Tzu Chi Medical Journal 27 (2015) 145–154

Contents lists available at ScienceDirect

Tzu Chi Medical Journal

journal homepage: www.tzuchimedjnl.com

Review Article

Effects of subthalamic nucleus deep brain stimulation on quality of life and motor and depressive symptoms in Parkinson's disease

Jiin-Ling Jiang [a], Sheng-Tzung Tsai [b, c], Shin-Yuan Chen [b, c, *]

[a] Department of Nursing, Tzu Chi University, Hualien, Taiwan
[b] Department of Neurosurgery, Buddhist Tzu Chi General Hospital, Hualien, Taiwan
[c] Department of Medicine, Tzu Chi University, Hualien, Taiwan

ARTICLE INFO

Article history:
Received 26 August 2015
Received in revised form
15 September 2015
Accepted 27 October 2015
Available online 9 December 2015

Keywords:
Parkinson's disease
Quality of life
Subthalamic nucleus stimulation
Symptoms

ABSTRACT

The objective of this paper is to review the available literature concerning the effects of subthalamic nucleus deep brain stimulation (STN-DBS) on quality of life (QoL) and motor and depressive symptoms in patients with Parkinson's disease (PD). These studies demonstrate that STN-DBS has an effect on QoL and symptoms in patients with PD. There was a significant improvement in QoL following STN-DBS compared with no improvement after medical therapy. PD patients treated with STN-DBS had a 40–50% improvement in motor function. Nevertheless, depressive symptoms did not reveal consistent change.

1. Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disease that places a substantial burden on patients and their families and caregivers, as well as society. It is characterized by muscle rigidity, resting tremor, bradykinesia, and postural instability [1]. Although optimal pharmacological therapy with levodopa and other adjuvant regimens can be achieved, complications associated with the treatment of PD, such as dyskinesia and motor fluctuation, inevitably occur around 5 years after the initiation of therapy [2–4]. The progressive decline in motor function and the comorbidity associated with PD negatively affect quality of life (QoL) [5]. Depression is one of the most common psychiatric disorders in PD [6], with 35% of patients reporting some level of depressive symptoms, including 17% with major depressive disorders and 22% with minor depression [7]. Depressive symptoms have been recognized as a major contributor to poor QoL, poor motor and cognitive function, and caregiver burden [8].

Subthalamic nucleus deep brain stimulation (STN-DBS) therapy has emerged as an additional option for PD treatment and provides PD patients with improved QoL and control of motor symptoms. Although the precise mechanism by which deep brain stimulation (DBS) exerts benefits is still elusive, increasing evidence suggests that it might involve multidisciplinary effects on the target where afferent nerves are stimulated and neurotransmitters are released [9,10]. Despite a rapid increase in the number of studies of STN-DBS in patients with PD, there is still some disagreement on its impact.

Clinical evaluation of PD is usually carried out by assessing a variety of functional and mental aspects in addition to data gathered from medical examinations. The Core Assessment Program for Surgical Intracerebral Therapies protocol [11] recommends assessment of QoL using an instrument such as a rating scale before starting the preoperative evaluation and, thereafter, at 6 months, 1 year, and 2 years, and then every year if evaluation is continued. Comparison of pre- and postoperative findings is important in this group of STN-DBS patients. This review seeks to identify studies that provide information regarding outcomes of STN-DBS in patients with PD, and summarize and compare changes in QoL and motor and depressive symptoms from these studies.

Conflict of interest: none.

* Corresponding author. Department of Neurosurgery, Buddihist Tzu Chi General Hospital, 707, Section 3, Chung-Yang Road, Hualien, Taiwan. Tel.: +886 3 8561825x2151; fax: +886 3 8463164.
E-mail address: willam.sychen@msa.hinet.net (S.-Y. Chen).

http://dx.doi.org/10.1016/j.tcmj.2015.10.001

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 in patients with PD. An expert panel was established to guide the review process. The search for eligible studies was comprehensive and involved multiple strategies. Data were sought from published studies in English language journals. Searches were limited to human-based studies. An initial limited literature search of PubMed was conducted to identify relevant keywords contained in the title, abstract, and subject descriptions. We used Medical Subjects Headings to select search terms. STN-DBS was first applied for PD in 1993 [12]. Similar strategies were used in searching other bibliographic databases (Table 1) for relevant research articles published between 1993 and 2014. 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.

We used the following terms as keywords: *deep brain stimulation*, *subthalamic nucleus stimulation*, *neurostimulation*, *quality of life*, *health-related quality of life*, *motor symptom*, *nonmotor symptom*, *psychiatric symptom*, *mood*, and *Parkinson's disease*. The key words used to search for publications that met the design criteria were *randomized controlled trial/s*, *controlled trial/s*, *random allocation*, and *clinical trials*. Figure 1 shows the flow of information through the different phases.

To identify potentially eligible articles, two authors (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 those studies that had at least 6 months of follow-up. In addition, authors scanned abstracts to ensure the presence of outcome data, including pre- and postsurgical QoL scores. If a decision could not be made regarding 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 inclusion criteria reported below.

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 treatment of idiopathic Parkinson's disease. 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.

Excluded from the review were investigations that primarily examined factors that predicted changes in QoL and other systematic reviews relevant to this topic [13,14]. Studies documenting only nonmotor outcomes (for example, cognitive function) or surgical parameters (such as microelectrode recording) were not considered in our review. We also excluded studies if the electrode implantation site was not the subthalamic nucleus. Only articles meeting the inclusion criteria were retained for analysis.

Table 1
Electronic databases searched.

