



Spinal cord stimulation in chronic pain: technical advances

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Chronic severe pain results in a detrimental effect on the patient's quality of life. Such patients have to take a large number of medications, including opioids, often without satisfactory effect, sometimes leading to medication abuse and the pain worsening. Spinal cord stimulation (SCS) is one of the most effective technologies that, unlike other interventional pain treatment methods, achieves long-term results in patients suffering from chronic neuropathic pain. The first described mode of SCS was a conventional tonic stimulation, but now the novel modalities (high-frequency and burst), techniques (dorsal root ganglia stimulations), and technical development (wireless and implantable pulse generator-free systems) of SCS are becoming more popular. The improvement of SCS systems, their miniaturization, and the appearance of new mechanisms for anchoring electrodes results in a significant reduction in the rate of complications and revision surgeries, and the appearance of new waves of stimulation allows not only to avoid the phenomenon of addiction, but also to improve the long-term results of chronic SCS. The purpose of this review is to describe the current condition of SCS and up-to-date technical advances.

Key Words: Chronic Pain; Complex Regional Pain Syndromes; Failed Back Surgery Syndrome; Low Back Pain; Neck Pain; Neuralgia; Pain; Pain Management; Spinal Cord Stimulation.

INTRODUCTION

The high prevalence of chronic pain syndromes and serious detrimental effect on the patients' quality of life are the reasons why chronic pain remains one of the most important problems of global healthcare. The situation is particularly worse, due to high incidence of chronic pain becoming refractory to conventional treatment. Drug

resistance, for example, may be as high as 5% overall [1]. The prevalence of drug resistance may be much higher for certain groups of pain syndromes. For some, including chronic pelvic pain, it may reach 20%-65% [2], and in patients with chronic neuropathic pain after spinal cord injury, drug resistance occurs to 96%. Such patients have to take large number of medications, including opioids, without satisfactory effect, sometimes leading to medication

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abuse and pain worsening. According to a recent study, the average dosage of top gabapentin users for the treatment of neuropathic pain is 9,534 mg/day, which is almost 3-fold higher than recommended dosage [3]. In addition to this, chronic pain has been shown to be associated with an increased risk of suicidal intent and social isolation.

Since the spinal cord stimulation (SCS) was discovered, it has become one of the most impressive tools in the field of treatment for chronic neuropathic pain. The purpose of this review is describing the current condition of SCS and up-to-date technical advances.

MAIN BODY

1. History of SCS

Fortunately, medically refractory pain may frequently be controlled with interventional approaches, including electrical neurostimulation. Back in March 2017, the medical community commemorated the 50 year anniversary of the first-ever implantation of a SCS device by a neurosurgeon from La Crosse, Wisconsin, named Norman Shealy, who introduced the concept of stimulation of the posterior columns for treatment of severe refractory pain. Since then, SCS has become the most frequently performed surgical procedure for the treatment of chronic pain around the world, replacing all destructive and ablative procedures. SCS was, in essence, a huge step forward in pain management, furthering the understanding of the fundamental mechanisms of nociception. Since that time, the conventional tonic stimulation used by Shealy, and everyone else for the first several decades, has become supplemented by new SCS paradigms, primarily high-frequency (HF), and ‘burst’ stimulation.

2. Effect of SCS

The mechanisms of tonic SCS action are not understood completely. The main mechanism is thought to be related to the ‘gate-control’ theory of Melzack and Wall [4,5]. According to this theory, electrical stimulation of large-fiber neurons blocks transmission of neuropathic pain impulses from primary small-fiber afferents. Other explanations include the effect of SCS on the central mechanisms of pain, in particular, on the phenomenon of central sensitization [6]. Moreover, the studies of SCS in an animal model have shown that stimulation affects the hyperexcitability of the neurons, and this effect may be related to the intracellular glutamate concentration. The effects of SCS on the neurotransmitter systems have been demonstrated in a number of studies [7,8] and are summarized in **Table 1**.

