SZEIDL, Olga, SZYDZIAK, Joanna, HRAPKOWICZ, Aleksandra, JANOWSKA, Kinga, REHAN, Dominika, WOŁOSZCZAK, Julia, MIOSKOWSKA, Agnieszka and DĄBKOWSKA, Daria. DBS in the treatment of Parkinson's disease. Quality in Sport. 2024;31:55864 eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.31.55864
https://apcz.umk.pl/QS/article/view/55864

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assig589 ned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 30.10.2024. Revised: 07.11.2024. Accepted: 08.11.2024. Published: 12.11.2024.

DBS in the treatment of Parkinson's disease

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1. ABSTRACT

Introduction: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by both motor and non-motor symptoms, primarily due to dopaminergic neuron loss and Lewy body accumulation. While early-stage PD often responds well to dopaminergic therapy, advanced stages exhibit severe motor fluctuations and reduced treatment efficacy, necessitating alternative therapeutic options.

Purpose of the Study: This review examines the role of Deep Brain Stimulation (DBS) as a therapeutic intervention for advanced PD, focusing on indications, patient selection criteria, and potential complications.

Materials and Methods: A comprehensive literature review was conducted, analyzing 37 studies from the PubMed database (English-language, up to October 2024) that assess the efficacy, safety, and long-term outcomes of DBS in managing advanced PD symptoms.

Conclusions: DBS, involving the implantation of electrodes in regions such as the subthalamic nucleus or globus pallidus internus, has proven effective in enhancing motor function and quality of life in advanced PD cases. Appropriate patient selection is essential; DBS is generally reserved for patients meeting specific criteria, including a confirmed PD diagnosis, disease duration of more than four years, a positive response to levodopa, and the absence of severe cognitive or unmanaged psychiatric disorders. Although generally safe, DBS can present risks, including infections, dyskinesia, and psychiatric side effects. Emerging research on genetic factors may enhance patient selection in the future.

Keywords: Parkinson's disease, Deep Brain Stimulation, Motor symptoms, Dopaminergic therapy, Quality of life, Surgery, New therapy

2. INTRODUCTION

Parkinson's disease (PD) is a complex, progressive neurodegenerative disorder and the second most prevalent neurodegenerative disease after Alzheimer's disease. It primarily affects individuals over the age of 60, with a global incidence of approximately 1% in this age group. [1] PD is characterized by the degeneration of dopaminergic neurons in the nigrostriatal pathway, leading to hallmark motor symptoms such as tremors, rigidity, bradykinesia, and postural instability. The motor symptoms become clinically evident when dopamine levels in the striatum decrease by 70%. In addition to these motor symptoms, non-motor symptoms—including autonomic dysfunction, cognitive disturbances, and sleep abnormalities—contribute significantly to the disease burden. The pathological hallmarks of PD include the accumulation of Lewy bodies (neuronal inclusions of alpha-synuclein in neuronal cell bodies). Recent research highlights the significant role of inflammatory processes in the pathogenesis of PD. Sustained activation of glial cells, particularly microglia and astrocytes, is believed to contribute to the degeneration of dopaminergic neurons. [2] Microglial activation in PD was first identified in 1988 and has since been observed in both human patients and animal models. Astrocytes also play a crucial role, as astroglial reactivity has been detected in the SN of PD patients. Dysfunctional astrocytes contribute to PD pathogenesis by reducing glutathione levels, promoting mitochondrial damage, and accumulating extracellular toxins. [3]. Pathology extends to other areas of the brain, such as basal forebrain, amygdala, medial temporal lobe and cortical neurons. All nerve cells are affected, including glutamatergic, cholinergic, GABA-ergic, tryptaminergic, noradrenergic and adrenergic. [4]

While the majority of PD cases are idiopathic, around 10% are linked to genetic mutations, such as the most known PARK-1 mutation, which may influence the disease's presentation and progression. [5] As the disease advances, pharmacological treatment, such as levodopa therapy, becomes less effective, leading to motor fluctuations and dyskinesias. For patients who no longer benefit adequately from medication, deep brain stimulation (DBS) has emerged as an effective surgical treatment option. DBS involves the implantation of electrodes in specific brain regions, such as the subthalamic nucleus (STN) or globus pallidus internus (GPi), to modulate abnormal neural activity and improve motor function. Since its development in the late 1980s, DBS has been proven to be a transformative therapy not only for PD but also for other movement disorders and psychiatric conditions.