Database searched	Publication dates
PubMed	1993–Nov 2014
Cochrane Library	1993–Nov 2014
MEDLINE via Ovid online	1993–Nov 2014
EBSCO host	1993–Nov 2014
CINAHL	1993–Nov 2014
CEPS + CETD	1993–Nov 2014

2.2.2. Participants

Studies of human individuals were included, and 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. Intervention

The intervention of interest was STN-DBS used to change QoL, motor symptoms and psychiatric symptoms in patients with idiopathic PD.

2.2.4. Outcome measurements

2.2.4.1. QoL: Disease-specific 39-item PD questionnaire. The World Health Organization defines QoL as "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" [15]. Several QoL tools have been used in PD. A movement disorder society task force was commissioned to rate the psychometric quality of available QoL scales as applied to PD. Siderowf et al [16] reported that generic instruments may represent relatively lower sensitivity to change as shown by the 36-Item short-form health survey compared with the 39 item Parkinson's disease questionnaire (PDQ-39).The PDQ-39 is the most thoroughly tested and applied questionnaire for PD [17]. It has adequate psychometric properties and adequately covers physical, mental, and social domains. It is composed of 39 items grouped in eight subscales: mobility, activities of daily living (ADL), emotional well-being, stigma, social support, cognition, communication, and bodily discomfort [18].

2.2.4.2. Motor symptoms: unified PD rating scale. PD is characterized by motor symptoms. The unified PD rating scale (UPDRS) is the most commonly used scale in the clinical study of PD.

2.2.4.3. Depressive symptoms: Beck depression inventory. Depression is one of the most common psychiatric disorders in PD. The Beck depression inventory is one of the most widely used instruments for measuring the severity of depression.

3. Results

The database search and reviewed references from included articles yielded 39 citations published between January 1, 1993, and November 30, 2014. Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Twenty-eight studies met the inclusion criteria. Eight studies reported on QoL, 12 on motor symptoms, and eight on depressive symptoms in patients with PD after STN-DBS surgery.

3.1. STN-DBS effects on QoL

Kuehler et al [19] suggested that there is a need to determine whether such a sophisticated and costly treatment is not only safe and effective, but also whether it enhances QoL. Several RCTs of DBS have confirmed its efficacy [20–23]. The end points of these trials included QoL, mood, or 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. Six RCTs (1184

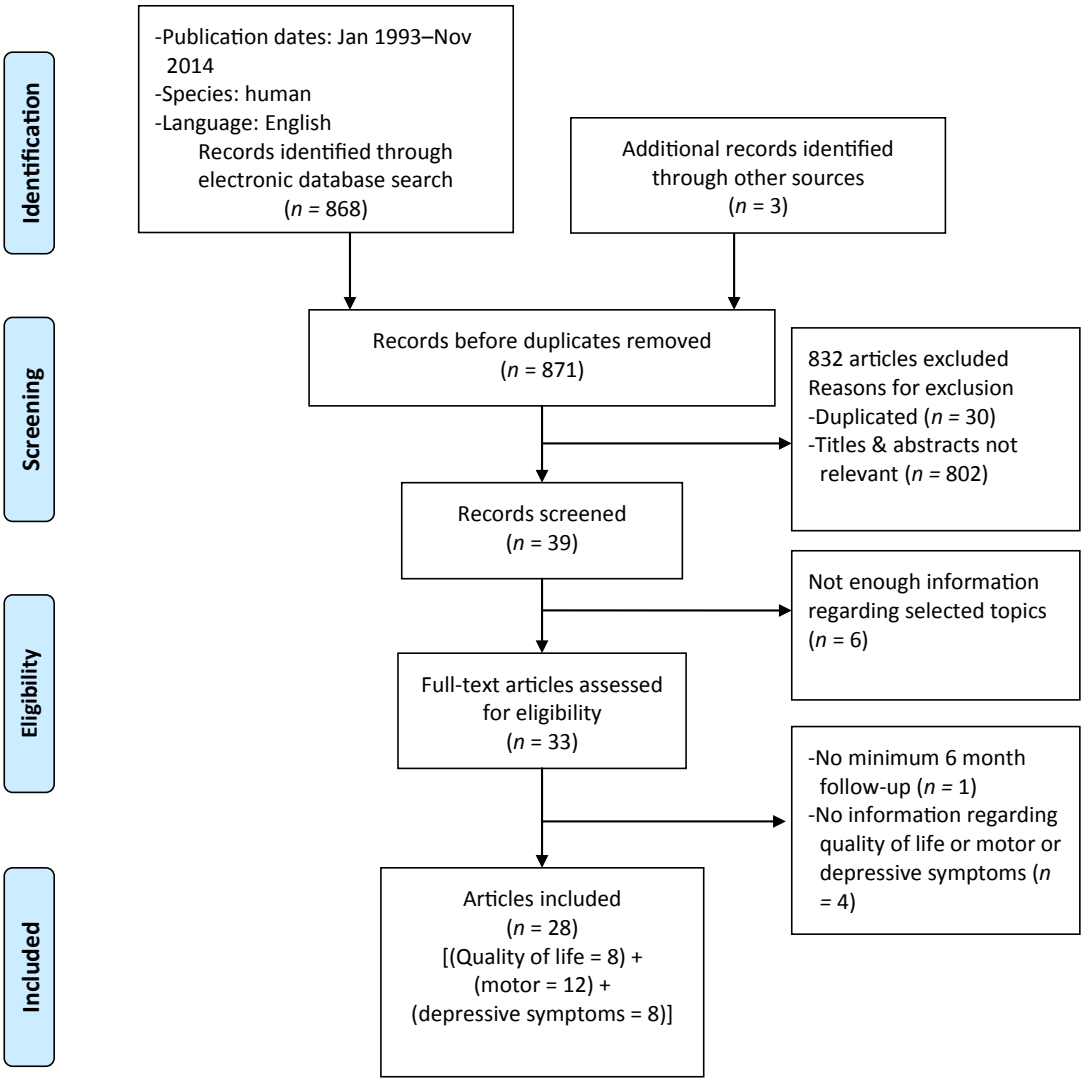

Fig. 1. Literature search flow diagram.

patients) that compared DBS plus medication versus medication alone were included in a meta-analysis study [24]. The results showed that DBS significantly improves patients' symptoms, functionality, and QoL. QoL significantly improved in the majority of patients after STN-DBS [20–22,25–29]. These results are summarized in Table 2. Lyons et al [30] found that the significant improvements in QoL following STN-DBS were strongly correlated with improvements in motor function, primarily with regard to bradykinesia.