A different mechanism of SCS action involves its effect on peripheral structures, particularly changes in blood microcirculation in the limbs and at the spinal segmental dermatomes corresponding to levels of electrode implantation [9]. Recent investigations studied the potential role of SCS in neuroprotection, synaptic plasticity, nociceptive signaling, and immune regulation. Studies of cerebrospinal fluid samples in 14 patients with a good effect from SCS showed a statistically significant increase in the cerebrospinal fluid concentrations of certain proteins, including those responsible for neuroprotection (clusterin, gelsolin, mimecan, and amyloid beta-A4 protein), nociceptive signaling (neurosecretory protein VGF), and synaptic plasticity (gelsolin) [10].

3. Indications and patient selection

When discussing SCS effectiveness, it is important to mention the patient selection criteria. Incorrect patient selection is likely to be one of the most important reasons for ineffectiveness of stimulation. For example, SCS is often used in patients with nociceptive pain, whereas in the past, the lack of improvement with SCS in these patients has been well documented. Other important criteria that have to be considered in patient selection are the psychological and psychiatric aspects. According to contemporary views, anxiety-depressive disorders can be both a consequence of chronic pain and its immediate cause. In patients with secondary psychological disturbances, SCS results in a reduction of the severity of anxiety-depressive symptoms as demonstrated in many studies. At the same time, SCS is not expected to work well in patients with psychiatric conditions when pain is only a manifestation of the underlying disease (such as somatization, or undiagnosed or undertreated depression). The presence of ‘red flags’ in psychological tests is associated with an unfavorable prognosis [11,12]. The effectiveness of neurostimulation may also be influenced by a so-called ‘delay’ period—the time that passes between the trial and permanent SCS implantation. Studies have shown that a longer ‘delay’ pe-

Table 1. The Influences of the SCS on Neurotransmitter Concentrations

Neurotransmitter	SCS effect on concentration
GABA	Increase
Serotonin	Increase
Substance P	Increase
Noradrenaline	Increase
Acetylcholine	Increase
Adenosine	Increase
Glutamate	Decrease
Aspartate	Decrease

SCS: spinal cord stimulation, GABA: gamma-aminobutyric acid.

riod is associated with lower effectiveness of neurostimulation [12].

Current recommendations suggest use of SCS in medically refractory pain. These are criteria of the medical refractoriness of pain syndromes [13]:

- 1) There should have been a trial of treatment with at least 4 drugs of known effectiveness in neuropathic pain;
- 2) each of these drugs should have been tried for at least 3 months or until adverse effects prevent adequate dosage or continued treatment;
- 3) despite this treatment, the intensity of pain should not have been reduced by more than 30%, or should remain at a level of at least 5 on a 0-10 scale; and/or it should continue to contribute significantly to poor quality of life.

As to the chronicity of pain needed for patients to qualify for SCS, the 3-6-month duration is defined as shortest period to call the condition chronic.

The credibility of neurostimulation has gained significant momentum with completion of several large prospective randomized controlled studies. Overall, SCS has a wide range of indications for the treatment of various chronic pain syndromes that come with different levels of evidence (Table 2) [14-18]. The U.S. Food and Drug Administration has approved SCS for the treatment of pain in the trunk and extremities, including patients with failed back surgery syndrome (FBSS) [19]. According to a systematic review by Taylor et al. [20] involving 78 studies, the use of SCS is associated with significant pain relief (an average 30% reduction in the visual analogue scale [VAS] compared to baseline). The PROCESS (prospective, randomized, controlled, multicenter trial aims to assess the clinical effectiveness and cost-effectiveness of SCS) study included 100 patients with FBSS, 52 of them making up the SCS group, and 48—the conventional medical treatment group. After 6 months of treatment, half of patients in the SCS group received satisfactory pain relief (50% and higher), whereas only four patients in the non-SCS group obtained similar results [21].

The evidence of the efficacy of SCS, however, does not

reach level A in patients with refractory angina pectoris, with contraindications for cardiac surgery (angioplasty or coronary bypass surgery), and/or with syndrome X. However, many studies point out the potential effectiveness of neurostimulation for these indications. A recent meta-analysis, which included 14 studies and 518 patients, demonstrated the positive effect of SCS on physical activity, a reduction in nitrite consumption, and a lower frequency of heart attacks [22]. This may serve as a rationale for use of SCS as an adjuvant therapy in such patients.

