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Review Article

A systematic review of the impact of subthalamic nucleus stimulation on the quality of life of patients with Parkinson's disease

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ABSTRACT

The objective of this paper is to systematically and critically review the available literature on the effects of subthalamic nucleus (STN) stimulation on the quality of life (QoL) of patients with Parkinson's disease (PD). A systematic review of the literature published from 1993 to May 2013 was conducted using PubMed, Cochrane Library, MEDLINE, EBSCO host, CINAHL, and CEPS + CETD, in addition to hand searching selected periodicals and checking reference lists. The review included randomized and non-randomized controlled trials, published in English, comparing STN stimulation with the best medical therapy on the QoL of patients with PD. The time over which QoL was evaluated ranged from baseline to 24 months. Two reviewers independently assessed the study quality and the extracted data. Of the over 273 potential studies examined, we identified seven pertinent articles published between 2002 and 2013 involving 1193 participants. Six of the seven studies were randomized controlled trials (RCTs). Almost all reported statistically significant outcomes. All the studies using QoL outcome variables included the Parkinson's Disease Questionnaire-39 (PDQ-39) ($n = 7$) and two also used the Short Form-36 (SF-36) questionnaire ($n = 2$). There was significant improvement in QoL (PDQ-39) up to 6 months following STN-deep brain stimulation (DBS) in three RCTs and in one nonrandomized trial and up to 12, 18, and 24 months postoperatively in one RCT each, compared with no improvement in the medical therapy groups. There was a 22% improvement in the physical summary score on the SF-36 questionnaire versus no change in the drug-only group. The quality of the trials was limited by the potential for bias associated with inadequate concealment, no reported intention-to-treat analysis, and small sample size. Moreover, there were problems in some studies with confounding factors. The main points to emerge from this review of studies on STN-DBS in patients with PD demonstrate an overall positive effect on QoL. Based on these studies, the benefits may last for 2 years. The review clearly highlights the need for well-designed, methodologically standardized outcome measurement research into the effectiveness of STN stimulation in PD.

1. Introduction

Parkinson's disease (PD) is a common progressive bradykinetic disorder that can be accurately diagnosed. It is characterized by severe pars compacta nigral cell loss and accumulation of aggregated alpha-synuclein in specific brain stem, spinal cord, and cortical regions [1]. The crude prevalence rate of PD has been reported to range from 15 to 12,500 per 100,000, and the incidence of PD from 15 to 328 per 100,000, with the disease being less common in Asian countries [2]. There is currently no cure for the disease, but symptoms related to PD can be treated by both medicine and surgery. Since the late 1960s, levodopa and other dopaminergic-based therapies have been the basis of medical treatment for PD. Despite effective control of symptoms, especially in the early stages of the disease, the use of levodopa and other dopaminergic therapies eventually results in motor fluctuations and dyskinesia, side effects that may be equal to or worse in severity than the motor impairment of the disease itself [3]. Given these limitations, surgical therapy has emerged as an additional option for PD treatment and has provided PD patients with improved clinical control of symptoms and/or reduced adverse events.

Conflicts of interest: none.

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Deep brain stimulation (DBS) evolved from experience with thalamotomies for PD in the 1950s and 1960s. Early in surgical therapy, many DBS groups implanted the ventral intermediate (Vim) nucleus of the thalamus target in PD patients. However, this approach gradually fell out of favor with realization that stimulation of the Vim was most effective for upper extremity tremors, with much less measured efficacy for the other cardinal motor features of PD (e.g., bradykinesia and rigidity) [4]. The globus pallidus interna (GPi) emerged in the early 1990s as a potential target for DBS therapy. However, the GPi target was quickly overtaken by the subthalamic nucleus (STN) [5,6], following studies showing that STN lesions were very effective in reducing major motor disturbances in parkinsonian primates [7] and that drastic reduction in medication could be realized in some human cases [8]. At present, STN-DBS is the most common surgical procedure for PD [3].

Because levodopa-responsive parkinsonian symptoms are improved by high-frequency stimulation of the STN [3,9], neurostimulation has become an established treatment for advanced PD with medically intractable fluctuations and dyskinesia. It is typically used after the disease has been present for 11–13 years [10–12] when quality of life (QoL), social adjustment (psychosocial competence) [13], and professional activity are already severely impaired [14].