The following work explores the mechanisms, clinical applications, and outcomes of DBS in Parkinson's disease, while also addressing potential complications and side effects associated with the therapy. As the field of DBS continues to evolve, it is crucial to understand its limitations, risks, and future directions to optimize patient outcomes and expand its use in managing neurodegenerative and psychiatric disorders.

3. STATE OF KNOWLEDGE

3.1. TREATMENT OF PARKINSON'S DISEASE

Parkinson's disease (PD) was first described in 1817 by British physician James Parkinson in his work *An Essay on the Shaking Palsy*. Motor symptoms have been signature features of the disease, for which most treatments have been aimed at. In the mid-20th century, anticholinergic medications were introduced and became beneficial especially for tremor. In the 1960s, an American scientist George Cotzias, popularized the use of levodopa, showing that high doses of this drug could improve motor symptoms in PD patients. By 1967, levodopa had become the standard treatment for Parkinson's, revolutionizing care for the disease. This marked the beginning of dopamine replacement therapy, which remains a central component of PD treatment. [6]. Over the years, additional drugs were developed, including dopamine agonists, MAO-B inhibitors and COMT inhibitors, extending the effectiveness of dopamine therapy.

However, pharmacotherapy of PD has its limitations. A good response to treatment is observed early in the course of the disease, which is sometimes called "honeymoon period" and lasts about five years. In the further course of the disease, the loss of nerve cells progresses and the damage includes more areas of the brain. Patients are experiencing gait and balance disturbances and difficulties in swallowing. The next stage is the period of advanced disease, in which response to pharmacotherapy is worse and drug interruptions occur. Initially, the patient feels well during the period of their action (the so-called on phase) and after 3 hours his condition begins to deteriorate (off phase). Frequent dosing of drugs is needed to avoid the return of symptoms. [8]

Over the years surgical therapies have become important for treating patients with advanced stages of the disease. The first published surgical treatments for PD occurred in the early 1950s, and involved lesioning regions of the basal ganglia (pallidotomy and thalamotomy). History of DBS began in 1980 when Brice and McLellan used chronic electrical stimulation of the midbrain and basal ganglia to suppress intention tremor. They reported significant improvement in the patient's state. Since then DBS has become the predominant surgical procedure for advanced stages of PD. [9]

3.2. DEEP BRAIN STIMULATION METHOD

Deep brain stimulation (DBS) is a neurosurgical procedure developed by modifying pacemakers. It enables targeted circuit-based neuromodulation and is used in many diseases such as Parkinson's, essential tremor, and dystonia. Research is also being conducted on the use of this therapy in severe depression and Alzheimer's disease. Since the "new era" of DBS in the late 1980s, it has faced limitations such as large battery size, limited battery life, and frequency of replacement.

However, there are now many manufacturers on the market, which drives competition, progress, and greater availability of equipment. The development of this technology may carry risks such as the prospect of modulating cognitive processes and decision-making and the possibility of acquiring data for their misuse and brain theft. Currently, DBS systems consist of an intracranial electrode, an extension cable, and a pulse generator [10].

