BURST STIMULATION TECHNOLOGY
A Novel Stimulation Mode for the Management of Chronic Intractable Pain

St. Jude Medical has the first and only CE-marked neurostimulation system that delivers both Burst and tonic spinal cord stimulation (SCS). Burst stimulation technology has been shown to further reduce pain in tonic responders with a reduction in paresthesia and recapture pain relief in non-responders to traditional tonic stimulation.

When used to manage chronic, intractable pain of the trunk and/or limbs, Burst stimulation is:

- **Clinically proven** – Significant pain reductions over tonic stimulation, often with the reduction of paresthesia as well as proven ability to recapture pain relief in patients who become unresponsive to tonic SCS.

- **Preferred** – Preferred over tonic stimulation by majority of patients

- **Safe and reliable** – Approximately 90.0% of patients were free from device or system complications

Although it is an accepted standard of care for treatment of chronic pain, traditional tonic stimulation exhibits substantial heterogeneity in the level of pain relief with up to 20 to 30% of patients classified as non-responders to the therapy. In addition, the paresthesia produced by tonic stimulation may introduce many challenges, including 1) inability to achieve adequate coverage in some areas such as the low back, 2) changes in intensity of paresthesia in response to changes in body position, 3) intolerance of the sensation by some patients, which can lead to a failed SCS trial and accommodation to the sensation such that it no longer provides adequate analgesic benefit. Burst stimulation, an alternative mode of stimulation where groups of pulses (rather than just a single pulse) are delivered to the spinal cord, has recently been introduced and may address many of the issues associated with tonic SCS. This clinical compendium summarizes key studies demonstrating the safety and efficacy of Burst technology.
BURST STIMULATION PROVIDES GREATER PAIN RELIEF WITHOUT PARESTHESIA IN MOST PATIENTS

St. Jude Medical neurostimulation systems have the ability to deliver either tonic (typical frequency range 40 to 60 Hz) or Burst stimulation (i.e. 40 Hz Burst frequency containing five spikes at 500 Hz per spike) to the spinal cord. Studies have shown that, when compared to tonic stimulation, Burst stimulation results in greater pain relief and improvement in other secondary measures, including cognition, sleep, disability, function, often in the absence of paresthesia,2,5,7,8 and that patients prefer Burst stimulation over tonic stimulation.2,3,5-8 The following studies support the clinical safety and effectiveness of Burst stimulation. Table 1 summarizes key findings.

### Table 1. Key findings from studies demonstrating Burst stimulation efficacy.

<table>
<thead>
<tr>
<th>Study</th>
<th># of patients</th>
<th>% Pain Relief</th>
<th>% Patients who Preferred Burst SCS</th>
<th>% Patients Experiencing Paresthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Ridder, et al. 20102</td>
<td>12</td>
<td>Tonic: 30.2%</td>
<td>100%</td>
<td>Tonic: 92.0% Burst: 17.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Burst: 84.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Ridder, et al. 20133</td>
<td>15</td>
<td>Tonic: 31.0%</td>
<td>100%</td>
<td>Not Reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Burst: 54.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wahlstedt, et al. 20144</td>
<td>15</td>
<td>Tonic: 29.7%</td>
<td>Not Reported</td>
<td>Not Reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Burst: 40.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Courtney, et al. 20155</td>
<td>22</td>
<td>46.7% over Tonic Baseline</td>
<td>90.9%</td>
<td>Tonic: Not Reported Burst: 25%</td>
</tr>
<tr>
<td>Schu, et al. 20144</td>
<td>20</td>
<td>16.1% over Tonic Baseline</td>
<td>80%</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Baledeschi, et al. 20157</td>
<td>37</td>
<td>73% over Baseline</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Tjepkema-Cloostermans, et al.20158</td>
<td>39</td>
<td>30% additional pain relief with low or high amplitude burst</td>
<td>74%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Burst Spinal Cord Stimulation:**

**Toward Paresthesia-Free Pain Suppression**

De Ridder, et al. *Neurosurgery,* 20102

- In this prospective, crossover study, 12 patients underwent a one-month SCS trial and received two one-hour sessions of both tonic and Burst SCS.