Several randomized, controlled trials of DBS have confirmed its efficacy [10,11,15,16]. The end points of these trials included QoL, the severity of motor symptoms when the patient was not taking medication, and the number of hours per day spent in the "on" state without dyskinesia. QoL significantly improves in the majority of patients after STN-DBS, but not in all [17]. The reasons for this may be multidimensional, but their identification seems to be important for optimized treatment results [18]. When movement disorders cannot be adequately controlled with available treatments, there may be profoundly detrimental effects on patients' health-related QoL (HRQoL) [19]. Therefore, the focus has shifted to the measurement of patient-based outcomes to assess (1) the impact of the disease and (2) the efficacy of interventions. Moreover, the major patient-based outcome is QoL or HRQoL [20].

Despite a rapid increase in the number of studies on STN-DBS in people with PD, there is some disagreement on the impact of STN stimulation. The New England Journal of Medicine Quality of Life Study revealed improvements in Parkinson's Disease Questionnaire-39 (PDQ-39) scores, including subscales for mobility, activities of daily living (ADLs), emotional well being, stigma and bodily discomfort, after treatment with bilateral STN-DBS [10]. This review seeks to identify studies that provide information about outcomes of STN-DBS in patients with PD, and summarize and compare QoL and other results from these studies with the disease-specific PDQ-39 [21,22].There are two types of HRQoL instruments, namely, generic and disease specific [23]. Generic instruments are multidimensional questionnaires that cover a variety of areas. Therefore, this study used disease-specific and generic instruments as useful tools. They provide more information about the impact of STN stimulation on the QoL of patients with PD.

The aim of this study is to systematically and critically review the available literature on the impact of STN stimulation on QoL outcomes among patients with PD.

2. Materials and methods

2.1. Search methods

A search strategy was developed to identify published studies on the impact of STN stimulation on QoL or HRQoL in patients with PD. An expert panel was established to guide the systematic review process. The search for eligible studies was comprehensive and involved multiple strategies. Data were sought from published studies in English and Chinese language journals. Searches were limited to human-based studies. An initial limited literature search of PubMed was conducted to identify relevant keywords contained in title, abstract, and study descriptions. We used medical subjects headings to select search terms. STN-DBS was first applied for PD in 1993 [24]. Similar strategies were used in searching other bibliographic databases for relevant research articles published between 1993 and May 2013 (Table 1). In addition, we reviewed references from articles identified in the aforementioned searches to include any additional papers related to outcomes of DBS that may have been missed.

Table 1
Electronic databases searched.

Database		Data searched
PubMed	1993 to May 2013	March 2013 to May 2013
Cochrane Library	1993 to May 2013	March 2013 to May 2013
MEDLINE via Ovid online	1993 to May 2013	March 2013 to May 2013
EBSCO host	1993 to May 2013	March 2013 to May 2013
CINAHL	1993 to May 2013	March 2013 to May 2013
CEPS + CETD	1993 to May 2013	March 2013 to May 2013

We used the following terms as keywords: "deep brain stimulation", "subthalamic nucleus stimulation", "neurostimulation", "quality of life", "health-related quality of life", and "Parkinson's disease". The keywords used to search for publications that met the design criteria were "randomized controlled trial/s", "controlled trial/s", "random allocation", "clinical trials", and "random".

The reference lists of all relevant articles were checked. The literature search was carried out on May 31, 2013, and papers were included in the review if retrieved before July 1, 2013.

To identify potentially eligible articles, two reviewers (J.-L.J. and S.-T.T.) screened the titles and abstracts obtained from the electronic search strategy. Retrieved abstracts were further scrutinized to include only studies that had at least 6 months of follow-up time. In addition, authors scanned abstracts to ensure the presence of outcome data, including presurgical and postsurgical QoL or HRQoL scores. If a decision could not be made regarding the eligibility for inclusion, the full text of the article was examined. Full-length articles of all selected abstracts were retrieved and assessed by the same reviewers for the following inclusion criteria.

2.2. Inclusion criteria

2.2.1. Types of studies

The selection criteria were studies restricted to randomized or nonrandomized control trials on the effectiveness of STN-DBS for the treatment of idiopathic PD. Randomized controlled trials (RCTs) provide the best possible evidence on clinical outcomes. If filtering only identified a small number of RCTs, clinical controlled trials could also be included. The use of nonrandomized data required careful consideration of the comparability of the treatment and control groups in those studies. Retrieved abstracts were further scrutinized to include only those studies with at least 6 months of follow-up time.