The DBS method was developed based on the observation that high-frequency stimulation has effects similar to those seen after surgical procedures. In DBS, a neural interface known as the implanted pulse generator (IPG) continuously delivers electrical impulses to specific areas of the brain [11]. The device produces a pulse in the IPG. This pulse is then carried through an extension cable to the neural contacts, which stimulate the appropriate area. The stimulating wires or electrodes consist of four cylindrical 80/20 platinum/iridium alloy wires at the distal end connected to four non-interlacing fluoropolymer-insulated platinum/iridium wires leading to a set of four nickel alloy contacts. The distal cable is made of a nickel-cobalt alloy, embedded in ethylene-tetrafluoroethylene, and covered with polycarbonate polyurethane [12]. Electrodes are carefully placed into the specific target in the brain, which is identified using a three-dimensional MRI image. Thanks to modern imaging technology, the surgical procedure can be performed without causing harm to health. The electrodes are secured in the skull opening and connected to cables that run under the skin to a pocket created underneath the collarbone. From there, the cables are linked to the implantable neuropacemaker. The precise position of the electrodes is confirmed using intra- or postoperative imaging on an MRI machine or computed tomography. A few days after the surgery, electrostimulation is administered by a neurologist, neurosurgeon, or a dedicated DBS nurse. The electrical current used has a frequency of 130 Hz, a pulse width of 60 ms, and the amplitude is adjusted in the range of 1 to 4 milliamperes based on the clinical response. Interestingly, different contacts are utilized, which can be activated independently or together depending on the clinical indications. The battery in a neuropacemaker typically lasts 3-5 years or is rechargeable and has a lifespan of 15-25 years [13].

This therapy is typically used in patients who have undergone years of dopamine replacement that has lost its effectiveness and caused dyskinesia. The electrical current in DBS is delivered via electrodes implanted in specific nuclei of the brain, specifically the subthalamic nuclei (STN) and the globus pallidus internus (GPi) [14].

There is an ongoing debate about the best brain target for deep brain stimulation (DBS) in treating Parkinson's disease (PD). The subthalamic nucleus (STN) and the internal globus pallidus (GPi) are potential targets. The ventralis intermedius nucleus of the thalamus may help with tremors in PD, but does not alleviate other symptoms like bradykinesia, rigidity, and dyskinesia. STN-DBS has the most evidence for producing the best results and is the preferred target. It allows for a reduction in medication, with an average reduction of 50% in antiparkinsonian medications one year after surgery. The reduction in dyskinesias is similar after STN-DBS (20%-85%) and after GPi-DBS (40%-87%). For older, frail, and weaker patients with mild cognitive impairment, GPi-DBS seems to be a safer option. In patients with certain profiles of cognitive and behavioral problems, the possibility of reducing antiparkinsonian medications with STN-DBS, especially dopamine agonists, may also play a positive role [15].

The procedures for DBS surgery may vary slightly depending on the surgical team and available equipment. The main steps include preoperative assessment, installation of the stereotactic head frame, imaging localization, skin incision and skull perforation, electrode implantation, intraoperative imaging or microelectrode recording, assessment of the stimulation effect, fixation, pulse generator implantation, and postoperative parameter adjustment [16].

3.3. PATIENT SELECTION

In the literature, an increasing number of publications on DBS can be found, addressing the treatment of various types of disorders. It has been demonstrated that DBS can be beneficial for treating dystonia, tremor, pain, progressive supranuclear palsy, epilepsy, Tourette syndrome, autism, Alzheimer's disease, as well as several psychiatric conditions such as obsessive-compulsive disorder, depression, anorexia nervosa, addiction, and post-traumatic stress disorder [17]

Deep brain stimulation (DBS) is an effective treatment option for patients with dopaminergic complications of Parkinson's disease (PD) and medication-resistant PD tremor. Proper patient selection is the first step to achieving a successful surgical outcome. To meet the criteria for a good candidate for DBS, patients must have at least one indication and fulfill all five prerequisites [18]

The indications include:

- Motor complications (motor fluctuations and dyskinesias),
- Tremor resistant to optimized levodopa treatment,
- Intolerance to dopaminergic agents (patients experience side effects such as drowsiness, hypotension, nausea, vomiting, impulse control disorders, and drug-induced psychosis, preventing dose escalation to a level that would alleviate symptoms).