In 2014, members of the Neuromodulation Appropriateness Consensus Committee (NACC) published recommendations on the use of spinal cord and peripheral stimulation in patients with chronic pain and ischemic diseases. Special attention was drawn to the use of SCS in the treatment of critical limb ischemia. The authors pointed out that neurostimulation cannot be considered a true alternative to conventional medical treatment, but significantly improves outcomes when used as an adjuvant treatment [23].

SCS application for the treatment of specific neuropathic pain conditions is supported by multiple studies. Very good results can be achieved with the use of SCS in patients with diabetic painful polyneuropathy (DPN). Slanzen et al. [24] demonstrated the great long-term efficacy of spinal neurostimulation in comparison with conventional treatment. SCS significantly reduced pain intensity and improved the quality of life in DPN patients [25,26].

Complex regional pain syndrome (CRPS) has become a great indication for SCS. Published results suggest SCS efficacy in patients with CRPS types I and II [27]. Pain relief of greater than 50% was demonstrated in 67% of patients after 33 months of follow-up. According to some authors, it would be advisable to consider the option of SCS implantation after 12-16 weeks of ineffective conservative treatment [28].

Table 2. Results of the Most Significant Latest Investigations of Spinal Cord Stimulation for the Treatment of Different Pain Syndromes

Study	Year	Pain syndrome	Design	Result
Slanzen et al. [14]	2014	Diabetic painful neuropathy	Prospective, randomized	36 patients: 77% responders; 59% with good effect (significant pain relief/sleep improvement)
Zipes et al. [15]	2012	Refractory angina pectoris	Multi-center	Mean decrease in heart attacks by 1.2 ± 2.1 times
Özdemir et al. [16]	2017	CRPS	Retrospective	62 patients with refractory CRPS: significant pain relief, improvement in sleep and daily activity in all patients
Kapural et al. [17]	2010	Refractory visceral pain	Retrospective	35 patients, pain relief more than 50% in 30 patients
Kapural et al. [18]	2011	Refractory visceral pain (chronic pancreatitis)	Retrospective	30 patients, 50% pain relief in 80%, a year after implantation Absolute pain relief from 8.0 ± 1.6 to 3.6 ± 2.0 on VAS Decrease of opioid uptake

CRPS: complex regional pain syndrome, VAS: visual analogue scale.

Table 3. Results of the Most Significant Investigations of Conventional SCS Application for the Treatment of Patients with Low Back and Leg Pain

Study	Year	Design	Result
Kumar et al. [21]	2005	Prospective, randomized, controlled	52 patients implanted with SCS, 42 responders Significant pain relief in 50% of patients after 6 mo of stimulation
Barolat et al. [29]	2001	Prospective multi-center	Significant pain relief in 88% of patients with leg pain and in 88% of patients with low back pain after 12 mo of follow-up
North et al. [30]	2005	Prospective, randomized, controlled	Significant pain relief

SCS: spinal cord stimulation.

Table 4. The Most Significant Investigations of HF and 'Burst' SCS in Patients with Different Chronic Pain Syndromes

Study	Year	Method	Material	Result
Al-Kaisy et al. [31]	2014	HF SCS	82 patients with low back and leg pain	Successful trial in 72 patients Low back pain relief from 8.4 ± 0.1 to 3.3 ± 0.3 Leg pain relief from 5.4 ± 0.4 to 2.3 ± 0.3 after 24 mo in course of stimulation
Deer et al. [32]	2018	Burst vs. tonic SCS ^a	Totally 100 patients: 45 tonic, 55 burst	Subjects withdrawn: 4 70.8% preferred burst stimulation over tonic stimulation ($P < 0.001$) After 1 yr: 68.2% preferred burst SCS, 23.9% tonic SCS, and 8.0% no preference
Kapural et al. [33]	2016	HF SCS ^b	101 patients with low back and leg pain	Mean relief of low back pain $66.9\% \pm 31.8\%$; leg pain $65.1\% \pm 36.0\%$
Thomson et al. [34]	2018	HF SCS	PROCO-RCT, total of 34 patients	Pain relief (NRS) $\geq 30\%$ in 21 patients, $< 30\%$ in 10 patients After randomization, significant efficacy for all frequencies
De Andres et al. [35]	2017	HF vs. CF SCS	Randomized blind effect-on-outcome study 55 patients with FBSS: 26 HF SCS and 29 CF SCS	No significant difference between groups in change of pain intensity, painDetect Questionnaire scores, Short Form-12 scores (except social function)
Al-Kaisy et al. [36]	2017	HF SCS	21 patients with low back pain in patients without preceding spinal surgery	21 patients, positive test stimulation in 20 patients 73% pain relief on VAS after 12 mo of stimulation
Kinfe et al. [37]	2016	8 burst and 6 HF SCS	14 patients with FBSS	Decrease of opioid uptake by 64% Trial failure 2 patients (HF SCS) Pain relief with 'burst' SCS 1.8 ± 0.7 on VAS; HF SCS 2.2 ± 1.0
Muhammad et al. [38]	2017	8 HF and 8 burst SCS	16 patients with FBSS, with predominant back pain	87.5% pain relief in burst stimulation group and 54.9% in HF SCS group
Lambru et al. [39]	2016	Cervical HF SCS	4 patients with chronic migraine; 2 patients with chronic SUNA; 1 patient with chronic cluster headache	Pain relief minimum 50% in all the patients after 28 mo in course of stimulation Complete pain regress in one patient with chronic SUNA
Arcioni et al. [40]	2016	Cervical HF SCS	17 patients with chronic migraine	System implantation in 14 points Decrease in number of days with headache by 30% in 7 points