Deuschl et al [20] and Weaver et al [22] reported significant improvement in the PDQ-39 subscales for mobility, ADL, stigma, and bodily discomfort at the 6-month follow-up. Another study showed significant improvements in mobility, ADL, and bodily discomfort. All of these studies reported no improvement in the social support and communication dimensions.

3.2. STN-DBS improvement of motor symptoms

The cardinal clinical manifestations of PD are resting tremor, rigidity, bradykinesia, and gait disturbance/postural instability. According to some reports, the motor improvement induced by STN-DBS is sustained for up to 5–8 years after surgery [3,31–38]. A prospective, multicenter study [39] of STN-DBS was performed in 96 patients with advanced PD. At 6 months, stimulation in the *off-medication* state was associated with a mean improvement of approximately 50% in the ADL and motor scores on the UPDRS. The benefits of stimulation were confirmed in a double-blind crossover component of the study, which demonstrated a 40–50% improvement in UPDRS motor scores. STN-DBS improves dopaminergic sensitive symptoms and dyskinesia and allows for reduced drug doses [40]. However, it may have isolatable effects on verbal fluency and related function [41]. Table 3 shows the summaries of included studies related to motor symptoms.

3.3. Influence of STN-DBS on depressive symptoms

PD is frequently accompanied by mood disturbance, with 35% of patients reporting some level of depressive symptoms, including 19% with major depressive disorders [7]. One study showed that the degree of depression and disease severity were significantly correlated with the QoL of PD patients.

Several studies investigating the psychiatric symptoms of patients following STN-DBS did not reveal any cognition and mood changes [23,42,43], while others documented improvements in

Table 2
Summaries of included studies related to quality of life.

Author (y) [Ref] Country	Design	Participant	Treatment	Outcome measured	Results
Sobstyl et al (2014) [29] Poland	(1) Nonrandomized, prospective trial. (2) Assessments were scheduled at baseline, 1 y, & 2 y.	All 16 patients with PD were assessed 1 y after STN-DBS & 14 were studied 2 y after surgery.	Bilateral STN-DBS	PDQ-39	All dimensions of PDQ-39 as well PDQ-39 summary index score were highly significantly improved after 1 y. The same improvements were visible in 2 y follow-up with the exception of social support & communication.
Schuepbach et al (2013) [28] Germany France	(1) Randomized, multicenter, parallel-group design. (2) Assessments were scheduled at baseline, 5 mo, 12 mo, & 24 mo.	A total of 251 patients with PD. Neurostimulation plus medical therapy ($n = 124$) vs. medical therapy alone ($n = 127$).	STN-DBS plus medical therapy vs. medical therapy	PDQ-39	For the primary outcome of quality of life, the mean score for the neurostimulation group improved by 7.8 points, & that for the medical-therapy group worsened by 0.2 points (between-group difference in mean change from baseline to 2 y, 8.0 points; $p = 0.002$).
Daniels et al (2011) [27] Germany	(1) Multicenter randomized, controlled trial. (2) Assessments were scheduled at baseline & 6 mo.	A total of 121 patients with PD. STN-DBS group ($n = 61$). Control group ($n = 60$).	STN-DBS vs. best medical treatment	(1) PDQ-39 summary index (2) Physical composite score 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 physical composite score are negatively correlated with the UPDRS dyskinesia score on at baseline, so fewer dyskinesia are associated with greater QoL improvement.
Williams et al (2010) [21] UK	(1) Randomized, open-label trial. (2) Assessments were scheduled at baseline & 12 mo.	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 vs. best medical therapy	PDQ-39 summary index	At 1 y, the mean improvement in PDQ-39 summary index score compared with baseline was 5.0 points in the surgery group & 0.3 points in the medical therapy group (difference −4.7, 95% CI −7.6–−1.8; $p = 0.001$).
Weaver et al. (2009) [22] USA	(1) Randomized controlled trial. (2) Assessments were scheduled at baseline & 6 mo.	A total of 255 patients with PD. Bilateral STN-DBS ($n = 60$) or GPi ($n = 61$). vs. best medical therapy ($n = 134$).	Bilateral STN or GPi DBS vs. best medical therapy	PDQ-39	Compared with the best medical therapy group, the DBS group experienced significant improvements in the summary measure of QoL & on 7 of 8 PDQ-39 scores ($p < 0.001$).
Schüpbach et al (2007) [26] France	(1) Prospectively randomized. Matched for age, duration, & severity of disease, & impairment in socioprofessional functioning. (2) Assessments were scheduled at baseline & 18 mo.	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 vs. optimized medical treatment	PDQ-39	QoL was improved by 24% in surgical & 0% in nonsurgical patients ($p < 0.05$).
Deuschl et al (2006) [20] Germany Austria	(1) Unblinded trial with a randomized-pairs design. (2) Assessments were scheduled at baseline & 6 mo.	78 pairs of patients ($n = 156$ patients) with PD were assigned to treatment.	Bilateral STN-DBS vs. best medical therapy	(1) PDQ-39 summary index (2) SF-36 physical & mental summary scores	For the neurostimulation group, the PDQ-39 summary index score was 41.8 ± 13.9 at baseline & 31.8 ± 16.3 at 6 mo. In the medication group, the PDQ-39 score was 39.6 ± 16 at baseline & 40.2 ± 14.4 at 6 mo. The results show an improvement of ~25% in the neurostimulation group compared with almost no change in the medication group.