The prerequisites include:

- A confirmed diagnosis of Parkinson's disease, as atypical parkinsonism is not beneficial for DBS,
- Disease duration of more than 4 years (these requirements were developed to exclude individuals with atypical parkinsonism due to a lack of benefit and the risk of harming patients without idiopathic Parkinson's disease) [19]
- A cutoff value of 33% in the levodopa challenge test – CAPSIT-PD recommends a dopaminergic response confirmed by the levodopa/apomorphine challenge test (LCT). The test must show at least a 33% reduction in the score on the Unified Parkinson's Disease Rating Scale (UPDRS) part III in the "defined state" (the best therapeutic effect after treatment agreed upon by the patient and physician) compared to the "off state" (at least 12 hours after the last dose of medication). A 33% improvement in the UPDRS score is considered significant to exclude possible misdiagnosis (i.e., the identification of atypical parkinsonism, for which DBS is not recommended) [20]
- No significant cognitive deficits or uncontrolled neuropsychiatric disorders, as patients with dementia do not benefit, and those with uncontrolled neuropsychiatric conditions have a higher risk of complications,
- The ability to attend frequent follow-up visits after surgery (it is crucial to ensure good post-operative programming, medication adjustments if needed, and rehabilitation).

The relative exclusions include: [21]

- Biological age over 75 years
- Reduced life-expectancy linked with severe/malignant comorbidity
- Chronic immunosuppresion
- Distinct brain atrophy
- Severe comorbid psychiatric disorder (such as major depression, substance abuse, personality disorders, manifest psychosis)

The growing power of genetic analyses has led to the identification of several chromosomal loci that cause or modulate the risk of Parkinson's disease. [22] Moreover, specific genetic mutations have been associated with distinct clinical features and different disease courses, which may impact DBS selection. There is still insufficient evidence to support or reject DBS solely based on a patient's genetic background, but in the future, certain genotypes may be considered unsuitable for DBS due to the improbability of benefiting. [23]

3.4. DBS OUTCOMES

The assessment of Parkinson's disease progression and therapy effectiveness often involves rating scales that focus on specific motor symptoms such as bradykinesia (the Modified Bradykinesia Rating Scale - MBRS) or dystonia (the Unified Dystonia Rating Scale - UDRS, the Global Dystonia Severity Rating Scale - GDS), and assessing psychosocial functions (the Beck Depression Inventory - BDI, the Montgomery-Åsberg Depression Rating Scale - MÅDRS), The Pain in Dystonia Scale (PIDS), as well as those assessing psychosocial function (the Beck Depression Inventory (BDI), the Montgomery-Åsberg Depression Rating Scale (MÅDRS)), cognition (Mattis Dementia Rating Scale (MDRS)) or sleep quality (Scales for Outcomes in Parkinson's Disease - Sleep (SCOPA-S)). A widely used scale is the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPRDS) questionnaire, which is divided into four sections describing:

- non-motor experiences of daily living (Part I)
- motor experiences of daily living (Part II)
- motor examination (Part III)
- motor complications (Part IV).

The wide range of information gained from the scale is a useful control tool both in clinical practice and in the conduct of studies [24]. The Parkinson's Disease Questionnaire Summary Index (PDQ-39-SI) is a quality of life (QoL) scale that assesses difficulties experienced in 8 levels of daily functioning. In 39 items, the patient identifies the severity of symptoms, their impact on their physical and psychological well-being, and possible limitations in performing social functions. Adaptation to independent living is also assessed with the Schwab&England scale of Activities of Daily Living (ADL), in which the patient's maintenance of independence is described as an S&E scale score $\geq 70\%$ [25, 26].

The therapeutic efficacy of Deep Brain Stimulation (DBS) is predominantly contingent upon the duration and severity of the disease. Noteworthy determinants of accelerated Parkinson's disease progression encompass cognitive impairment, autonomic dysfunction, and motor component scores on the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [27]. The implementation of STN-DBS during the advanced stage of the disease has been found to effectively mitigate the severity of dyskinesias.

Conversely, the early application of DBS has demonstrated a predisposition to delay the onset and potentially avert the development of dyskinesias [28]. Implementation of non-pharmacological therapy at an early stage of the disease, often also associated with a younger age than in patients at an advanced stage, increases the chance of patients reducing cognitive deficits, and axial symptoms. It can also result in the maintenance of a good response to levodopa allowing prolonged treatment with low doses [29].