SCS: spinal cord stimulation, HF: high-frequency, PROCO-RCT: pulse rate on clinical outcomes-randomized controlled trial, NRS: numeric rating scale, CF: conventional-frequency, FBSS: failed back surgery syndrome, VAS: visual analogue scale, SUNA: short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms.

^aSuccess using neuromodulation with burst (SUNBURST) study, ^bsystem of neurostimulation from 'Nevro' (SENZA) study.

4. Technical advances of SCS

The benefit of conventional SCS has been supported by multiple studies (Table 3) [21,29,30], but the lack of a uniform response to the paresthesia-based tonic SCS prompt-

ed introduction of new stimulation paradigms: HF SCS and burst stimulation (Table 4, Fig. 1) [31-40].

One of the main advantages of HF SCS is the absence of paresthesia. Based on published studies, the effectiveness of HF SCS is significantly higher than conventional tonic

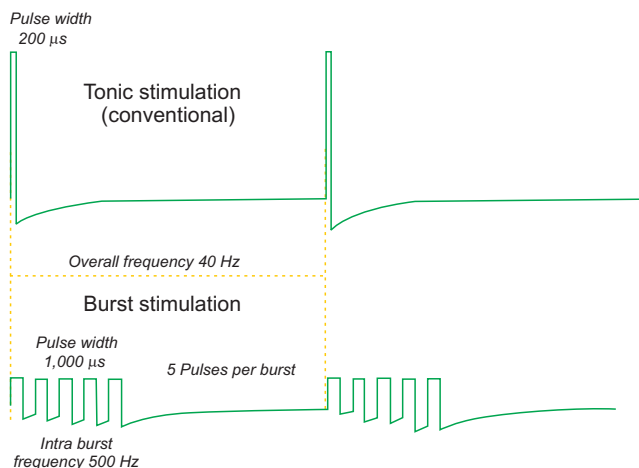


Fig. 1. Stimulation patterns in tonic (conventional) and burst stimulations.

SCS, resulting in claims of ‘superiority’. There is no general agreement on the HF SCS mechanism of action, but it is possible that HF SCS works on large axons (with 12-15 mm diameter), leading to the suppression of wide dynamic range neurons without paresthesia [41,42]. Russo et al. [43] performed a retrospective analysis of 256 patients with refractory pain syndromes treated with HF SCS. Mean pain relief after 6 months of follow-up was 50%, while the maximal pain relief (81% and higher) was seen in patients with simultaneous pain in the back and leg.

A multicenter study compared HF SCS with tonic (conventional) SCS and included 101 patients with HF and 97 patients with classic tonic SCS [33]. More than 80% of patients in both groups had a history of unsuccessful spinal surgery, and almost 90% of all the patients had received opioids. After 12 months of follow-up, pain relief was significantly higher in the group receiving HF stimulation (65% in the HF SCS group vs. 45% in group receiving tonic SCS). After 24 months of follow-up, mean pain relief was 50%, with the average relief of low back pain in the HF SCS group being $66.9\% \pm 31.8\%$ vs. $41.1\% \pm 36.8\%$ in the tonic SCS group, and leg pain relief was $65.1\% \pm 36.0\%$ in the HF stimulation group vs. $46.0\% \pm 40.4\%$ in the tonic SCS group. It should be pointed out that in both groups, the number of patients taking opioids significantly decreased, and the patients’ quality of life improved.