Just & Ostergaard (2002) [25] Denmark	(1) Nonrandomized, controlled prospective trial. (2) Assessments were scheduled at baseline (T0), 3 mo (T3), & 6 mo (T6).	A total of 24 patients with PD. STN-DBS ($n = 11$) & similar group of patients awaiting surgery ($n = 13$).	STN-DBS vs. nonsurgery	PDQ-39	Neurostimulation also resulted in a 22% improvement in the SF-36 physical summary score. The PDQ-39 scores from T0 to T3, the surgery group demonstrated significant improvement for subscales mobility, ADL, & bodily discomfort, in addition to significant improvement by 14.0 points in the PDQ-39 summary index. From T0 to T6, the surgery group improved 16.1 points. The nonsurgery group demonstrated no significant changes in PDQ-39 summary index or any of the subscales from T0 to T3 or from T0 to T6.

ADL = activity of daily living; DBS = deep brain stimulation; GPi = globus pallidus interna; PD = Parkinson's disease; PDQ-39 = Parkinson's disease questionnaire-39; QoL = quality of life; Ref = reference; SF-36 = short form-36; STN = subthalamic nucleus.

Table 3
Summaries of included studies related to motor symptoms.

Author (y) [Ref] Country	Design	Participant	Treatment	Outcome measured	Results
Jiang et al (2015) [40] Taiwan	(1) Prospective study. (2) Assessments were scheduled at baseline, 1y, & 5 y.	A total of 41 patients with PD.	Bilateral STN-DBS	(1) UPDRS (2) SEADL	When compared to the preoperative baseline off-medication condition, significant improvements were observed in the UPDRS Parts I, II, III, & IV, & SEADL ($p < 0.001$) scores 1 y after STN-DBS; 5 y after STN-DBS, improvements in UPDRS scores were observed only for Parts II, III, & IV ($p < 0.001$).
Harati & Muller (2013) [41] Germany	(1) Prospective study. (2) Assessments were scheduled at baseline, 12 mo, & 18 mo.	A total of 20 patients with PD.	Bilateral STN-DBS	(1) General cognitive screening (2) Memory (3) Language (4) Visuospatial abilities	(1) There was a significant decline of both semantic & phonemic verbal fluency & a mild trend for a deterioration of verbal memory after DBS. (2) The general cognitive screening & visuospatial abilities remained changed.
Moro et al (2010) [37] Canada France Spain Sweden Germany Italy UK The Netherlands	(1) Prospective multicenter study. (2) Randomized double-blind evaluation with cross-over on the 2nd day of the 3-mo follow-up & unblinded assessments at 1 mo,	51 consecutive patients with PD were assessed.	Bilateral STN-DBS ($n = 35$) & GPi-DBS ($n = 16$)	(1) UPDRS (2) Levodopa dosage	(1) STN- & GPi-DBS were significantly effective in improving the motor UPDRS scores (STN, $p < 0.0001$, 45.4%; GPi, $p = 0.008$, 20.0%) compared with off-stimulation, regardless of the sequence of stimulation. In open assessment, both STN- & GPi-DBS significantly improved the off-medication UPDRS-motor when compared with before surgery (STN, $p < 0.001$, 50.5%; GPi, $p = 0.002$,

(*continued on next page*)

Table 3 (*continued*)

Author (y) [Ref] Country	Design	Participant	Treatment	Outcome measured	Results
	6 mo, & 12 mo follow-up. (3) A subsequent extension of the study was performed to obtain long-term data (3–4 y & 5–6 y)				35.6%). Dyskinesias & ADL were significantly improved in both groups. (2) Anti-PD medications were significantly reduced only in the STN group.
Fasano et al.-(2010) [38] Italy	(1) Prospective study. (2) Assessments were scheduled at baseline, 3 y, 5 y, & 8 y.	20 consecutive patients with PD were assessed.	Bilateral STN-DBS	(1) UPDRS (2) Levodopa dosage	(1) The overall motor improvement reported at 5 y (55.5% at UPDRS—motor part, $p < 0.001$ compared with baseline) was only partly retained 3 y later (39%, $p < 0.001$, compared with baseline; −16.5%, $p < 0.01$, compared with 5 y), with differential effects on motor features: speech did not improve & postural stability worsened ($p < 0.05$). (2) The preoperative levodopa equivalent daily dose was reduced by 58.2% at 5 y & by 60.3% at 8 y. In spite of subtle worsening of motor features, a dramatic impairment in functional state (−56.6% at UPDRS-ADL, $p < 0.01$) emerged after the 5th y of stimulation.
Piboolnurak et al (2007) [36] Canada	(1) Patients were assessed in a nonblinded fashion before & after the surgery. (2) Assessments were scheduled at baseline, 3 y, & 5 y.	33 consecutive patients with PD were assessed.	Bilateral STN-DBS	(1) Levodopa response (2) UPDRS	Levodopa response significantly decreased postoperatively by 31.1% at 3 y & 32.3% at 5 y, possibly related to the reduction in medication requirement, direct STN stimulation effect, or PD progression. STN-DBS alone significantly improved motor scores (37.2% at 3 y & 35.1% at 5 y) & ADL scores (27.1% at 3 y & 19.2% at 5 y).
Rodriguez-Oroz et al (2005) [34] Spain Canada Germany France Italy UK	(1) Prospective multicenter study. (2) Assessments were scheduled at baseline & 3–4 y.	A total of 69 patients with PD.	STN-DBS ($n = 49$) & GPi-DBS ($n = 20$)	UPDRS	Stimulation of the STN or GPi induced a significant improvement (50% & 39%; $p < 0.0001$) of the off-medication UPDRS-III score at 3–4 y with respect to baseline. Stimulation improved cardinal features & ADL ($p < 0.001$ & $p < 0.02$ for STN & GPi, respectively) & prolonged the "on" time spent with good mobility without dyskinesias ($p < 0.001$). Comparison of the improvement induced by stimulation at 1 y with 3–4 y showed a significant worsening in the "on" medication motor states of the UPDRS-III, ADL & gait in both STN & GPi groups, & speech & postural stability in the STN-treated group.
Schüpbach et al (2005) [35] France	(1) Prospective study. (2) Assessments were scheduled at baseline, 6 mo, 24 mo, & 60 mo.	37 consecutive patients with PD were assessed.	Bilateral STN-DBS	UPDRS	6 patients died & 1 patient was lost to follow up. 5 y after neurosurgery: (1) UPDRS II was improved by stimulation of the STN by 40% (*off* drug) & 60% (*on* drug); (2) parkinsonian motor disability (UPDRS III) was improved by 54% (*off* drug) & 73% (*on* drug); & (3) the severity of levodopa related motor complications was decreased by 67% & the levodopa daily doses were reduced by 58%.
Krack et al (2003) [3] France	(1) Prospective study.	43/49 patients with PD were assessed 1 y after STN-DBS & 42/49 were	Bilateral STN-DBS	UPDRS	As compared with baseline, the patients' scores at 5 y for motor function while off-medication improved by 54% ($p < 0.001$) & those for ADL