Excluded from the review were investigations that primarily examined factors that predicted changes in QoL and other systematic reviews relevant to this topic [20,25]. Studies documenting only nonmotor outcomes (e.g., cognitive function) or surgical parameters (e.g., microelectrode recording) were not considered in our review. We also excluded publications if the electrode implantation site was not the STN. Only articles meeting the inclusion criteria were retained for analysis.

2.2.2. Type of participants

Studies on human patients were included, while animal and laboratory studies were excluded. There were a number of animal and laboratory studies in this area, but the generalizability from laboratory animal models to clinical patients is problematic.

2.2.3. Type of intervention

The intervention of interest was STN-DBS can change the QoL in patients with idiopathic PD.

2.2.4. Type of outcome measurement

A generic or disease-specific QoL measure was applied as a primary or secondary variable of interest.

2.3. Critical appraisal

The screening of relevant studies for inclusion was conducted independently by two reviewers using titles, publication years, and abstracts. To assess the quality of the studies, a checklist developed by Melnyk and Fineout-Overholt [26] was used in the critical appraisal of RCTs. A total of seven study elements were critically appraised to determine a study quality score. Each item had a possible score of 0–2 (0 for not done, 1 for unclear, and 2 for done), with possible total scores ranging from 0 to 30. Any study with a quality score below 60% (raw score < 18) of the total possible score was eliminated from this review.

2.4. Data extraction and synthesis

A standardized data-extraction form was developed to obtain key information relevant to the review. The data from each selected study were transferred to a data-extraction sheet. For all the trials, baseline data, study design, statistical analysis, ethics, participants' characteristics, and outcome measures were extracted. To extract relevant data from included studies accurately and without bias, the same reviewers who had previously conducted the study assessment performed the data extraction. Standardized mean differences (for continuous data) and their 95% confidence intervals were calculated for each individual study. For cases in which group data were heterogeneous and not suitable for meta-analysis, a narrative summary was used. Discrepancies in the quality appraisal form and completed data extraction were discussed using *a priori* decision rules to complete the assessment form.

3. Results

3.1. Selection of studies

The number of hits on the aforementioned specified databases using the initial combined search terms "deep brain stimulation or subthalamic nucleus stimulation or neurostimulation and quality of life or health-related quality of life and Parkinson's disease" was as follows: PubMed ($n = 155$), Cochrane Library ($n = 0$), MEDLINE ($n = 85$), EBSCO host ($n = 31$), CINAHL ($n = 2$), CEPS + CETD ($n = 0$). The full texts of the remaining 32 articles were retrieved and assessed for inclusion. One additional study was identified from searches of the reference lists of the retrieved articles. Items were then reviewed to see whether they could be included based on their reporting of a study on an STN-DBS intervention for PD. A total of seven papers remained that met our critical appraisal score between 23 and 28 (Table 2) [10,11,14,15,18,27,28].

3.2. Methodological quality of the research

Included papers were published between 2002 and 2013. There were six published RCTs [10,11,14,15,18,27] and one controlled before and after trial [28]. J.-L.J. and S.-T.T. examined the papers that described nonrandomized, controlled prospective before and after trial approach (e.g., Just and Ostergaard 2002) [28]. All studies compared subthalamic DBS with best medical treatment. In three studies, the intention-to-treat principle, last observation carried forward, and sample-size estimation were applied in the analysis [10,14,15]. The studies originated from six countries, the United Kingdom, France, Germany, Austria, Denmark, and the United States. All seven trials reported that the type of health-care setting in which the study was conducted was a hospital. No studies mentioned allocation concealment, and all but two studies reported that movement-disorder neurologists carried out the outcome measurements [14,15].

