Science Behind Quell™ Wearable Pain Relief Technology for Treatment of Chronic Pain

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Abstract

Quell is a novel transcutaneous electrical nerve stimulator for the treatment of chronic pain. It uses wearable intensive nerve stimulation to provide pain relief. The device is placed on the upper calf and includes sophisticated electrical stimulation technology, automation algorithms and electrode arrays. It may be used with an optional mobile app. This monograph covers scientific and technical principles of non-invasive nerve stimulation for chronic pain relief, Quell technology and supporting clinical data.

Background

Transcutaneous electrical nerve stimulation (TENS) is the delivery of electricity across the intact surface of the skin to activate underlying nerves; generally with the objective of pain relief. The technology was originally developed in the early 1970s as a screening technique for predicting which chronic pain patients would respond to implantable stimulators.[1] However, it became apparent that a significant percentage attained pain relief from TENS alone, thereby obviating the need for implantable stimulators. Since that time, the efficacy of TENS for the treatment of chronic pain has been extensively studied.[2,3] This scientific literature suggests TENS can be effective[2,4-6] with minor skin irritation as the only side effect.[7]

Wearable Intensive Nerve Stimulation (WINS) is an emerging form of TENS in which the device is wearable, automated, and designed for intensive use. This enables regular use throughout the day and night, whenever the patient experiences pain, which is essential for the management of chronic pain.[8] Quell is a commercial WINS device that is available without a prescription. It is a Class II medical device that is FDA cleared for symptomatic relief and management of chronic pain, including during sleep.

Pain Gate Theory

A conceptual model for how peripheral nerve stimulation leads to pain relief was proposed by Melzack and Wall in 1965.[9] Their theory stipulates that activation of sensory nerves (Aβ fibers) closes a "pain gate" in the spinal cord that inhibits the transmission of pain signals carried by nociceptive afferents (C and Aδ fibers) to the brain. In the past 20 years, the anatomic pathways and molecular mechanisms that may underlie the pain gate have been elucidated. Sensory nerve stimulation activates the descending pain inhibition system, primarily the periaqueductal gray (PAG) and rostroventral medial medulla (RVM) located in the midbrain and medulla sections of the brainstem respectively.[10] The PAG has neural projections to the RVM, which in turn has diffuse bilateral projections into the spinal cord dorsal horn.[11-13] Peripheral nerve stimulation activates the PAG which triggers the RVM to broadly inhibit pain signal transmission in the spinal cord dorsal horn.[10] Although it is activated by localized peripheral nerve stimulation, the descending pain inhibition system has analgesic effects that may extend beyond the stimulation site to provide broad pain relief.[14-18]

Various neurotransmitters are involved in mediating descending pain inhibition

including GABA and serotonin.[10,19] However, the most important are the endogenous opioids.[10,20] Elevated levels of these natural pain modulating chemicals can be measured in the cerebrospinal fluid (CSF) in response to high frequency peripheral nerve stimulation.[21,22] A statistically significant increase in CSF opioid concentration can be measured after 20-45 minutes of stimulation and remains elevated for 60 minutes.[21] Continuing stimulation beyond 60 minutes decreases opioid levels back to baseline.[21] This data provides a biological basis for the clinical observation that analgesia requires at least 30 minutes of stimulation.[8,16] The time course data also supports 60-minute therapy duration because longer stimulation is ineffective in maintaining elevated opioid levels.

The role of endogenous opioids in descending pain inhibition has important clinical implications. High frequency nerve stimulation, such as with a WINS device, induces an elevation in enkephalins that act through the δ-opioid receptor.[20,23] Prescription opioids (e.g., hydrocodone, meperidine, oxycodone) act through a different receptor, the μ-opioid receptor. Both receptors are involved in descending pain inhibition, including in the dorsal horn of the spinal cord where they act to inhibit pain signal transmission.[10,20] Individuals who are taking prescription opioids or have developed tolerance to such medications remain responsive to high frequency induced analgesia because it acts through the δ rather than μ opioid receptor.[24] Another implication of the role of opioids is that neuropathic pain appears to be a low endogenous opioid state.[22] Therefore the efficacy of high frequency nerve stimulation in reducing neuropathic pain[2,7,25] may be related to a normalization of opioid levels.[22]