	(2) Assessments were scheduled at baseline, 1 y, 3 y, & 5 y.	studied 3 y & 5 y after surgery.			improved by 49% ($p < 0.001$). Speech was the only motor function for which off-medication scores did not improve. On-medication akinesia, speech, postural stability, & freezing of gait worsened between y 1 & y 5 ($p < 0.001$ for all comparisons).
The DBS for PD Study Group (2001) [39] Spain France Canada Italy USA Germany UK Australia	(1) Prospective, double-blind, crossover, multi-center study. (2) Assessments were scheduled at baseline, 1 mo, 3 mo, & 6 mo.	A total of 134 patients with PD.	Bilateral STN-DBS ($n = 96$) & GPi-DBS ($n = 38$)	UPDRS	(1) 3 mo after surgery, evaluations demonstrated that stimulation of the STN-DBS was associated with a median improvement in the motor score (as compared with no stimulation) of 49%, & the GPi-DBS with a median improvement of 37% ($p < 0.001$ for both comparisons). (2) Between the preoperative & 6-mo visits, the percentage of time during the day that patients had good mobility without involuntary movements increased from 27% to 74% ($p < 0.001$) with STN-DBS & from 28% to 64% ($p < 0.001$) with pallidal stimulation.
Moro et al (1999) [32] Italy	(1) Prospective study. (2) The average follow-up was 16.3 ± 7.6 mo.	7 consecutive patients with PD were assessed.	Bilateral STN-DBS	(1) UPDRS, (2) SEADL	Compared with the presurgical condition, off-drug UPDRS motor scores improved by 41.9% on the last visit ($p = 0.0002$), UPDRS ADL scores improved by 52.2% ($p = 0.0002$), & the SEADL improved by 213% ($p = 0.0002$).
Kumar et al (1998) [33] Canada	(1) Double-blind, prospective study. (2) Assessments were scheduled at baseline, 6 mo, & 12 mo.	7 consecutive patients with advanced PD were assessed.	Bilateral STN-DBS	1. UPDRS	(1) In the medication-off state, improvement in mean total UPDRS motor score by 58%. (2) In the medication-on state, UPDRS motor score improved 41% compared with before surgery. (3) ADL were improved while off medication 30%, & levodopa-induced dyskinesias were reduced 83% while total drug dosage was decreased 40%.
Limousin et al (1995) [31] France	(1) The 1st demonstration in human beings by the subthalamic nuclei in PD patients. (2) Assessments were scheduled at baseline & 3 mo.	3 patients with PD were assessed.	Bilateral STN-DBS	UPDRS	(1) UPDRS PartII-ADL scores had improved by 58–88% & UPDRS Part III-motor scores by 42–84%.

ADL = activity of daily living; DBS = deep brain stimulation; GPi = globus pallidus interna; PD = Parkinson's disease; Ref = reference; SEADL = Schwab & England Activities of Daily Living Scale; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale.

Table 4
Summaries of included studies related to depressive symptoms.