- Pain intensity was measured using a visual analogue scale (VAS) and the Short Form McGill Pain Questionnaire (SF-MPQ) was used to assess pain quality. Paresthesia during each stimulation condition was scored as present (= 1) or not present (= 0).

- Patients with a 50% reduction in pain during the SCS trial received permanent implantation of the SCS device and received Burst stimulation for an average follow-up of 20.5 months.

- During the trial period, VAS scores were significantly reduced from a baseline score of 6.3 cm for axial pain to 4.4 cm during tonic stimulation (p = 0.05) and to 1 cm during Burst stimulation (p < 0.001).

- Baseline VAS scores for limb pain were also significantly reduced from a score of 7.4 cm to a score of 3.1 cm during tonic stimulation (p < 0.001) and 0.25 cm during Burst stimulation (p < 0.001).

- A significant improvement in the sensory (14 points, p < 0.001) and affective (3.4 points, p = 0.022) dimensions of pain was obtained one-year after permanent implant compared to baseline.

- More patients experienced paresthesia with tonic stimulation (92%) than with Burst stimulation (17%).

- After one-year of Burst stimulation, there was still a significant reduction in VAS scores for axial pain (3.7 points; p = 0.01) and for limb pain (5.2 points; p = 0.01).

- No adverse events were reported.
Key takeaways:

- In this cohort, Burst stimulation resulted in a 58.7% reduction in axial pain and a 70.2% reduction in limb pain after one-year.
- More than 80% of patients did not experience paresthesia during Burst stimulation.
- All patients chose Burst stimulation for the remainder of the trial period, suggesting patient preference for Burst stimulation over tonic stimulation.
- Significant reductions in pain intensity at one-year follow-up provides evidence to support the long-term efficacy of Burst stimulation.

Comparing Burst and tonic stimulation:
- Significantly reduced VAS scores compared to placebo in back pain with a 51.3% vs. 18.9% reduction, respectively; leg pain reduction compared to placebo was 52.7% vs. 11.7%, and general pain reduction was 55.0% vs. 10.9% (all p < 0.05).
- Burst stimulation resulted in a significant reduction in back pain compared to tonic stimulation with 51.3% vs. 30.3% (p < 0.01) while general pain reduction was 55.0% vs. 30.9% (p < 0.01).
- Compared to tonic stimulation, Burst stimulation had better results in VAS scores for both least pain and worst pain (p < 0.05); there were no significant differences for pain at the moment.
- Tonic stimulation created significantly more paresthesia compared to placebo and Burst stimulation (p < 0.05).
- There was not a statistically significant difference in patient-reported paresthesia between placebo and Burst stimulation.
- Burst stimulation significantly reduced PVAQ scores compared to both tonic stimulation and placebo, indicating an improvement in the amount of attention the patient pays to pain.

Key takeaways:

- This single-center study compared three stimulation paradigms (Burst stimulation, tonic stimulation and placebo) in a randomized trial on consecutive patients (n = 15).
- All patients received one week each of tonic stimulation, Burst stimulation and placebo (sham stimulation).
- Primary outcome was measured by VAS for back, leg and general pain.
- Secondary outcome measures included VAS scores for pain now, worst pain and least pain during the last week and the Pain Vigilance and Awareness Questionnaire (PVAQ).
- After four weeks, all 15 patients (100%) preferred Burst stimulation.
- Burst stimulation significantly reduced VAS scores compared to placebo in back pain with a 51.3% vs. 18.9% reduction, respectively; leg pain reduction compared to placebo was 52.7% vs. 11.7%, and general pain reduction was 55.0% vs. 10.9% (all p < 0.05).
- Burst stimulation resulted in a significant reduction in back pain compared to tonic stimulation with 51.3% vs. 30.3% (p < 0.01) while general pain reduction was 55.0% vs. 30.9% (p < 0.01).
- Compared to tonic stimulation, Burst stimulation had better results in VAS scores for both least pain and worst pain (p < 0.05); there were no significant differences for pain at the moment.
- Tonic stimulation created significantly more paresthesia compared to placebo and Burst stimulation (p < 0.05).
- There was not a statistically significant difference in patient-reported paresthesia between placebo and Burst stimulation.
- Burst stimulation significantly reduced PVAQ scores compared to both tonic stimulation and placebo, indicating an improvement in the amount of attention the patient pays to pain.