In a study involving a small group of early-stage Parkinson's disease (PD) patients, the development of resting tremors 'off' after treatment with optimal drug therapy (ODT) and extended by deep brain stimulation (DBS+ODT) was compared. Patients in the ODT group experienced a systematic worsening of resting tremor, progression to unoccupied limbs was noted in 86% of subjects. In DBS+ODT patients, no worsening of symptoms was noted, and spread to unoccupied limbs affected about half of the subjects (46%). These findings may indicate not only a reduction in symptom severity at the time of treatment but also a potential slowing of progression in the postoperative period [29].

In a study that compared DBS patients with malignant and benign phenotypes in terms of motor improvement and fluctuation inhibition, it was observed that both groups showed a similar degree of postoperative improvement. However, during the follow-up period, the malignant phenotype group had a 16-fold higher risk of experiencing loss of independence and S&E<70%, as well as a 20% incidence of loss of ADLs within the first year. A key factor in these outcomes may be the significantly higher burden of non-motor symptoms in patients with severe disease, which can impact the improvement and maintenance of ADLs after DBS [26].

QoL improves in the majority of patients after DBS. Still, the degree of improvement is closely linked to the presence and severity of preoperative non-motor symptoms such as depression, anxiety, cognitive impairment, or pain. The effect of DBS in patients with high QoL preoperatively, despite improving motor performance, resembles that of pharmacological treatment. In contrast, in patients with low QoL, in whom the non-motor component predominates, as reflected in PDQ-39 scores, DBS has much better outcomes than drug treatment alone and results in a significant enhancement in QoL post-treatment. QoL is also strongly correlated with the ‘off’ time during the day. Patients with a higher cumulative daily ‘off’ time had significantly improved PDQ-39 scores in the post-DBS period. At the same time, these changes correlated with a post-operative reduction in total ‘off’ time, an improvement in UPRDS III during 'off' periods, and an overall improvement in patient mood [30].

3.5. COMPLICATIONS

Although DBS is considered a safe treatment option, it can induce some side effects [31]. As the usage of DBS grows, the percentage of complications related to the therapy increases [32]. They can be produced by the misplacement of electrodes, which leads to targeting undesirable areas [31], but the cause may also be device malfunction, migration or infection. Usually, side effects are neurologic or psychiatric [32], and most of them are partly reversible [31].

Surgical complications of DBS may be divided into short and long-term. The most dangerous short-term complications are vessel rupture with the formation of a hematoma and surgical site infection. According to the study conducted by J. Eiamcharoenwit and P. Akavipat, intraoperative complications occur in 2.2%–13% of patients.

The study included 46 patients - 30 of them were hypertensive during electrode placement and 14 of them were hypotensive during battery placement. Other intraoperative complications were bradycardia, excessive sedation, desaturation, nausea, vomiting [33], seizures and lead migration [34].

Studies point at various postoperative side effects as the most frequent ones. Research conducted by W. Wu et al. proved that both dyskinesia and dizziness are the most prevalent side effects among elderly patients who underwent DBS [35]. According to J. Eiamcharoenwit and P. Akavipat, however, delirium is the most common complaint among treated patients and during the study, 6 out of 46 have experienced it [33]. Frequent postoperative side effects include dysarthria and balance disturbance. They happen primarily during bilateral stimulation and are caused by the current reaching the motor internal capsule. Patients may also experience ocular symptoms such as oculomotor dysfunction [31] and eyelid opening dyspraxia [35]. The coordination of ocular muscles is affected when the current reaches limbic coral structures. This dysfunction can be successfully treated by botulinum toxin injection [31].

Other postoperative side effects include decreased memory and intelligence [32] or behavioral disturbances, such as manic or depressive episodes. Changes in demeanor occur when limbic coral structures are affected by the current. Manic episodes may happen after a DBS session if medications with dopaminergic effects are not decreased after surgery, as DBS potentiates their effect [31]. M. Lange et al. suggested that the average estimated risk of mood changes or depression is 30,6% [36]. Among cognitive effects, delayed recall has been reported. It was greater in patients treated with DBS compared to patients treated with oral drugs. Another frequent side effect was decreased verbal fluency, which could be caused by reduced activity of the left temporal and inferior frontal cortex after DBS. It could, however, also be caused by cognitive deterioration due to the progression of the disease [34].