Author (y) [Ref] Country	Design	Participant	Treatment	Outcome measured	Results
Pinsker et al (2013) [49] Germany	(1) Prospective study. (2) Assessments were scheduled at baseline & mean follow-up of 37 mo.	A total of 65 PD patients underwent implantation of DBS. (43 STN, 10 GPi, 12 VIM)	STN-DBS GPi-DBS VIM-DBS	Neuropsychiatric inventory	Depression was the most common psychiatric side-effect after DBS, occurring in 47.7% of all patients (31/65 patients), without significant preference to a specific target (STN: 42%, GPi: 60%, VIM: 58%).
Okun et al (2009) [23] USA	(1) Nonrandomized, prospective trial. (2) Assessments were scheduled at baseline & 7 mo.	52 patients were randomized to unilateral STN- or GPi-DBS. 45 patients (23 GPi, 22 STN) completed the protocol.	Unilateral STN- or GPi-DBS.	Visual analog mood scale	(1) The study revealed no difference between STN- & GPi-DBS in the change of co-primary mood & cognitive outcomes pre- to post-DBS in the optimal setting (2) Patients in both targets were less happy, less energetic, & more confused when stimulated ventrally.
Witt et al (2008) [45] Germany	(1) Randomized, prospective study. (2) Assessments were scheduled at baseline & 6 mo.	(1) 123 patients had neuropsychological & psychiatric examinations to assess the changes (2) 60 patients were randomly assigned to receive STN-DBS & 63 patients to have best medical treatment.	Bilateral STN-DBS vs. best medical therapy	(1) Cognitive functioning. (2) Executive function, depression, anxiety, psychiatric status, manic symptoms, & QoL	STN-DBS does not reduce overall cognition or affectivity, although there is a selective decrease in frontal cognitive functions & an improvement in anxiety in patients after the treatment. These changes do not affect improvements in QoL.
Heo et al (2008) [43] Korea	(1) Prospective study. (2) Assessments were scheduled at baseline, 6 mo, 12 mo.	46 consecutive patients with PD	Bilateral STN-DBS	BDI	BDI was not significantly changed.
Zibetti et al (2007) [42] Italy	(1) Prospective study. (2) Assessments were scheduled at baseline, 12 mo, & 24 mo.	36 consecutive patients with PD	Bilateral STN-DBS	Nonmotor symptoms	No significant variations were detected in intellectual impairment, depression, thought disorders, motivation, falling unrelated to freezing, nausea, orthostatic hypotension, & urological dysfunction.
Kalteis et al (2006) [47] Australia	(1) Prospective study. (2) Patients were assessed 3 times prior to surgery & at 3 wk, 9 wk, 3 mo, 6 mo, & 12 mo after surgery.	33 consecutive patients with PD.	Bilateral STN-DBS	(1) Bech–Rafaelsen melancholia scale (2) Profile of mood states (3) BDI (4) State–trait anxiety inventory	Significant improvements in depression, anxiety, psychological symptoms & distress after surgery.
Drapier et al (2005) [46] France	(1) Prospective study. (2) Assessments were scheduled at baseline & 12 mo.	27 consecutive patients with PD	Bilateral STN-DBS	(1) UPDRS (2) PDQ-39 (3) SF-36	(1) Using clinician's based rating scale (UPDRS), bilateral STN DBS showed significant improvement in PD patients at 12-mo follow-up. (2) Using patient's self-assessment scales (PDQ-39 & SF-36), the physical items of QoL significantly improved, whereas mental items such as emotional well-being, social support, cognition, & communication showed no improvement.
Funkiewiez et al (2004) [44] France	(1) Prospective study. (2) Assessments were scheduled at baseline, 1 y, & 3 y.	77 consecutive patients with PD. 7 patients died or were lost for follow up.	Bilateral STN-DBS	(1) BDI (2) Reports of the behavioral changes	(1) Depression improved whereas apathy & thought disorders worsened. (2) Major behavioral changes were 2 transient aggressive impulsive episodes, 1 suicide, 4 suicide attempts, 1 permanent apathy, 1 transient severe depression, 4 psychoses (1 permanent), & 5 hypomania (1 permanent).

BDI = Beck depression inventory; DBS = deep brain stimulation; GPi = globus pallidus interna; PD = Parkinson's disease; PDQ-39 = Parkinson's disease questionnaire-39; QoL = quality of life; Ref = reference; SF- 36 = short form 36 health survey questionnaire; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale; VIM = ventral intermediate nucleus.

mood, such as an amelioration of symptoms of depression and anxiety [44,45]. Using a clinician-based rating scale, Drapier et al [46] reported that PD patients showed significant improvement 12 months after bilateral STN-DBS. Kalteis et al [47] found significant improvements in depression, anxiety, psychological symptoms, and distress after STN-DBS. The direct antidepressive mechanism is probably associated with the impact of STN-DBS on the medial forebrain bundle and stimulation of the limbic system, and indirectly from improvement in motor functions [48]. By contrast, depression was the most common psychiatric side effect after DBS, occurring in 47.7% of all patients (31/65 patients), without significant preference for a specific target (subthalamic nucleus, 42%; globus pallidus, 60%; ventral intermedius nucleus, 58%). These results are summarized in Table 4. Preoperative evaluation for depressive symptom is crucial to identify patients who are at specific risk of psychiatric complications [49].

4. Applications of the review

The present findings contribute to the field's understanding of improvements in QoL and clinical features as health care professionals prepare explanations of STN-DBS for PD patients. Gronchi-Perrin et al [50] found that when the same patients were assessed retrospectively using the same questionnaire, no significant changes in QoL emerged, thus showing a postoperatively modified perception of the preoperative level of general functioning. In other words, PD patients tended to overestimate their preoperative functioning when asked about it after successful STN-DBS. This review collected prospective cohort studies to evaluate changes in QoL. The findings of this review will be useful to improve evaluation systems and particularly to unify evaluation criteria among patients having STN-DBS surgery. Lastly, we hope that it will pave the way for clinical research projects that will help consolidate the study of QoL and mood status of PD patients, and not just assess their physical symptoms. Martínez-Martin [51] highlighted the following: (1) QoL assessment contributes to a better understanding of the disease's consequences, and its treatment, on the patient, and thus helps in decision making; (2) QoL evaluations reflect the point of view of patients (who may disagree with the clinical ratings); (3) although usually correlated, QoL may not be equated with disability; and (4) many relevant aspects related to the emotional and psychosocial well-being of patients cannot be evaluated appropriately using clinical methods. Health care professionals can be more attuned to the visible and invisible manifestations of PD that are associated with motor and nonmotor symptoms through the incorporation of a multidisciplinary assessment to identify treatment effects in persons living with PD.