3.3. Characteristics of participants and intervention

All seven trials had different numbers of participants ranging from 20 [27] to 366 [11], with a combined total of 1193. The studies compared STN-DBS ($n = 527$) or STN-DBS combined with GPi stimulation ($n = 65$) [11,15] versus medical therapy. The mean age was 59.1 years (range: 52.2–62.4; 71.18% were male) and the mean disease duration was 11.9 years (range: 7.3–16.0) in the studies reporting these variables. Two trials did not have details of the participants' ages or sexes. All 1193 participants in the review had a diagnosis of idiopathic PD. Participants had moderate to severe PD with Hoehn and Yahr (H and Y) [29] staging (range: 2–5). One report [11] included individuals with mild to moderate PD (H and Y ≤ 2) within their sample although these individuals made up less than 10% of the total sample in the study. The time over which QoL was evaluated ranged from baseline to 24 months.

3.4. Outcome measures

The instruments that are used to measure QoL or HRQoL in PD can be classified into two categories, namely, disease-specific and generic measure of health status. The most frequently used disease-specific measure was the PDQ-39, and the Short Form-36 (SF-36) was selected as a generic tool. All the studies using the QoL outcome variables included the PDQ-39 ($n = 7$) and two used the SF-36 questionnaire ($n = 2$) [10,18]. The PDQ-39 is a questionnaire with 39 items covering the following eight discrete dimensions: mobility (10 items), ADLs (6 items), emotional well-being (6 items), stigma (4 items), social support (3 items), cognition (4 items), communication (3 items), and bodily discomfort (3 items). The score for each item ranges from zero (0) to four (4) with *never* = 0; *occasionally* = 1; *sometimes* = 2; *often* = 3; and *always* = 4 (range of scores: 0–156). A higher score signifies a poorer QoL [30]. The SF-36 is a measure of health status consisting of 36 questions with scores in eight domains, namely, physical function (10 items), physical performance (4 items), physical pain (2 items), general health (5 items), vitality (4 items), social function (2 items), emotional performance (3 items), and mental health (5 items). Summary scores for physical and mental function can be calculated, with higher scores representing better health status [31].

3.5. Changes in QoL as measured by the PDQ-39

There was a significant improvement in QoL (PDQ-39) up to 6 months following STN-DBS in three RCTs [10,15,18] and in one nonrandomized trial [28], and up to 12, 18, and 24 months post-operatively in one RCT each [11,14,27], compared with no

Table 2
Details of included studies.

