing the probability that the groups differed only by chance) or in the form of an estimate (for example, the mean or median difference, or a difference in proportions, or number needed to treat, or a relative risk or hazard ratio) and its confidence interval.

**Criterion 11** A point measure is a measure of the size of the treatment effect. The treatment effect may be described as a difference in group outcomes, or as the outcome in (each of) all groups. Measures of variability include standard deviations, standard errors, confidence intervals, interquartile ranges (or other quantile ranges), and ranges. Point measures and/or measures of variability may be provided graphically (for example, SDs may be given as error bars in a Figure) as long as it is clear what is being graphed (for example, as long as it is clear whether error bars represent SDs or SEs). Where outcomes are categorical, this criterion is considered to have been met if the number of subjects in each category is given for each group.
Appendix II: Best Evidence Synthesis by Steultjens et al.\textsuperscript{17}

Strong evidence: provided by consistent, statistically significant findings in outcome measures in at least two high quality RCTs*

Moderate evidence: provided by consistent, statistically significant findings in outcome measures in at least one high quality RCT and at least one low quality RCT or high quality CCT*

Limited evidence: provided by statistically significant findings in outcome measures in at least one quality RCT* or:

Indicative findings: provided by consistent, statistically significant findings in outcome and/or process measures in at least one high quality CCT or low quality RCT* (in the absence of high quality RCTs)

*If the number of studies that show evidence is <50\% of the total number of studies found within the same category of methodological quality and study design (RCTs, CCTs, or ODs), we will state no evidence.