5. Limitations of the review

We may have missed some studies as our literature research was restricted to a search of only a few databases. There were a variety of methodological weaknesses in the studies in this review. These limitations included small sample sizes, limited information on the setting of the study and qualifications and training of the investigators, and a lack of assessment of the reliability and validity of the outcome measures. A more general limitation of this approach is that several studies reporting only a small sample favored Type-II errors, although most of the interventions demonstrated a significant effect. Another limitation of this 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 complete review. It is acknowledged that inclusion of these studies may have influenced the findings of this review. Furthermore, the majority of studies did not report intention-to-treat analysis and/or the last observation carried forward analysis. Moreover, it is not always possible to retrieve all eligible evidence on a given topic, as many studies never get published. The nonpublication of study results is of great importance because it may distort the evidence base for clinical decision making. This highlights the need for replication of studies to evaluate fully the effectiveness of STN-DBS.

6. Suggestions

Evaluation after surgery is of paramount importance. Careful follow-up observation is recommended to look for neurological deficits or procedure-related complications and to modify pharmacological treatment. This review demonstrate that QoL and motor and depressive symptoms can be assessed in clinical practice. Long-term follow-up studies have demonstrated that motor score improvements are maintained over baseline, but diminish over 5 years following STN-DBS [41]. Longitudinal long-term follow-up studies of QoL are needed to review the stability of these results along the chronic course of PD. In addition, PD is a complex, multifaceted chronic illness that affects multiple clinical domains. Examination of potential moderating effects between the predictor variables is needed.

7. Conclusion

STN-DBS leads to significant improvement in QoL as well as motor symptoms in patients with PD after surgery. However, depressive symptoms did not reveal consistent change. Use of QoL and depressive symptom measurement scales should be an integral part of the clinical protocol for patients admitted to a Parkinson's disease surgical program. This would help identify symptoms that affect the overall health status of PD patients other than just physical symptoms.

References

[1] Lew M. Overview of Parkinson's disease. Pharmacotherapy 2007;27:153S–4S.
[2] Chen J, Swope D. Pharmacotherapy for Parkinson's disease. Pharmacotherapy 2007;27:161S–73S.
[3] Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349:1925–34.
[4] Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease. Neurology 2009;72:S1–136.
[5] Dowding CH, Shenton CL, Salek SS. A review of the health-related quality of life and economic impact of Parkinson's disease. Drugs Aging 2006;23:693–721.
[6] Chung TH, Deane KH, Ghazi-Noori S, Rickards H, Clarke CE. Systematic review of antidepressant therapies in Parkinson's disease. Parkinsonism Relat Disord 2003;10:59–65.
[7] Reijnders JE, Ehrt U, Weber WE, Aarsland D, Leetjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord 2008;23:183–9.
[8] Silberman CD, Laks J, Capitão CF, Rodrigues CS, Moreira I, Engelhardt E. Recognizing depression in patients with Parkinson's disease: accuracy and specificity of two depression rating scale. Arq Neuropsiquiatr 2006;64:407–11.
[9] Bekar L, Libionka W, Tian GF, Xu Q, Torres A, Wang X, et al. Adenosine is crucial for deep brain stimulation-mediated attenuation of tremor. Nat Med 2008;14:75–80.
[10] Gradinaru V, Mogri M, Thompson KR, Henderson JM, Deisseroth K. Optical deconstruction of parkinsonian neural circuitry. Science 2009;324:354–9.
[11] Defer GL, Widner H, Marié RM, Rémy P, Levivie M. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). Mov Disord 1999;14:572–84.
[12] Benabid AL, Pollak P, Gross C, Hoffmann D, Benazzouz A, Gao DM, et al. Acute and long-term effects of subthalamic nucleus stimulation in Parkinson's disease. Stereotact Funct Neurosurg 1994;62:76–84.
[13] Post B, Merkus MP, de Haan RJ, Speelman JD. Prognostic factors for the progression of Parkinson's disease: a systematic review. Mov Disord 2007;22:1839–51.
[14] Den Oudsten BL, Van Heck GL, De Vries J. Quality of life and related concepts in Parkinson's disease: a systematic review. Mov Disord 2007;22:1528–37.