Most recently published was the multicenter, double-blind, crossover randomized controlled trial aimed at evaluating the effects of rate on analgesia in HF SCS, which enrolled 34 patients with persistent or recurrent low back pain, with or without equal or lesser leg pain, for at least 90 days prior to the screening. Electronic diaries with numeric rating scale (ED-NRS) were used to evaluate pain intensity during the study. One patient had an unsuccessful stimulation trial, but the remaining subjects

were implanted with SCS systems. Ten of them experienced < 30% pain relief, 1 patient withdrew due to new onset pain, and 20 patients with $\geq 30\%$ pain relief were randomized and received HF stimulation with frequencies of 1, 4, 7, and 10 kHz in random order. All frequencies were found to be equally effective in providing pain relief as measured by ED-NRS ($P \leq 0.002$). However, mean charge per second differed across frequencies, with 1 kHz SCS requiring 60%-70% less charge than higher frequencies ($P < 0.01$) [34].

Some other studies, however, have reported that HF SCS lacks absolute superiority over conventional tonic stimulation. De Andres et al. [35] completed a prospective, randomized, blind, effect-on-outcome study of conventional versus HF SCS in patients with pain and disability due to FBSS. The authors claimed independence from manufacturer sponsorship. The study enrolled 55 patients with FBSS that were implanted with an SCS system. The study demonstrated that pain relief (measured with the NRS and painDetect questionnaire), in all patients, did not differ based on their treatment by spinal stimulation with conventional or HF SCS, at the one-year follow-up [35].

Burst SCS may act through simultaneous activation of the so-called lateral (somatosensory) and medial (emotional) pain pathways, producing activation of the anterior part of cingulate gyrus and the right dorsolateral prefrontal cortex [44]. Kriek et al. [45] reported that during burst stimulation, decreased hypersensitization of neurons in the posterior horn occurs with simultaneous activation of gamma-aminobutyric acid B-receptors, increasing the inhibitory effects of burst stimulation. De Ridder et al. [46] reported interesting data on the effectiveness of burst stimulation, indicating that burst SCS can be effective in patients with CRPS (pain relief 55% vs. 31% with tonic SCS). A double-blind, randomized, placebo-controlled trial, published by Schu et al. [47] compared the efficacy of burst SCS and 500 Hz HF SCS in patients with FBSS. The study included 20 patients (13 female and 7 male) divided into three groups: placebo (sham) stimulation, 500 Hz HF stimulation, and burst stimulation. Mean pain intensity was primarily 5.6 ± 1.7 on the VAS. After stimulation, pain intensity on the VAS scale was 7.1 ± 1.9 in the 500 Hz stimulation group, 4.7 ± 2.5 in the burst stimulation group, and 8.3 ± 1.1 in the placebo group. Mean value in the Oswestry disability index (ODI) before the stimulation was 22.3 ± 8.0 ; after stimulation it was 19.2 ± 8.0 in the burst group it was; 24.6 ± 7.3 in the 500 Hz stimulation group, and 29.5 ± 10.3 in the placebo group.

A prospective multicenter randomized controlled study success using neuromodulation with burst (SUNBURST) by Deer et al. [32] was aimed to determine the safety and efficacy of a device delivering both traditional tonic

stimulation and burst stimulation (Fig. 1) to patients with chronic pain of the trunk and/or limbs. The study enrolled a total of 100 subjects with successful results in the tonic trial, that were randomized to receive either burst or tonic stimulation mode for the first 12 weeks, and then the other stimulation mode for the next 12 weeks. The study demonstrated that significantly more subjects (70.8%) preferred burst stimulation over tonic stimulation ($P < 0.01$). Preference was sustained through one year: 68.2% of subjects preferred burst stimulation, 23.9% preferred tonic, and 8.0% had no preference. No unanticipated adverse events were reported and the safety profile was similar to other SCS studies.