Key takeaways:

- This is the first double-blinded placebo-controlled study demonstrating that Burst stimulation significantly and clinically suppresses pain compared to placebo for all pain measures.
- In this study of 15 patients, Burst stimulation provided pain relief with reduced paresthesia and significantly decreased the patient’s preoccupation of pain, as measured by PVAQ.
- This is underscored by the fact that 100% of the patients in this study preferred Burst stimulation over tonic stimulation or placebo.
Reproducibility and Feasibility of Burst Stimulation: Preliminary Results

- The reproducibility and feasibility of Burst stimulation was evaluated in 15 patients with chronic pain in the trunk and limbs.

- All patients, who were previously implanted with an SCS device and were not naive to SCS received Burst stimulation for two weeks.

- VAS scores during both tonic and Burst stimulation were significantly different than those reported at baseline (*p* < 0.001).

- For tonic stimulation, baseline VAS scores were significantly reduced by 29.7% (from 9.1 cm to 6.4 cm).

- Burst stimulation resulted in a 40.7% reduction with VAS scores being reduced to 5.4 cm.

**Key takeaways:**
- Results in this study provide further support the effectiveness of Burst stimulation for treatment of chronic pain in the trunk and limbs.

- Burst stimulation resulted in greater pain relief than tonic stimulation after two weeks.

Improved Pain Relief With Burst Spinal Cord Stimulation for Two Weeks in Patients Using Tonic Stimulation: Results From a Small Clinical Study

- In this prospective, multi-center, open label study, 22 patients received tonic stimulation for at least six months; SCS devices were re-programmed with Burst stimulation and followed for 14 days.

- Overall average VAS scores were reduced by 46.7% from 5.4 cm during tonic stimulation to 2.9 cm during Burst stimulation (*p* < 0.001).

- Paresthesia was reduced in 19/20 (95%) patients while using Burst stimulation; 15/20 (75%) patients reported no paresthesia during Burst stimulation.

- 20/22 (90.9%) patients preferred Burst over tonic stimulation with better pain relief cited as the primary reason.

**Key takeaways:**
- Burst stimulation significantly reduces pain relief compared to tonic stimulation and often in the absence of paresthesia.

- The majority of patients preferred Burst stimulation over tonic stimulation.
A Prospective, Randomised, Double-blind, Placebo-controlled Study to Examine the Effectiveness of Burst Spinal Cord Stimulation Patterns for the Treatment of Failed Back Surgery Syndrome


- This prospective, randomized, double-blind, placebo-controlled crossover study assessed the efficacy of Burst stimulation in 20 patients diagnosed with FBSS who were receiving tonic stimulation for a minimum of three months.

- Patients were randomized to 1 of 6 treatment sequences (ABC, BCA, CAB, ACB, CBA, BAC), where A represents sub-threshold tonic stimulation (500 Hz), B represents Burst stimulation, and C represents placebo. All patients then underwent one week of each stimulation mode according to their assigned group.

- The mean numerical rating scale (NRS) score increased from 5.6 (baseline) to 7.1 and 8.3 during high frequency tonic stimulation and placebo SCS, respectively (p > 0.05 between tonic stimulation and placebo group, see Figure 1 below).

- Burst stimulation significantly reduced NRS scores and Short-Form McGill Pain Questionnaire scores (SF-MPQ) compared to both tonic stimulation and placebo (both p values < 0.05, see Figure 1 below).

- Significantly more patients (80%) preferred Burst stimulation over all other stimulation modes (p = 0.0004).

- No adverse events were reported.

Key takeaways:

- Burst stimulation achieved significantly better pain relief and improved pain quality (indicated by Short-Form McGill Pain Questionnaire) than tonic SCS.

- The pain relieving effects of Burst stimulation may not be related to frequency alone as tonic stimulation at the same frequency (500 Hz) failed to reduce pain.

- The majority of patients preferred Burst stimulation over tonic stimulation.

Figure 1: Mean pain intensity (NRS) and mean pain quality (SFMPQ) scores under baseline conventional tonic stimulation, one week of 500 Hz tonic stimulation, one week of Burst stimulation and one week of no stimulation (placebo).
Burst stimulation was evaluated in a total of 37 patients across nine Italian centers.

