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Spinal Cord Stimulators: An Analysis of the Adverse Events Reported to the Australian Therapeutic Goods Administration

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Background: Spinal cord stimulators are used to treat intractable pain. Placebo-controlled trials of spinal cord stimulators typically involve short-term treatment and follow-up, so long-term safety and efficacy are unclear.

Aim: The aim of the study was to describe the adverse events relating to spinal cord stimulators reported to the Therapeutic Goods Administration of Australia between July 2012 and January 2019.

Methods: Adverse events were coded by seriousness, severity, body system affected, type of event, action taken, and attribution of fault. Data on the number of stimulators implanted and removed were sourced from the Admitted Patient Care Minimum Data Set.

Results: Five hundred twenty adverse events were reported for spinal cord stimulators. Most events were rated as severe (79%) or life-threatening (13%). Device malfunction was the most common event (56.5%). The most common action taken in response to an adverse event was surgical intervention with or without antibiotics (80%). The ratio of removals to implants was 4 per every 10 implanted.

Conclusions: Spinal cords stimulators have the potential for serious harm, and each year in Australia, many are removed. In view of the low certainty evidence of their long-term safety and effectiveness, our results raise questions about their role in providing long-term management of intractable pain.

Key Words: spinal cord stimulators, adverse events

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Spinal cord stimulators are devices implanted under the skin, which deliver electric impulses via leads placed in the epidural space.[1] The impulses interfere with how nociceptive signals are interpreted by the brain.[1] They are promoted as providing long-term pain relief, particularly when other interventions including surgery have failed.[2–4] They are commonly used for intractable back pain such as failed back surgery syndrome but are also used to treat other painful conditions including complex regional pain syndrome, angina, ischemic leg pain, and peripheral neuropathy.[2] Their use for the last 3 indications is not common in Australia.

The efficacy of spinal cord stimulators is uncertain because available trials are small, typically at high risk of bias and test brief treatment regimens.[5,6] A 2020 systematic review of 8 small randomized placebo-controlled trials (n = 185) reported a pooled effect on neuropathic pain of −1.15 points (95% confidence interval, −1.75 to −0.55) on a 0- to 10-point pain scale.[5] Effects on pain across individual trials were as large as 4 units to as low as zero units, with larger effects seen in studies at high risk of bias. No trial had a treatment regimen beyond 3 weeks, and some were as short as 12 hours.[5] Other trials by Kapural et al,[7] Kumar et al,[8] and Deer et al[9] commonly cited as evidence of efficacy of spinal cord stimulators only compared different types of regimens or stimulation levels without a placebo control and therefore do not provide information about their efficacy. Uncertainty about the efficacy of spinal cord stimulators is also reflected in guideline recommendations; some guidelines endorse their use[4,6] whereas others do not.[10]

Evidence for the long-term safety of spinal cord stimulators is also lacking. A narrative review reported average lead migration rates of 15.5%, device malfunction of 6.4%, and infection of 4.9%.[11] A recent trial examining 2 types of stimulators followed participants for 12 months and found that 67% had an adverse event with 13% experiencing a serious adverse event.[12] Long-term safety data could be derived from long-term observational registries but currently none exist. An alternate source of information on safety is the notifications of adverse events made to government regulators such as Australia's Therapeutic Goods Administration (TGA). The TGA's data are voluntarily reported by patients or healthcare providers and therefore do not contain all safety data relevant to a device and cannot be used to determine absolute risk.

The aim of this study was to describe the adverse events relating to spinal cord stimulators reported to the TGA between July 2012 (start date of the TGA's searchable database of notifications) and January 2019.

METHODS

Reports of adverse events associated with spinal cord stimulators were sourced from the TGA. To provide a context for the safety data, we sourced information on the number of spinal cord stimulators implanted each year in Australian hospitals.

Number of Spinal Cord Stimulators Implanted and Removed

Data on the number of spinal cord stimulators implanted and removed per year in Australia were sourced from the Australian Institute of Health and Welfare's National Hospital Morbidity Database (which are based on the Admitted Patient Care National Minimum Dataset) from July 2012 to June 2019.[13] We used the codes "39134-01 NEUROSTIMULATOR or RECEIVER, subcutaneous placement of, including placement and connection of extension wires to epidural or peripheral nerve electrodes, for the management of chronic intractable neuropathic pain or pain from refractory angina

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pectoris" for implants and the code "39135-00 NEUROSTIMULATOR or RECEIVER, that was inserted for the management of chronic intractable neuropathic pain or pain from refractory angina pectoris, removal of, performed in the operating theatre of a hospital" for removals.