Technology

Technical Specifications

TENS is characterized by a number of electrical parameters including the stimulation pulse shape, amplitude, duration, pattern, and frequency.[26] Although all the parameters can be adjusted in an attempt to achieve maximal analgesia, only pulse intensity[2,27-29] has a clear influence. Intensity is defined as the effective strength of the stimulation pulse and is determined by its shape, amplitude and duration. A symmetrical bi-phasic pulse shape maximizes intensity.[30-32] Increasing pulse amplitude and duration increases the intensity although the relative effectiveness of the stimulation decreases with longer duration due to the strength-duration curve.[33] Stimulation at an intensity below the level of sensory perception does not provide pain relief, and the degree of analgesia is correlated to the stimulation intensity.[34] Scientific studies and clinical experience suggest that therapeutically effective stimulation occurs at an intensity that feels "strong but comfortable" to the patient.[8] Electrical stimulation has a narrow dynamic range[35] so determining this intensity level may be challenging. One that is slightly too low may be ineffective and one that is slightly too high may be uncomfortable. Both low (<10 Hz) and high (>50 Hz) stimulation frequency can be effective in providing analgesia.[36] The two frequency modes operate through distinct molecular mechanisms[10] with important clinical implications as noted above.

Limitations of Conventional TENS Devices

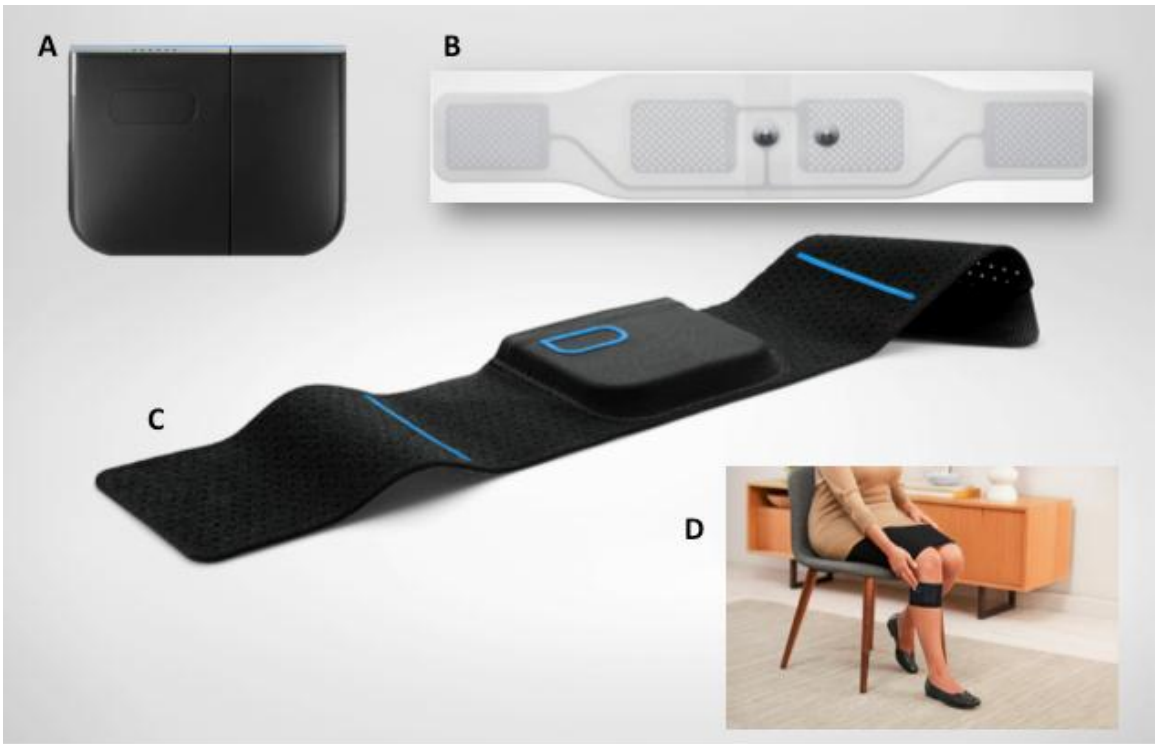
There are many commercially available TENS devices with various characteristics and features.[26] These devices are not ideal for managing chronic pain.[37,38] The reasons include that they are not wearable, have limited technical specifications, present awkward electrode and user interfaces, and lack sophisticated automation.[26] In a large CDC sponsored population-based survey of chronic pain, 70% reported constant pain or at least daily pain.[39] Moreover, 50-70% of people with chronic pain report difficulty sleeping.[40,41] Devices that cannot be worn while the patient is active or overnight therefore have limited utility and may even

be counterproductive because they constrain the patient.