VAS and quality of life improvements (EQ-5D) were assessed before implantation and at one, three, and six months follow-up.

Burst stimulation provided paresthesia-free pain relief in all patients with 100% of the patients satisfied or totally satisfied with Burst stimulation.

Average VAS scores significantly improved from 8.3 at baseline to 2.2 at six months follow-up (p < 0.005 vs. baseline); EQ-5D scores significantly improved from 0.2 at baseline to 0.62 at six months follow-up (p < 0.005 vs. baseline).

There were no adverse events.

Key takeaways:
- Results in this study provide further support the effectiveness of Burst stimulation without the sensation of paresthesia in some patients.
- In this study, patients had significant improvements in VAS scores and QoL scores after six months of Burst stimulation.

The purpose of this double-blind randomized study was to evaluate low amplitude Burst stimulation (0.1 mA) and high amplitude burst stimulation (0.25-6.4 mA) in patients who have already received tonic SCS (30-80 Hz) for at least six months (n = 39).

Patients were randomized to one of two groups, receiving each stimulation for two weeks:
- Group A: Tonic-low Burst-tonic-high burst-tonic
- Group B: Tonic-high Burst-tonic-low burst-tonic

59.0% (23/39) patients obtained over 30% additional pain reduction during high and/or low amplitude burst stimulation.

There was no statistical difference in average VAS scores between low amplitude burst and high amplitude burst.

15 patients preferred high amplitude Burst stimulation, 14 preferred low amplitude Burst stimulation, and nine patients preferred tonic stimulation. Many patients liked the absence of paresthesia, but several patients missed the feedback.

Key takeaways:
- This study adds to the growing body of evidence supporting the use of Burst stimulation for chronic pain management.
- Further studies are warranted to investigate the differences between low and high Burst stimulation, as defined by the investigators.
BURST STIMULATION MAY RECAPTURE PAIN RELIEF IN CHRONIC NON-RESPONDERS TO TONIC STIMULATION

The following studies show the ability of Burst stimulation to recapture pain relief in patients who have become unresponsive to tonic stimulation. A few of these studies also add to the clinical evidence supporting the safety and effectiveness of Burst stimulation. Table 2 summarizes key findings.

Table 2: Studies supporting the ability of Burst stimulation to recapture pain relief in non-responders to tonic stimulation.

<table>
<thead>
<tr>
<th>Study</th>
<th># of patients</th>
<th>% of Pain Relief in Tonic Non-Responders After Burst SCS</th>
<th>% of Patients Converted to Responder (50% Pain Relief) With Burst SCS</th>
<th>Incidence of Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Vos, et al. 2014</td>
<td>48</td>
<td>22.0%</td>
<td>0%</td>
<td>10.4%</td>
</tr>
<tr>
<td>Bara, et al. 2013</td>
<td>29</td>
<td>66.7%</td>
<td>Not Reported</td>
<td>0%</td>
</tr>
<tr>
<td>Vanneste, et al. 2013</td>
<td>102</td>
<td>Not Reported</td>
<td>62.5%</td>
<td>Not Reported</td>
</tr>
<tr>
<td>De Ridder, et al. 2014</td>
<td>102</td>
<td>59.0%</td>
<td>Not Reported</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Pajuelo A, et al. 2015</td>
<td>10</td>
<td>56%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Sheikh U, et al. 2015</td>
<td>15</td>
<td>Back pain scores dropped by 27.7% while limb pain scores dropped 44.4%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

BURST STIMULATION MAY RECAPTURE PAIN RELIEF IN CHRONIC NON-RESPONDERS TO TONIC STIMULATION

This prospective study assessed the efficacy of Burst stimulation in 24 FBSS patients, 12 painful diabetic neuropathy (PDN) patients and 12 FBSS patients who over time became poor tonic responders (PR).

All patients, who had previously experienced tonic stimulation for at least six months (mean 2.5 years), were reprogrammed with Burst stimulation for a period of two weeks.

Tonic stimulation reduced VAS scores by 37% from baseline. Burst stimulation led to an additional 25% reduction in VAS scores compared with tonic stimulation.