Reports of Adverse Events

The TGA has a searchable log of reported adverse events associated with devices from posttrial use, created in July 2012.[14] To ensure completeness of information, we submitted a Freedom of Information request to the TGA and we obtained all reported adverse events from community members (outside of clinical trials) from July 2012 to January 2019. The requested list of adverse events is published on the TGA's website.[15]

Adverse Events Coding

We obtained the following information from the TGA: date of adverse event report, adverse event report number, key search words, device class, sponsor name, manufacturer name, clinical event information, and outcomes. The descriptions of the events varied in detail between 1 sentence to multiple paragraphs. Synthesis and coding were required as the clinical event information was free text of varying structure and detail, for example:

"A report was received that the patient underwent an explant procedure due to pain under the IPG site. The physician explanted the IPG and one lead, however, the other lead was left implanted due to scar tissue. The patient was reportedly doing well following the procedure."

The adverse event information from the clinical event column was coded as follows: seriousness, severity, body system affected, the type of event, the action taken with regard to the event, and which party was at fault if specifically stated.

Coding was completed by one researcher and a random sample of 10% was independently coded by a second researcher. There were 324 judgments made (6 coding systems for 55 events). Agreement between coders was 72%. Differences were mostly systematic, for example, coding all events requiring intravenous (IV) antibiotics as grade 4 versus grade 3 and were resolved with discussion. One researcher then made minor adjustments to the entire data set to reflect the coding decisions made, for example, ensuring that all events requiring IV antibiotics were coded as grade 4. No further double coding was done because of very high interrater agreement after the systematic differences were adjusted. Some events could be coded with multiple codes of each category. In these cases, the most serious (in terms of patient harm) code in relation to patient harm was selected.

Seriousness

Adverse events were coded as "serious" or "not serious" according to the Australian National Health and Medical Research Council (NHMRC) safety monitoring and reporting in clinical trials involving therapeutic goods guidelines.[16] A serious adverse event is any adverse event that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. Adverse events requiring surgical intervention were classified as serious as the patient would require hospitalization.

Severity

The severity of each event was graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).[17] The CTCAE is a grading scale originally developed for grading the toxicity of cancer treatments but is now commonly used as a standardized way to report adverse events from any clinical trial. The grades were as follows:

-Grade 1 Mild
-Grade 2 Moderate
-Grade 3 Severe
-Grade 4 Life-threatening or disabling
-Grade 5 Death

Adverse events requiring surgical intervention were classified as at least grade 3 (assuming that hospitalization was required). Adverse events involving infection that required hospital admission for intravenous antibiotics were classified as grade 4 because of the urgent and potentially life-threatening nature of infection in the epidural space.[18]

Body System Affected

The *International Classification of Diseases, Tenth Revision* (*ICD-10*) classification of disease codes[19] was used to classify the effect of the adverse event on the patient. Although it was not possible to select a code relating the patient's medical status, the code Y75.8 was used as a nonspecific representation that the event was associated with an implanted medical device.

Type of Event

Events were categorized into either device or patient issues. Device issues were events such as malfunction or damage to the hardware and issues with insertion or use. Patient issues were events such as a medical issue or adverse reaction. The events were further subcategorized using ad hoc categories based on the variety of events that were observed in the log.

Clinical Action Taken in Response to Adverse Event

Coding labels were created ad hoc based on the variety of actions observed in the log.

Fault

Where the party at fault was explicitly stated, the events were coded as either physician (e.g., accidentally severing electrode during implant), patient (e.g., failing to recharge to device as per recharge schedule), or device (e.g., hardware or software fault).

Data Analysis

The adverse events were counted and were calculated as a percentage of the total within each coding system. The devices implanted versus removed were described as ratios (devices removed per 1000 implanted).

RESULTS

The number of spinal cord stimulators implanted and removed each year and TGA reported events for the period 2012–2019 are shown in Table 1. There were a total of 26,786 devices implanted, 10,702 devices removed, and 520 reported adverse events.