Another approach that utilizes a new target for neurostimulation, the dorsal root ganglia (DRG), was recently introduced and investigated. DRG stimulation appears to affect neuronal activity through a complex cascade of chemical and electrical responses mediated by its influence on glial cells and microglial cells [48,49]. The multicenter prospective randomized controlled trial of DRG stimulation *versus* SCS analyzed treatment effectiveness in 152 patients with CRPS in the lower extremities and conclusively showed the superiority of DRG stimulation in terms of pain relief, improvement in quality of life, less postural variation, and higher rate of treatment success [50]. According to Eldabe et al. [51], DRG stimulation may also be an option in the treatment of phantom pain: in a small series of 8 patients, significant pain relief (initial mean pain intensity was 83.5 mm on the VAS, the average pain duration was 14.4 months, mean pain intensity after stimulation was 43.5 mm on the VAS), and decrease of medication uptake were demonstrated. Weiner et al. [52] reported a pilot study on the efficacy of DRG stimulation using a very different, miniaturized wireless device, in patients with FBSS. Mean pain relief was 59.9%.

In a paradigm-changing concept of closed-loop stimulation, Russo et al. [53] reported the results of a pilot study of the novel SCS system showing remarkably higher success rates. Trial leads were implanted in 51 patients; the final implantation was performed in 36 cases. Three months later, 50% or more pain relief was found in 92.6% of patients with low back pain and 91.3% of patients with leg pain. After 6 months of follow-up, 50% or more pain relief was seen in 85.7% of patients with low back pain and 82.6% of patients with leg pain. At the same time, at least 80% pain relief was observed in 64.3% of patients with back pain and in 60.4% of patients with pain in the leg.

One of the most significant technical advances of recent years is the creation of wireless SCS systems. Systems appeared with an external source of current. With their use, the trial period and the risk of complications associated with the implantable pulse generator and extension cables

can be avoided. Contacts are located at the distal end of the electrode and built-in microprocessor (receiver) at the proximal end. The receiver gets electrical impulses from an antenna located outside (at a distance of up to 6 cm), which, in turn, receives impulses from an external source. Bolash et al. [54] compared wireless HF (10 kHz) and multi-waveform low-frequency (LF) SCS. Wireless devices reduced FBSS chronic pain substantially with both LF and HF stimulation waveforms over a seven-month period. The patient's VAS scores for back and leg pain decreased significantly: 77% and 76% in the cases of HF SCS and 64% and 64% in LF SCS patients respectively. In addition, the majority of patients experienced significant improvements in the ODI, European Quality of Life 5 Dimension questionnaire, Patient Global Impression of Change, and sleep duration [54].

Despite the impressive technical developments in the field of SCS made in recent years, the question of the effectiveness of the method in comparison with a placebo continues to be raised. A recent meta-analysis showed limited effectiveness of SCS compared to sham stimulation. The results of this work are disputed, due to methodological issues (small sample sizes, differing SCS modalities, and a possible carryover effect in the crossover design study) [55].

5. New approaches to reduce the incidence of complications

Despite the relatively low incidence of complications for conventional SCS (an average incidence of 5% according to various studies), there are major efforts to reduce them, especially electrode migration. In 2017, NACC published recommendations and guidelines on prevention and management of the main surgical complications of neurostimulation [56-58]. For this, new fixation mechanisms providing a better securing of the electrode position were proposed, and neuromonitoring was suggested to reduce complications related to the electrode insertion. To reduce infectious complications, multiple recommendations have been introduced, with the goal of reducing the prevalence of infections to 1%. Additional improvements in surgical techniques could make spinal stimulation safer for a variety of different patient groups [11,59].

CONCLUSIONS

Based on recent clinical experience, it may be possible to create an algorithm for choosing the optimal approach to each clinical situation. The algorithm may be based on a combination of the currently available modalities: (a) conventional paresthesia-based stimulation, (b) HF

stimulation, (c) 'burst' stimulation, and (d) stimulation of DRG. Moreover, the introduction of nanotechnology-based miniaturized stimulators may significantly reduce the general invasiveness of spinal stimulation.

Overall, 50 years after its introduction, SCS has come out of a period of relative stagnation, and is rapidly advancing towards diversification and the creation of the strong evidence base necessary for making science-based decisions in choosing the optimal approach in individual clinical cases.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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