Other postoperative effects include lack of stimulation effect and infection [32], with infection being the most common surgery-related complication according to a meta-analysis performed by M. L. Lachenmayer, as it is estimated to occur in 5.1% of cases [37]. Intracranial hemorrhage, subdural hygroma and pulmonary embolism were also observed [33]. The average risk of intracerebral hemorrhage is estimated at the level of 4.4% [36].

Deep brain stimulation is a promising treatment option in patients with Parkinson’s disease. However, to prevent side effects and complications, it is crucial to carefully place electrodes so the area of active stimulation and volume of electrode contact are precise.

4. CONCLUSION

Developed in the late 1980s, deep brain stimulation (DBS) is an effective treatment option for advanced Parkinson's disease. It is intended for patients who meet specific criteria. The patient must have a confirmed diagnosis of PD, must have been ill for more than four years, must have a good response to levodopa, must not have severe cognitive impairment and must not have untreated psychiatric conditions. The last two criteria are related to the fact that patients with dementia do not benefit and patients with uncontrolled neuropsychiatric disorders are at higher risk of complications. Typically, this therapy is used on patients who have undergone many years of dopaminergic therapy that has lost its effectiveness and caused dyskinesia. DBS has required many modifications since its discovery. The battery required changes - it was too large and had too short an operating time.

Current DBS systems consist of an intracranial electrode, an extension cord, and a pulse generator. The battery usually lasts 3-5 years or is rechargeable and has a 15-25 year lifespan. The subthalamic nucleus (STN) and the globus pallidus internus (GPi) are potential targets for deep brain stimulation (DBS) in Parkinson's disease. STN-DBS has the most evidence for the best results and is the preferred method. It allows for the largest reduction in the use of antiparkinsonian drugs. However, in older, frail people with mild cognitive impairment, GPi-DBS is better. Similar levels of dyskinesia reduction characterize GPi-DBS and STN-DBS. The effectiveness of DBS treatment depends primarily on the duration and severity of the disease. The quality of life was improved in most patients who have had DBS. The degree of improvement is closely related to the presence and severity of preoperative non-motor symptoms – depression, pain, cognitive impairment, and anxiety. The effect of DBS in patients whose quality of life before surgery was high resembles the effect of pharmacological treatment. In contrast, in patients with low quality of life, in whom the non-motor component dominates, DBS has much better results than pharmacological treatment alone. DBS is considered a safe method, but various side effects do occur. According to studies, the most common side effects are postoperative. The main side effects include dyskinesia, dizziness, and delirium. Dysarthria and balance disorders are also common postoperative side effects. Memory disorders may also occur. In summary, deep brain stimulation (DBS) is a promising treatment option for patients with Parkinson's disease, and careful and precise electrode placement is important to prevent side effects and complications.

DISCLOSURE

Conceptualization: JK, AH, KJ, OS, JW, DD, DR, AM, Software: JK, AH, KJ, OS, JW, DD, DR, AM, Check: JK, AH, KJ, OS, JW, DD, DR, AM, Formal analysis:JK, AH, KJ, OS, JW, DD, DR, AM, Investigation: JK, AH, KJ, OS, JW, DD, DR, AM, Resources: JK, AH, KJ, OS, JW, DD, DR, AM, Data curation: JK, AH, KJ, OS, JW, DD, DR, AM, Writing rough preparation: JK, AH, KJ, OS, JW, DD, DR, AM, Writing review and editing: JK, AH, KJ, OS, JW, DD, DR, AM, Visualization: JK, AH, KJ, OS, JW, DD, DR, AM, Supervision: JK, AH, KJ, OS, JW, DD, DR, AM, Project administration: JK, AH, KJ, OS, JW, DD, DR, AM

Supplementary Materials:
They have not been provided.

Funding Statement:
This research received no external funding.

Institutional Review Board Statement:
Not applicable.

Informed Consent Statement:
Not applicable.

Data Availability Statement:
Not applicable.

Conflict of Interest:
The authors declare no conflict of interest.

All authors have read and agreed to the published version of the manuscript

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