There is a high concordance between chronic pain and poor health[39] and chronic diseases such as diabetes.[42] As a result, many people with chronic pain have abnormal physiology such as elevated skin electrical resistance[43] and peripheral nerve degeneration.[44] Furthermore, many of these individuals are overweight,[39] which may increase the distance from the stimulation electrodes to nerve. To overcome these pathophysiological factors, effective pain relief may require higher electrical power than most conventional devices, particularly those sold over-the-counter, can provide. Another issue is that most people with chronic pain have complicated treatment programs involving medications and other devices. It is difficult for these individuals to adopt pain relief technology that requires additional training and expertise. In fact, there is some evidence that a barrier to effective use of TENS is the amount of effort needed to regularly apply the available devices.[37,45]

Quell Wearable Pain Relief Technology

Quell is a wearable, automated electrical nerve stimulator designed for people with chronic pain, that includes advanced technology to provide convenience while optimizing pain relief. It consists of four components as shown in Figure 1: a therapy pod (A), an electrode array (B), a band (C), and a mobile app (not shown). The therapy pod, which contains the electronics, is placed in the band and then an electrode array is attached by snapping it to the therapy pod. The electrode array consists of 4 hydrogel pads that provide a large (60 cm^2) interface between the stimulator and the patient's sensory nerves. Large electrodes are more electrically efficient and comfortable then smaller electrodes, particularly when placed on areas with thicker fat layers and deeper nerves, such as the legs.[46,47] The hydrogel is robust, typically lasting 2 weeks or 100 hours of use, and is formulated to reduce skin irritation. The band is placed on the upper calf (Figure 1D) where therapy is initiated by pressing the button. The reason for



placement on the upper calf is that this area has a high density of cutaneous sensory innervation that enables robust stimulation of Aβ fibers. When placed on the upper calf, the electrode array is circumferential and will stimulate sensory dermatomes S2-L4 providing a broad neural input to trigger analgesia through the descending pain inhibition system. The upper calf is also discrete and accessible. As discussed above, the mechanism of action generates widespread analgesia and therefore the upper calf location should not limit pain relief to the ipsilateral lower leg.

The therapy pod utilizes a precise high power electrical stimulator to activate peripheral sensory nerves and trigger analgesia based on the biological mechanisms described above. High power is essential in many patients, particularly those that are obese, have pathologically dry skin such as due to diabetes, or have sensory neuropathies. Inadequate power leads to under stimulation and treatment failures due to under dosing. The output power of a nerve stimulator is defined as the output voltage times the output current. Whereas some over-the-counter TENS devices may have reasonable output voltage or current, none match the Quell specifications of simultaneously high maximum output voltage (100 volts) and maximum output current (100 milliamps). This output power is at least 2-5 times greater than other commercial devices. The therapy pod is powered by a Lithium-Ion battery that provides 30-40 hours of therapy (4-7 days of typical use) if fully charged. The battery can be recharged in 2-3 hours by plugging the device into an AC adapter.

Despite the high output power, the stimulation waveform is precisely controlled. Quell stimulates with a current-regulated pulse which provides stable nerve stimulation despite changes in the skin-electrode interface.[30] The pulse waveform is biphasic and symmetrical which is recommended for maximum stimulation efficiency[30-32] and to lessen skin irritation.[48] It is also important for establishing uniform stimulation across the entire electrode array. The device alternates the polarity of the leading phase with every pulse which eliminates residual iontophoretic effects to further minimize skin issues. The stimulation pattern is a randomly varying high frequency between 60 and 100 Hz, which may reduce the tendency to develop analgesic tolerance as compared to regular patterns.[49,50]