Seriousness and Severity of Reported Adverse Events Relating to Spinal Cord Stimulators

Of the 520 unique adverse events logged with the TGA, 484 (93%) were rated as serious according to the NHMRC criteria. Based on the CTCAE coding of event seriousness, 5 (1%) resulted in death, 66 (13%) were life-threatening, 412 (79%) were severe, 15 (3%) were moderate, and 13 (3%) mild. Thirteen events (3%) could not be categorized because of insufficient information (n = 9) or duplication (n = 4).

TABLE 1. Totals Per Year of Spinal Cord Stimulators Implanted and Removed and Number of TGA Reported Adverse Events

Year	Units Implanted	Units Removed	Adverse Events
2012/13	2307	897	120
2013/14	2918	1073	53
2014/15	3217	1251	29
2015/16	4280	1577	35
2016/17	4433	1788	40
2017/18	4837	1996	103
2018/19	4794	2120	140*
Total	**26,786**	**10,702**	**520**

*Includes reports until January 31, 2019, only.

Nature of Reported Events

A total of 34 *ICD-10* codes were used to qualify the nature of the reported events. The top 6 are shown in Table 2. The most common events were device malfunction (n = 296), pain (n = 110), infection/inflammatory reaction (n = 55), hemorrhage/hematoma (n = 7), headache (n = 6), and puncture/laceration (n = 5; used for dural tears sustained during the procedure, usually with cerebral spinal fluid leakage). See Appendix 1, http://links.lww.com/JPS/A450 for a full summary of *ICD-10* codes.

Specific Device Failures

There were 247 events (47.1%) describing failures of the device. Migration of the electrical lead or fracture accounted for 87 of the events (35%). The device was faulty in 42 events (17%), half of which were found to be faulty immediately upon implant and half developed over time. The device was poorly positioned in 23 events (9%). There was an unspecified issue with a lead in 19 events (8%). See Appendix 2, http://links.lww.com/JPS/A450 for a summary of specific event details.

TABLE 2. Nature of Reported Events Qualified by the *ICD-10* Codes

Nature of Event (*ICD-10* Code)	Count	% of Total
Device malfunction (Y75.8)	296	56.5%
Pain (R52.9)	110	21.0%
Infection/inflammatory reaction (T85.7)	55	10.5%
Hemorrhage/hematoma (T81.0)	7	1.3%
Headache (R51.0)	6	1.1%
Puncture/laceration (T81.2)	5	1.0%
Other	45	8.6%

Y75.8—Neurological devices associated with adverse incidents—miscellaneous devices, not elsewhere classified (used for events where the device malfunctioned but a code describing the specific patient harm could not be used, e.g., the device migrated and needed to be surgically relocated).

R52.9—Pain, not otherwise specified (used when the patient complained of pain at the implant site or in another body part but no reason for the pain was described).

T85.7—Infection and inflammatory reaction due to other internal prosthetic devices, implants and grafts (used mostly for postoperative infections).

T81.0—Hemorrhage and hematoma complicating a procedure, not elsewhere classified (used mostly for postoperative hematomas that required surgical evacuation).

R51.0—Headache (used for headaches, some in relation to occipitally placed devices).

T81.2—Accidental puncture and laceration during a procedure, not elsewhere classified (used for dural tears sustained during the procedure, usually with cerebral spinal fluid leakage).

Other—all remaining *ICD-10* codes combined.

TABLE 3. Frequency of Clinical Actions Taken in Response to an Event

Action Taken	Count	% of Total
Single surgical intervention	383	73.1%
Single surgical intervention and IV antibiotics	21	4.0%
Multiple surgical interventions	16	3.1%
Single surgical intervention and oral antibiotics	13	2.5%
Admitted to hospital for medical management	12	2.3%
Not stated/insufficient information	9	1.7%
Single surgical intervention planned but not confirmed	9	1.7%
No action taken	7	1.3%
Other	54	10.3%

See Appendix 3, http://links.lww.com/JPS/A450 for full breakdown under "other" category.

Clinical Action Taken in Response to Event

The clinical actions taken in response to an event are described in Table 3. The most common action was a single surgical intervention with or without antibiotics (79.6%).