Burst stimulation resulted in significant reductions in VAS scores from baseline for all diagnoses (VAS reductions: 77% in PDN, 57% in FBSS, 23% in PR; all p values < 0.05). When compared with tonic stimulation, Burst stimulation led to a significant additional pain reduction of 44% in PDN patients (p < 0.001) and 28% in FBSS patients (p < 0.01). See Figure 2 below.

Adverse events were reported in five out of the 48 patients (10.4%).

Key takeaways:

- About 60% of tonic stimulation patients experienced further pain relief following Burst stimulation, generally without eliciting paresthesia.
- Over half the patients (67% of PDN, 50% of FBSS, 50% of PR) preferred Burst stimulation over tonic stimulation.

Figure 2: VAS scores for pain of patients with painful diabetic neuropathy (PDN), failed back surgery syndrome (FBSS) and poor responders (PR).
In this prospective study, the long-term efficacy of Burst stimulation was evaluated in 29 patients diagnosed with failed back surgery syndrome (FBSS) who failed to achieve long-term pain relief with conventional tonic stimulation.

All patients had been implanted with a paddle lead and a rechargeable IPG for 12 months but had completely lost pain relief while maintaining complete paresthesia coverage of the painful area.

In these 29 patients, Burst stimulation reduced VAS scores by 66.7% from a baseline score of 9.3 (± 0.7) cm to a score of 3.1 (± 0.5) cm at 12 months.

No adverse events were reported.

**Key takeaways:**
- The results from this study support the ability of Burst stimulation to recapture pain relief over the long-term in patients who have become unresponsive to tonic stimulation.
- The results also support long-term safety of Burst stimulation.

This study assessed efficacy and cost-effectiveness of Burst stimulation in a large sample of patients (n = 102) diagnosed with FBSS who were both responders (patients who achieved 50% or greater pain relief based on percent change from baseline in VAS score) and non-responders (patients who achieved less than 50% pain relief based on percent change from baseline in VAS score) to conventional tonic stimulation.

23.5% of patients were non-responders to tonic stimulation and 62.5% of these patients were converted to responders after being reprogrammed with Burst stimulation (for two weeks).

In the 76.5% patients who were considered responders to the tonic stimulation, 94.9% reported improved pain relief during Burst stimulation as compared to tonic stimulation.

Cost savings were observed for Burst stimulation as compared to conventional medical management (CMM) and tonic stimulation with a non-rechargeable IPG.

**Key takeaways:**
- The results provide further evidence to support the ability of Burst stimulation to recapture pain relief in patients who have become unresponsive to tonic stimulation.
- Burst may also produce pain relief above that seen with tonic stimulation in patients who continue to experience at least 50% pain relief.
A Two Center Comparative Study on Tonic Versus Burst Spinal Cord Stimulation: Amount of Responders and Amount of Pain Suppression


- In this two-center (Belgium and Netherlands) retrospective analysis (n = 102), neuropathic pain patients who received tonic stimulation for at least six months were divided into two groups:
  - Non-responders to tonic stimulation (n = 24)
  - Responders to tonic stimulation (n = 78)
- Patients provided pain scores on numeric rating scale (NRS) for overall, leg and back pain at three time points:
  - Prior to SCS system implant (baseline)
  - Prior to Burst stimulation reprogramming (tonic stimulation)
  - Two weeks after Burst stimulation
- Average baseline NRS scores for overall pain were significantly reduced by 59% following Burst stimulation (p < 0.001 for baseline vs. tonic, baseline vs. Burst, and tonic vs. Burst).
- Similar results were seen for leg and back pain
- 23.5% of the total patients had less than 10% pain reduction while 76.5% were responsive to tonic SCS with an average reduction in NRS of 50.6%.
- 62.5% of the patients unresponsive to tonic stimulation (15/24) responded to Burst stimulation with an average reduction in NRS score of 43.0%.
- 37.5% (9/24) of patients did not respond to either form of stimulation.
- Almost 95% of tonic responders experienced a greater reduction in NRS score during Burst stimulation.