Quell continuously optimizes pain relief by automatically regulating stimulation intensity. Currently published evidence suggests that stimulation intensity directly influences the degree of analgesia.[2,27-29] A recent placebo controlled study demonstrated a dose response relationship between intensity and analgesia.[34] Stimulation below the level of sensory perception does not produced analgesia, and the degree of analgesia is correlated to the stimulation intensity.[34] These and other studies suggest that stimulation should be delivered at a "strong but comfortable" level.[8] It has also been shown that increasing simulation intensity during treatment increases analgesia, most likely because the stronger stimuli overcome nerve desensitization and activate deep tissue sensory afferents.[51]

For the reasons noted above, Quell includes a patented calibration procedure that determines the optimal therapeutic stimulation intensity for each patient. This is accomplished by an algorithm that automatically determines an intensity within the recommended therapeutic range.[8] Once calibrated, all subsequent therapy is automatically delivered at the required intensity. The patient has the option of manually adjusting intensity at any time and the device incorporates these changes in subsequent therapy sessions. Quell automatically compensates for nerve desensitization by adaptively increasing the intensity over the course of the one hour therapy session. The device enables long-term unattended therapy, such as overnight,

by automatically restarting hour-long therapy sessions every other hour as long as the device remains on the leg. The one-hour therapy session exceeds the minimum recommended time of 30 minutes[8] but is shorter than the period of time during which the biological response appears to fade.[21] The device monitors the amount of time it is on the same region of skin and alerts the patient to ventilate the area to reduce the risk of irritation. Finally, Quell has embedded intelligence to determine if the patient is sleeping and automatically reduces the intensity to provide overnight pain relief without disturbing sleep.

Mobile App

Quell may be used with an optional mobile app to which it communicates via *Bluetooth*® Smart. The primary objective of the app is to enhance device usability and physiological efficacy. This is accomplished by providing the user with a dashboard and trending data on usage and sleep. The dashboard helps the patient achieve their daily therapy utilization and sleep goals. It includes the elapsed time in the current therapy session, time to the next scheduled therapy session, battery power information, and the most recent therapy and sleep metrics. The trending data provides a look back at therapy utilization and sleep quality over progressively longer time periods from 1 day to 1 month. This information helps the patient achieve their long-term therapy goals and assess the impact of therapy on their sleep. By keeping the patient informed on their progress, the mobile app attempts to positively re-enforce the patient's use of the device. Recent research shows that patients with a high expectation of success are more likely to continue using TENS.[25]

Regulatory

Quell is a class II medical device with FDA 510(k) clearance for the symptomatic relief and management of chronic intractable pain, without a prescription. Quell has unique regulatory labeling for use during sleep. All other transcutaneous electrical nerve stimulators (prescription or over-the-counter) carry a warning against use during sleep because of the risk of injury due to unattended electrode dislodgement from the skin. Quell has technology to detect electrode peeling and consequently it is specifically approved for use during sleep. Per FDA regulations on TENS devices, Quell is contraindicated in patients who have a cardiac pacemaker, implanted defibrillator, or other implanted electronic device.

Clinical Data

SENSUS Data

Quell is related to the SENSUS® Pain Management System, a prescription WINS device, which has been available for several years and prescribed to thousands of patients for chronic pain. Quell and SENSUS have identical technical specifications, use the same electrode array, and are both used to treat chronic pain. The two devices differ in the therapy pod form factor and the band materials. Furthermore, only Quell includes *Bluetooth*® Smart and mobile device integration. In light of the comparability of the two devices, the two years of clinical experience with SENSUS are relevant to Quell. Since January 2013, over 7000 SENSUS devices have been prescribed by hundreds of physicians in the US for treatment of chronic pain. There have been an estimated 2.5 million hours of pain therapy with SENSUS. The most common clinical indication has been lower extremity neuropathic pain, usually painful diabetic neuropathy.

Based on an analysis of prescription data, over 50% of SENSUS devices are used for 6-months or longer indicating long term pain relief benefits. Continued use of a pain therapy can be regarded as an index of a patient's assessment of the efficacy of the treatment versus its inconvenience and side effects. As such, it is an outcome measure that is patient based and clinically

significant.[52] The over 50% long-term continued use of SENSUS compares favorably with similar patient satisfaction outcomes for pain medications such as pregabalin.[53]

Published Studies of High Frequency Intensive TENS

Quell has Food and Drug Administration (FDA) clearance for the treatment of chronic pain, including during sleep. The FDA cleared labeling is "… the symptomatic relief and management of chronic intractable pain." This regulatory labeling was obtained based on the agency's review of the safety and clinical efficacy of the high frequency intensive nerve stimulation methods used by Quell. Summaries of key clinical studies supporting these methods are provided below.