Attribution of Fault

Most reports did not include a comment on responsibility. The reports noted that the clinician was at fault in 20 events (e.g., "during the procedure, the physician inadvertently cut the lead…"), the device in 14 events, and the patient in 2 events. Responsibility for the event was not clearly stated in the other 484 event reports.

DISCUSSION

This study provides policy makers, clinicians, and prospective patients with important safety information relating to spinal cord stimulators in Australia. The TGA received notifications of 520 adverse events in a period where 26,786 spinal cord stimulator devices were implanted. Of the adverse events reported, 93% met the NHMRC's criteria for a serious adverse event and most events were rated as severe (79%) or life-threatening (13%) according to the CTCAE criteria. Each year in Australia, for every 10 spinal cord stimulators implanted, approximately 4 are removed. For every 100 adverse events relating to spinal cord stimulators logged with the TGA, approximately 83 of them required at least 1 surgical procedure to correct.

To our knowledge, this is the first study to examine TGA data on reported adverse events relating to spinal cord stimulators. These data provide important information relating to their long-term safety not captured in short-term trials. A limitation of our study is that we likely underestimate the true number of adverse events as we used data that were voluntarily reported to the TGA rather than data obtained by prospectively monitoring all implanted devices. The TGA has acknowledged this issue on their website by citing a review that reports that 90% to 95% of adverse events go unreported.[20] Another potential limitation of this voluntary data set is that there may be a particular underrepresentation of minor adverse events. It is possible that consumers may see minor adverse events as less important and therefore not take the time to lodge a

report. This could have impacted our estimates of proportions of serious and severe adverse events.

Previous reviews of adverse events relating to spinal cord stimulators have concluded that the devices are safe and have downplayed the potential for serious adverse events.[11] In contrast, our study shows that many events reported to the TGA are neither minor nor easily resolved. There were 5 reports of death, an outcome that has not been identified in trials or considered in narrative reviews of spinal cord stimulators. Because of the limitations of the data, we cannot comment on whether the deaths were directly attributable to the device or implantation procedure (see Appendix 4, http://links.lww.com/JPS/A450 for all 5 reports).

We also for the first time highlight the issue that devices are being removed in Australia at a rate of 4 for every 10 implanted. Other than the high number of adverse events reported, the TGA data do not provide details about why these were removed. Other reasons could include device faults, lack of efficacy, or resolution of the pain. Previous spinal cord stimulator safety data have relied on short-term clinical trials. Given that the devices are marketed as long-term solutions to intractable pain and have been used in routine clinical care for approximately 50 years, it seems remarkable that no longer-term reliable data have been available to attest to their longer-term safety.

At present, spinal cord stimulators are of uncertain efficacy and this study has shown a distinct and concerning pattern of serious adverse events and device removal not previously reported. More stringent evaluation of the long-term efficacy and safety of these devices is a priority, including both high-quality and adequately powered randomized placebo-controlled trials and clinical quality registries that evaluate longer-term use and safety. The current method of passive surveillance is arguably insufficient. Many patient information websites[21,22] and patient fact sheets[23] describe the treatment as minimally invasive and safe and fail to mention the potential harms that we noted here. At present, robust evidence on the balance of harms and benefits is not available to allow patients to make an informed decision about these devices.

There is a need for larger and better quality trials to evaluate the long-term efficacy, safety, and cost-effectiveness of spinal cord stimulators. It would arguably be in the interest of funders such as the Department of Health and Aging, private health, and workers' compensation insurers to sponsor or cosponsor such a trial to determine their value. If it is determined that the benefits outweigh the harms and they are cost-effective, their place on the subsidy list will be confirmed. If results do not support their ongoing use, funders may need to disinvest from spinal cord stimulators. Given the relatively high number of spinal cord stimulators that are removed each year in Australia, it would be useful to closely study a representative sample to better understand why they are being removed.

CONCLUSIONS

Our study raises concerns about the safety and durability of spinal cord stimulators. We found that most adverse events reported to the TGA are serious and required at least 1 surgery to correct. Each year in Australia, for every 100 spinal cord stimulators implanted, approximately 40 are removed. Our results raise questions about the safety and utility of this approach to treating chronic intractable pain. A national registry to track the long-term safety of these devices is needed.

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