Key takeaways:
- The results from this study indicate that Burst stimulation provides a greater reduction in pain than tonic stimulation in both tonic responders and non-responders after a short duration:
  - Over half of the patients who failed to achieve adequate pain relief with tonic stimulation achieved significant pain relief with Burst stimulation.
- Burst stimulation has the ability to salvage non-responders to tonic stimulation, resulting in more personalized and effective chronic pain management (see Figure 3 below):
  - 23.53% (24/102) of the patients failed to respond to tonic stimulation, but Burst stimulation recaptured pain relief for 62.5% (15/24) of those patients.
  - Of the 78 patients who responded to tonic stimulation, 94.87% (74/78) had further improvement upon Burst stimulation.
- This article provides further evidence to support Burst stimulation for chronic pain.

Figure 3: Flowchart representing the number of patients implanted with an SCS device who did and did not respond to tonic stimulation. Burst stimulation salvaged 62.5% (15/24) of the tonic nonresponders and further improved the pain response in 94.9% (74/78) of the patients who responded to tonic stimulation.
In this retrospective follow-up, 10 patients from two different centers were implanted with a Burst stimulation system, all of whom had failed to receive > 50% pain relief with tonic SCS systems.

Assessments were made at baseline (pre-implant), “tonic initial” (post-implant with tonic stimulation), “tonic final” (last follow-up prior to switching to Burst stimulation system; average months on tonic stimulation: 15.7), and “Burst final” (last follow-up after implant of Burst stimulation system).

Pain relief was evaluated using the Numeric Rating Scale and patient satisfaction was assessed on a scale of 1-5, with one being very satisfied and five being very unsatisfied.

NRS scores dropped from nine at baseline to three following Burst stimulation (average follow-up 6.8 months).

Tonic stimulation initially provided a 65% reduction in NRS scores compared to baseline, but pain increased by 56% at the “tonic final” timepoint, though this was still significantly better than NRS scores at baseline (p < 0.001).

Following conversion to Burst stimulation, patients reported a 65% decrease in NRS scores compared to baseline (p < 0.001) and 56% compared to tonic stimulation (p < 0.001).

80% of the patients converted to Burst stimulation were very satisfied or satisfied with their stimulation system.

As expected, due to the small study, there was no significant correlation between the outcome for tonic stimulation and Burst stimulation. The authors state this finding suggests that the outcome on Burst stimulation is independent of the outcome on tonic.

Key takeaways:
- In this small retrospective study, patients who had become non-responders to tonic stimulation reported improved pain relief following conversion to Burst stimulation, suggesting that Burst stimulation may have the potential to salvage patients who have developed stimulation tolerance, or habituation, to traditional tonic stimulation.
- Longer term studies are needed to confirm that Burst stimulation provides long-term pain relief and to confirm these findings.

Figure 4: Burst may have the potential to salvage patients who have developed a tolerance to tonic stimulation.15
The purpose of this retrospective follow-up was to evaluate the effectiveness of Burst stimulation in 15 patients.

67% (10/15) of the patients had previously received tonic stimulation prior to switching to Burst stimulation.

After an average follow-up of 19.8 weeks (0.7-39.0 weeks), back pain scores dropped by 27.7% while limb pain scores dropped 44.4%.

At baseline, the average EQ5D5L index score was 0.56 ± 0.14 and increased to 0.66 ± 0.11 at follow-up, an improvement of 20.9%.

PVAQ scores improved 20.7% at follow-up.

Patients who had previous tonic systems and were converted to Burst had comparable results to patients who had de novo implants.

Approximately 93% of the patients reported either “pleasant paresthesia” or “no paresthesia”. The authors suggest this may be due to the patient cohort who had previously used tonic stimulation and were seeking to achieve a similar sensation and therefore driving up their parameters.

Key takeaways:

- Burst stimulation provided effective pain relief, improvements in quality of life, and improvements in patients attention to pain scores in this cohort of patients.

- In this study, patients who had previous tonic stimulation and were converted to Burst stimulation had comparable results to patients who had de novo implants, suggesting that burst stimulation may be used in patients who do not respond to traditional tonic stimulation.
BURST STIMULATION MAY ALTER PAIN PERCEPTION THROUGH ACTIVATION OF DIFFERENTIATED PAIN PATHWAYS

The mechanism of action underlying Burst stimulation is not entirely understood. However, findings from several recent studies have begun to elucidate mechanistic differences between Burst stimulation and tonic stimulation. In De Ridder et al.’s double-blinded placebo-controlled study, the authors propose that Burst stimulation activates the medial affective pathway involved in the emotional component of pain whereas tonic stimulation activates the lateral discriminatory pathway. This study and others collectively suggest differential neuronal activation between Burst and tonic stimulation. Summaries of the key findings from these studies are provided below.