[15] World Health Organization. WHO-QOL study protocol: the development of the World Health Organization quality of life assessment instrument. Geneva: Division of Mental Health, World Health Organization; 1993.
[16] Siderowf A, Jaggi JL, Xie SX, Loveland-Jones C, Leng L, Hurtig H, et al. Long-term effects of bilateral subthalamic nucleus stimulation on health-related quality of life in advanced Parkinson's disease. Mov Disord 2006;21:746–53.
[17] Martinez-Martin P, Jeukens-Visser M, Lyons KE, Rodriguez-Blazquez C, Selai C, Siderowf A, et al. Health-related quality-of-life scales in Parkinson's disease: critique and recommendations. Mov Disord 2011;26:2371–80.
[18] Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. Qual Life Res 1995;4:241–8.
[19] Kuehler A, Henrich G, Schroeder U, Conrad B, Herschbach P, Ceballos-Baumann A. A novel quality of life instrument for deep brain stimulation in movement disorders. J Neurol Neurosurg Psychiatry 2003;74:1023–30.
[20] Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 2006;355:896–908.
[21] Williams A, Gill S, Varma T, Jenkinson C, Quinn N, Mitchell R, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. Lancet Neurol 2010;9:581–91.
[22] Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks Jr WJ, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease. JAMA 2009;301:63–73.
[23] Okun MS, Fernandez HH, Wu SS, Kirsch-Darrow L, Bowers D, Bova F, et al. Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. Ann Neurol 2009;65:586–95.
[24] Perestelo-Pérez L, Rivero-Santana A, Pérez-Ramos J, Serrano-Pérez P, Panetta J, Hilarion P. Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials. J Neurol 2014;261:2051–60.
[25] Just H, Ostergaard K. Health-related quality of life in patients with advanced Parkinson's disease treated with deep brain stimulation of the subthalamic nuclei. Mov Disord 2002;17:539–45.
[26] Schüpbach WM, Maltête D, Houeto JL, du Montcel ST, Mallet L, Welter ML, et al. Neurosurgery at an earlier stage of Parkinson disease: a randomized, controlled trial. Neurology 2007;68:267–71.
[27] Daniels C, Krack P, Volkmann J, Raethjen J, Pinsker MO, Kloss M, et al. Is improvement in the quality of life after subthalamic nucleus stimulation in Parkinson's disease predictable? Mov Disord 2011;26:2516–21.
[28] Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 2013;368:610–22.
[29] Sobstyl M, Ząbek M, Górecki W, Mossakowski Z. Quality of life in advanced Parkinson's disease after bilateral subthalamic stimulation: 2 years follow-up study. Clin Neurol Neurosurg 2014;124:161–5.
[30] Lyons KE, Pahwa R. Long-term benefits in quality of life provided by bilateral subthalamic stimulation in patients with Parkinson disease. J Neurosurg 2005;103:252–5.
[31] Limousin P, Pollak P, Benazzouz A, Hoffmann D, Le Bas JF, Broussolle E. Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet 1995;345:91–5.
[32] Moro E, Scerrati M, Romito LM, Roselli R, Tonali P, Albanese A. Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. Neurology 1999;53:85–90.
[33] Kumar R, Lozano AM, Kim YJ, Hutchinson WD, Sime E, Halket E, et al. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Neurology 1998;51:850–5.
[34] Rodriguez-Oroz MC, Obeso JA, Lang AE, Houeto J, Pollak P, Rehncrona S, et al. Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. Brain 2005;128:2240–9.
[35] Schüpbach WM, Chastan N, Welter ML, Houeto J, Mesnage V, Bonnet A, et al. Stimulation of the subthalamic nucleus in Parkinson's disease: a 5 year follow up. J Neurol Neurosurg Psychiatry 2005;76:1640–4.
[36] Piboolnurak P, Lang AE, Lozano AM, Miyasaki JM, Saint-Cyr JA, Poon YY, et al. Levodopa response in long-term bilateral subthalamic stimulation for Parkinson's disease. Mov Disord 2007;22:990–7.
[37] Moro E, Lozano AM, Pollak P, Agid Y, Rehncrona S, Volkmann J, et al. Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. Mov Disord 2010;25:578–86.
[38] Fasano A, Romito LM, Daniele A, Piano C, Massimiliano Z, Rita BA, et al. Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. Brain 2010;133:2664–76.
[39] The Deep-Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 2001;345:956–63.
[40] Jiang JL, Chen SY, Hsieh TC, Lee CW, Lin SH, Tsai ST. Different effectiveness of subthalamic deep brain stimulation in Parkinson's disease: A comparative cohort study at 1 year and 5 years. J Formos Med Assoc 2015;114:835–41.
[41] Harati A, Muller T. Neuropsychological effects of deep brain stimulation for Parkinson's disease. Surg Neuro Int 2013;4(Suppl. 6):S443–7.
[42] Zibetti M, Torre E, Cinquepalmi A, Rosso M, Ducati A, Bergamasco B, et al. Motor and nonmotor symptom follow-up in parkinsonian patients after deep brain stimulation of the subthalamic nucleus. Eur Neurol 2007;58:218–23.
[43] Heo JH, Lee KM, Paek SH, Kim MJ, Lee JY, Kim JY, et al. The effects of bilateral subthalamic nucleus deep brain stimulation (STN DBS) on cognition in Parkinson disease. Neurol Sci 2008;273:19–24.
[44] Funkiewiez A, Ardouin C, Caputo E, Krack P, Fraix V, Klinger H, et al. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:834–9.
[45] Witt K, Daniels C, Reiff J, Krack P, Volkmann J, Pinsker MO, et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. Lancet Neurol 2008;7:605–14.
[46] Drapier S, Raoul S, Drapier D, Leray E, Lallement F, Rivier I, et al. Only physical aspects of quality of life are significantly improved by bilateral subthalamic stimulation in Parkinson's disease. J Neurol 2005;252:583–8.
[47] Kalteis K, Standhardt H, Kryspin-Exner I, Brucke T, Volc D, Alesch F. Influence of bilateral STN-stimulation on psychiatric symptoms and psychosocial functioning in patients with Parkinson's disease. J Neural Transm 2006;113:1191–206.
[48] Lezcano E, Gómez-Esteban JC, Zarranz JJ, Lambarri I, Madoz P, Bilbao G, et al. Improvement in quality of life in patients with advanced Parkinson's disease following bilateral deep-brain stimulation in subthalamic nucleus. Eur J Neurol 2004;11:451–4.
[49] Pinsker M, Amtage F, Berger M, Nikkhah G, van Elst LT. Psychiatric side-effects of bilateral deep brain stimulation for movement disorders. Acta Neurochir Suppl 2013;117:47–51.
[50] Gronchi-Perrin A, Viollier S, Ghika J, Combremont P, Villemure JG, Bogousslavsky J, et al. Does subthalamic nucleus deep brain stimulation really improve quality of life in Parkinson's disease? Mov Disord 2006;21:1465–8.
[51] Martínez-Martin P. An introduction to the concept of "quality of life in Parkinson's disease". J Neurol 1998;245(Suppl. 1):S2–6.