Author/QS/country	Design	Participant	Treatment	Outcome measured	Results
Schuepbach et al (2013) [14] QS = 27/30 Germany and France	1. A randomized, multicenter, parallel-group design. 2. Assessments were scheduled at baseline and at 5, 12, and 24 months.	A total of 251 patients with PD. Neurostimulation plus medical therapy ($n = 124$) versus medical therapy alone ($n = 127$).	STN-DBS plus medical therapy versus medical therapy.	1. PDQ-39	1. For the primary outcome of quality of life, the mean score for the neurostimulation group improved by 7.8 points, and that for the medical-therapy group worsened by 0.2 points (between-group difference in mean change from baseline to 2 years, 8.0 points; $p = 0.002$).
Daniels et al (2011) [18] QS = 25/30 Germany	1. Multicenter randomized, controlled trial. 2. Assessments were scheduled at baseline and at 6 months.	A total of 121 patients with PD. STN-DBS group ($n = 61$). Control group ($n = 60$).	STN-DBS versus best medical treatment.	1. PDQ-39 summary index. 2. PCS of SF-36.	1. PDQ-39 summary index improved after STN-DBS for 57% of the patients. Patients with improvement in QoL showed significantly higher cumulative daily "off" time. 2. The changes in SF-36 PCS are negatively correlated with the UPDRS dyskinesia score at baseline, and therefore, fewer dyskinesia cases are associated with greater QoL improvement.
Williams et al (2010) [11] QS = 27/30 UK	1. Randomized, open-label trial. 2. Assessments were scheduled at baseline and at 12 months.	366 patients from 13 neurosurgical centers in the UK were assigned to the surgery group ($n = 183$) or to the best medical therapy group ($n = 183$).	STN-DBS ($n = 174$) or GPi DBS versus best medical therapy.	1. PDQ-39 summary index.	1. At 1 year, the mean improvement in PDQ-39 summary index score compared with baseline was 5.0 points in the surgery group and 0.3 points in the medical therapy group (difference: −4.7; 95% CI: −7.6 to −1.8; $p = 0.001$).
Weaver et al (2009) [15] QS = 28/30 USA	1. Randomized controlled trial. 2. Assessments were scheduled at baseline and at 6 months.	A total of 255 patients with PD. Bilateral deep brain stimulation of the STN ($n = 60$) or GPi ($n = 61$) versus best medical therapy ($n = 134$).	Bilateral STN or GPi DBS versus best medical therapy.	1. PDQ-39	1. Compared with the best medical therapy group, the DBS group experienced significant improvements in the summary measure of quality of life and on seven of eight PDQ-39 scores ($p < 0.001$).
Schüpbach et al (2007) [27] QS = 25/30 France	1. Prospectively randomized. Matched for age, duration and severity of disease, and impairment in socioprofessional functioning. 2. Assessments were scheduled at baseline and at 18 months.	A total of 20 patients with PD. Patients were assigned to undergo bilateral STN-DBS ($n = 10$) or receive medical treatment ($n = 10$).	Bilateral STN-DBS versus optimized medical treatment.	1. PDQ-39	1. QoL was improved by 24% in surgical and 0% in nonsurgical patients ($p < 0.05$).
Deuschl et al (2006) [10] QS = 25/30 Germany Austria	1. Unblinded trial with a randomized-pairs design. 2. Assessments were scheduled at baseline and at 6 months.	78 pairs of patients ($n = 156$ patients) with PD were assigned to treatment.	Bilateral STN-DBS versus best medical therapy.	1. PDQ-39 summary index. 2. SF-36 physical and mental summary scores.	1. For the neurostimulation group, the PDQ-39 summary index score was 41.8 ± 13.9 at baseline and 31.8 ± 16.3 at 6 months. In the medication group, the PDQ-39 score was 39.6 ± 16 at baseline and 40.2 ± 14.4 at 6 months. The results show an improvement of about 25% in the neurostimulation group compared with almost no change in the medication group. Neurostimulation also resulted in a 22% improvement in the SF-36 physical summary score.
Just and Ostergaard (2002) [28] QS = 23/30 Denmark	1. Nonrandomized, controlled prospective trial. 2. Assessments were scheduled at baseline (T_0), at 3 months (T_3), and at 6 months (T_6).	A total of 24 patients with PD. STN-DBS ($n = 11$) and similar group of patients awaiting surgery ($n = 13$).	STN-DBS versus nonsurgery.	1. PDQ-39	1. For the PDQ-39 scores from T_0 to T_3, the surgery group demonstrated significant improvement for subscales mobility, ADLs, and bodily discomfort, in addition to significant improvement by 14.0 points in the PDQ-39 summary index. From T_0 to T_6, the surgery group improved by 16.1 points. The nonsurgery group demonstrated no significant changes in the PDQ-39 summary index or in any of the subscales from T_0 to T_3 or from T_0 to T_6.

ADLs = activities of daily living; CI = confidence interval; DBS = deep brain stimulation; GPi = globus pallidus interna; PCS = physical composite score; PD = Parkinson's disease; PDQ-39 = Parkinson's Disease Questionnaire-39; QoL = quality of life; QS = quality score; SF-36 = Short Form-36; STN = subthalamic nucleus; UPDRS = Unified Parkinson Disease Rating Scale.

improvement in the medical therapy group. Neurostimulation resulted in improvements of 24–38% in the PDQ-39 subscales for mobility, ADLs, emotional well-being, stigma, and bodily discomfort [10]. Another study showed significant improvements in mobility, ADLs, and bodily discomfort [28].

3.6. Changes in QoL as measured by the SF-36

There was a 22% improvement in the physical summary score of the SF-36 questionnaire versus no change in the drug-only group [10]. Daniels et al (2011) reported that the changes in SF-36 physical composite score were negatively correlated with the Unified Parkinson's Disease Rating Scale dyskinesia score at baseline, and so less severe dyskinesia was associated with greater QoL improvement [18].

4. Discussion

After DBS treatment, patients can expect improvements in QoL. This review confirmed previous uncontrolled studies on QoL after STN-DBS, which consistently reported improvements in the PDQ-39 [19,32].