Comparison of Burst and Tonic Spinal Cord Stimulation on Spinal Neural Processing in an Animal Model

- This preclinical animal study compared Burst and tonic stimulation in rat models of acute, somatic (bodily) pain and acute, visceral pain (within organs).
- Acute, somatic pain was induced by pinching the skin and muscles surrounding the hind limbs of the rat. Acute, visceral pain was induced by inflating a latex balloon to distend the colon and rectum.
- Burst stimulation reduced visceromotor reflex (pain response) more than tonic stimulation (80.4% vs. 62.1%, respectively, p < 0.05).
- In contrast to Burst stimulation, traditional tonic stimulation significantly increased spontaneous activity of neurons in the gracile nucleus, which are known to project to the primary somatosensory cortex in the brain.
- This increased spontaneous activation of the spinal nucleus may account for the sensation of paresthesia that typically occurs during tonic but not Burst SCS.

Key takeaways:
- In this animal model, Burst stimulation produced a significantly greater reduction in visceral nociception (pain) compared to traditional tonic stimulation.
- Paresthesia may be reduced or abolished in patients receiving Burst stimulation compared to those receiving traditional tonic stimulation due to a lack of increased spontaneous activity of neurons in the gracile nucleus.
- The results from the study suggest that Burst stimulation may not activate a pathway associated with the sensation of paresthesia.

Stimulation Parameters Define the Effectiveness of Burst Spinal Cord Stimulation in a Rat Model of Neuropathic Pain

- The impact of altering stimulation parameters in Burst SCS on reduction in neuronal responses to noxious stimuli (pain) was investigated in a preclinical model of cervical radiculopathy.
- Compression of the nerve roots at C7 was used to induce cervical pain in rats.
- SCS was applied at the level of C3/C4 for 10 seconds and neuronal response to pinch of the forepaw (acute, mechanical pain) was measured and compared to neuronal firing before forepaw pinch.
- Stimulation parameters, including number of pulses per Burst, pulse frequency, pulse width, Burst frequency and amplitude, were varied and differences in neuronal firing in response to changes in the stimulation parameter were recorded.
- Pulse frequency and current amplitude significantly increased the percentage of neurons responsive to Burst stimulation (p < 0.05).
- Charge per Burst was significantly correlated with both reduction in neuronal firing and the percentage of neurons responsive to Burst stimulation (p < 0.03).

Key takeaways:
- Burst stimulation can be optimized by adjusting relevant stimulation parameters to regulate charge delivered to the spinal cord during stimulation.
- Modulating Burst stimulation parameters provides the ability to personalize therapy and potentially lead to more efficient and effective pain management.
Burst and Tonic Spinal Cord Stimulation Differentially Activate GABAergic Mechanisms to Attenuate Pain in a Rat Model of Cervical Radiculopathy
Crosby ND, et al. IEEE, 2015

- The purpose of this study was to evaluate the following after Burst and tonic stimulation in a rat model of cervical radiculopathy:
  - Compare the attenuation of spinal neuronal activity and tactile allodynia
  - Assess the role of the neurotransmitter γ-aminobutyric acid (GABA)

- Following painful nerve root compression, both Burst and tonic stimulation reduced spinal neuronal firing and pain symptoms in response to noxious stimuli, suggesting that the improved pain relief with Burst stimulation (vs. tonic stimulation) reported in the clinic may be due to modifications in pain perceptions not tested in this study.

- In the presence of a GABA<sub>B</sub> antagonist, CGP35348, the effects of tonic stimulation are abolished, but this GABA<sub>B</sub> antagonist does not alter the effect of Burst stimulation.

- Results also showed that tonic stimulation restores serum GABA while Burst stimulation did not.

**Key takeaways:**
- Both Burst and tonic reduce neuronal firing.
- The effect of tonic stimulation, but not Burst stimulation, is blocked by a GABA<sub>B</sub> antagonist, suggesting that the effects of Burst stimulation are not GABA-dependent and that Burst may exhibit a unique mechanism of action compared to tonic stimulation.
- Tonic stimulation mitigates injury-induced decreases in serum GABA, but GABA remains decreased from baseline during Burst stimulation, suggesting that Burst stimulation may not activate GABAergic signaling mechanisms.
- The findings in this study suggest that other signaling mechanisms may be responsible for the analgesic benefits of Burst stimulation. Future studies are needed to elucidate these mechanisms.
References


Additional Study References

### Table 3: Summary of Evidence (Key Takeaways)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Number of Patients</th>
<th>Follow-up Time-point</th>
<th>Burst SCS Results in Pain Relief without Paresthesia in Some Patients</th>
<th>Patient Preference for Burst over Tonic SCS</th>
<th>Burst SCS Can Recapture Pain Relief in Chronic, Tonic Non-responders</th>
<th>Burst SCS Positively Impacts Secondary Outcomes Important in Pain Treatment</th>
<th>Burst SCS Mechanism of Action</th>
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<tbody>
<tr>
<td>Courtney et al. 2015&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Prospective, multi-center, open label</td>
<td>22</td>
<td>Burst: 2 weeks Tonic: at least 6 months</td>
<td>X</td>
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<tr>
<td>Baldeschi et al. 2015&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Multi-center, open label, cross-over</td>
<td>37</td>
<td>Burst: 1, 3, 6 months</td>
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<td>Tjepkema-Cloostermans et al. 2015&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Double-blind, randomized</td>
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<td>Burst: 2 weeks Tonic: 2 weeks</td>
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<td>Pajuelo et al. 2015&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>10</td>
<td>Burst: Avg 6.8 months</td>
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<tr>
<td>Sheikh et al. 2015&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>15</td>
<td>Burst: Avg 19.8 weeks</td>
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<td>Crosby et al. 2015&lt;sup&gt;6&lt;/sup&gt;</td>
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<td>De Ridder et al. 2014&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>102</td>
<td>Burst: 2 weeks Tonic: at least 6 months</td>
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<tr>
<td>de Vos et al. 2014&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Prospective, single center, open label</td>
<td>48</td>
<td>Burst: 2 weeks Tonic: mean follow-up of 2.8 years</td>
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<td>Schu et al. 2014&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Randomized, double-blind, placebo-controlled crossover</td>
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<td>Placebo, Burst and 500 Hz Tonic: 1 week Tonic: at least 3 months</td>
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<td>Tang et al. 2014&lt;sup&gt;11&lt;/sup&gt;</td>
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<td>Vanneste et al. 2013&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Not Provided</td>
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<td>Not provided</td>
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<td>Wahstedt et al. 2013&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Feasibility</td>
<td>15</td>
<td>Burst: 2 weeks Tonic: not</td>
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<tr>
<td>Bara et al. 2013&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Prospective</td>
<td>29</td>
<td>Burst: 12 months Tonic: not provided</td>
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<tr>
<td>De Ridder, D. et al. 2013&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Randomized, placebo-controlled, crossover</td>
<td>15</td>
<td>1-week of Tonic, Burst and sham (placebo) SCS</td>
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<td>De Ridder, D. et al., 2010&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Prospective, single center, open label</td>
<td>12</td>
<td>After SCS trial: two 1-hour sessions of Tonic and Burst SCS After Permanent Implant: Burst SCS: 20.5 months</td>
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</table>
Brief Summary: Prior to using these devices, please review the Instructions for Use for a complete listing of indications, contraindications, warnings, precautions, potential adverse events and directions for use.

Indications for Use: Spinal cord stimulation as an aid in the management of chronic, intractable pain of the trunk and limbs. Contraindications: Patients who are unable to operate the system or who have failed to receive effective pain relief during trial stimulation. Warnings/Precautions: Diathermy therapy, implanted cardiac systems, magnetic resonance imaging (MRI), explosive or flammable gases, theft detectors and metal screening devices, lead movement, operation of machinery and equipment, postural changes, pediatric use, pregnancy, and case damage. Patients who are poor surgical risks, with multiple illnesses, or with active general infections should not be implanted. Adverse Effects: Painful stimulation, loss of pain relief, surgical risks (e.g., paralysis). Clinicians manual must be reviewed for detailed disclosure.

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