4.1. Limitations of the review

The systematic search and selection process revealed only seven studies in which these effects were rigorously examined. There was no limitation of language in the search strategy. However, no papers were found in languages other than English. There are, of course, scientific journals in other countries and in other languages to which we have no access or knowledge. Another limitation of this systematic review is that only accepted full-paper studies were reviewed. This decision was made for practical reasons based on the need for detailed, original study data to conduct a systematic review. It is acknowledged that inclusion of these studies may have influenced the findings of this systematic review. In addition, the quality-assessment tool used here was developed by Melnyk and Fineout-Overholt [26]. For RCTs, a large number of appraisal tools exist that have been subject to varying degrees of evaluation. However, how best to distinguish good quality before and after trial studies from poor quality ones is less clear. There is also little information on how best to appraise before and after trial studies.

4.2. Methodological issues

We may have missed some studies as our literature research was restricted to only certain databases. There were a variety of methodological weaknesses in the studies in this review. Common limitations were small sample size and limited information on the setting of the study, and the qualifications and training of the investigators, and a lack of reliability and validity outcome measures. A more general limitation of this approach was seen in two studies that reported only a small sample size, which favored Type-II errors (no rejection of false null hypothesis) although most of the interventions demonstrated a significant effect. The majority of studies provided no information on statistical power or effect size to adequately detect effect outcomes. Only three studies were definitely powered to use QoL as the primary outcome parameter [10,11,14]. Furthermore, the majority of studies did not report the intention-to-treat analysis and/or last observation carried forward analysis. This highlights the need for replication of studies to fully evaluate the effectiveness of STN-DBS.

Although there were problems with the methodological quality, these studies were not necessarily weak. Methodological weaknesses, such as missing details, may be due to the writing process. However, the format of reporting and lack of details can result in a lack of clarity.

4.3. Influences of STN-DBS on QoL

Previous reviews have shown that the effects of DBS on HRQoL correlate with improvement in motor complications, although psychological aspects may also play a role [19]. The good response of subthalamic DBS on the PDQ-39 summary index was also confirmed by another review [3]. A meta-analysis of PDQ-39 summary index scores showed that the results of the trials are generally consistent with each other (test for heterogeneity, $p = 0.2$), although there is evidence of heterogeneity of the treatment effect between the trials with 6 months of follow-up and those with 12 months of follow-up (test for interaction, $p = 0.04$) [11]. It is worth considering the potential alternative explanations based on differences in the trial designs. It is possible that there is a large immediate effect of surgery, whether real or, in part, related to an early so-called honeymoon effect [33]. If the benefits of surgery are relatively transient, its long-term value could be called into question [11].

Effective treatment is and will continue to be of major importance in the rapidly enlarging global population with PD. Therefore, what can be concluded in terms of clinical practice? Clearly, motor and nonmotor symptom controls are important to enhance QoL. Although most studies have concluded that DBS is a safe procedure, the risk of procedure-related complications is not negligible. There was one procedure-related death [11]. One study also found a small negative effect of DBS on some aspects of cognitive function and verbal fluency [15]. Gronchi-Perrin et al [34] found that, on average, patients perceived their postoperative ability to communicate to have worsened and their performance on ADLs to have remained unchanged. The clinical significance of these effects remains to be explored. In the absence of information from RCTs with a longer duration of follow-up, expert centers could provide valuable observational data on the frequency and clinical significance of adverse outcomes following DBS.

5. Conclusion

The main point to emerge from this review is that these studies on STN-DBS in patients with PD demonstrate an overall positive effect on QoL. Based on these studies, the benefits may last for 2 years. Nevertheless, a few studies had small samples, and one was not an RCT. Furthermore, this type of investigation might be fraught with the problem of confounding variables.

5.1. Implications for research

This review clearly demonstrates the need for further investigation. First, research needs to use standardized interventions and outcome measures, including analysis of patient-relevant outcomes such as motor function, disease severity, adverse events, and cost effectiveness. Second, qualitative data on patient expectations, and subjective experiences would reveal additional dimensions that can be tested in rigorous intervention studies. Such studies could clarify the types of impacts on patients living with PD and changes between presurgery and postsurgery. This should be included in all PD treatment protocols. Third, QoL depends on the severity of the disease, disability, severity of dyskinesia, depression, pain, and some other factors [35]. As we begin to explore the value of treatment interventions and try to draw conclusions on its efficacy, more research will be needed on the factors affecting outcomes in intervention trials. Finally, all of the studies in this review were conducted in Western countries. Therefore, there is a distinct need

to conduct quality clinical studies in health-care environments in Eastern countries.

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