Buchmuller et al. Value of TENS for relief of chronic low back pain with or without radicular pain. Eur J Pain. 2012.

Buchmuller and colleagues conducted a prospective, randomized, sham-controlled, multi-center study of the efficacy of TENS in patients with chronic low back pain (LBP).[7] A total of 236 adults with chronic LBP were enrolled. The majority of subjects (58.9%) were suffering from LBP associated with radicular pain and most subjects (88.0%) were taking at least one type of analgesic medication. Subjects were randomized to mixed frequency nerve stimulation (80 Hz with interspersed low frequency stimulation) at a strong but comfortable intensity or sham (no stimulation). Subjects self-administrated the therapy at home (active or sham) for four 1-h treatment sessions per day over 3 months. The primary outcome measure was improvement in functional status as assessed by the Roland–Morris Disability Questionnaire. This outcome did not differ, at a statistically significant level, between the active and sham groups when all subjects were considered. However, in a subgroup analysis, a strong trend in favor of the active device was observed in those subjects with radicular or neuropathic pain. A significant improvement in pain, as assessed by the visual analogue scale (VAS), was observed in subjects treated with the active device. 25% of subjects on active therapy had at least a 50% improvement in lumbar pain versus 6.7% of those on sham therapy. 33.8% of subjects on active therapy had at least a 50% improvement in radicular pain versus 15% of those on sham therapy.

Clinical Relevance: Intensive (4 hours every day) high frequency TENS decreases pain associated with chronic low back pain, particularly those with radicular pain. In these subjects, one-third experienced greater than 50% improvement in pain.

Szopinski et al. The effectiveness of analgesic electrotherapy in the control of pain associated with diabetic neuropathy. Southern African Journal of Anaesthesia & Analgesia. 2002.

Szopinski and colleagues conducted a prospective, randomized, sham-controlled study of the efficacy of TENS in 100 subjects with painful diabetic neuropathy.[54] The treatment group consisted of 80 subjects allocated to active therapy and the control group contained 20 subjects who received sham therapy. Subjects in the treatment group self administered a device at home that provided high frequency nerve stimulation at a strong but comfortable intensity for 20 to 40 minutes 2 to 3 times each day for 1 to 6 months. Control patients wore the same device but it provided no electrical output. Pain was assessed on a visual analog scale ranging from 0% for no pain to 100% for maximum imaginable pain. In the treatment group the mean level of pain decreased from 75% down to 22%. The control group had no significant decrease in pain. At the time of enrollment in the study, all subjects reported analgesic use with 38% reporting extensive use. At the conclusion of the study no subjects in the treatment group reported extensive analgesic use. There was

no change in the use of analgesic therapy in the control group. Subjects in the treatment group reported improvement in walking which was not seen in the control group.

Clinical Relevance: Intensive high frequency nerve stimulation (1-2 hours every day) decreases pain, analgesic use, and walking difficulty due to painful diabetic neuropathy.

Kilinc et al. Effects of transcutaneous electrical nerve stimulation in patients with peripheral and central neuropathic pain. J Rehabil Med. 2014.

Kilinc and colleagues conducted a prospective open-label study of the efficacy of TENS in subjects with peripheral or central neuropathic pain.[55] A total of 40 subjects were enrolled, 20 with peripheral neuropathic pain (e.g., entrapment neuropathy, peripheral neuropathy, and radiculopathy) and 20 with central neuropathic pain (e.g., cerebrovascular accident, multiple sclerosis, and spinal cord injury). High frequency nerve stimulation at a strong but comfortable intensity was administrated in a hospital clinic for 30 minutes a day (5 days a week) for 4 weeks. The mean pain intensity as assessed by the Brief Pain Inventory – Short Form (BPI-SF) decreased by 38% in the peripheral neuropathic pain group and by 15% in the central neuropathic pain group. Most BPI-SF pain interference domains, including sleep, mood and activity levels, were significantly improved in both groups.

Clinical Relevance: High frequency TENS is effective at reducing pain and pain interference in subjects with neuropathic pain. This benefit appears to be greatest in those with neuropathic pain of peripheral origin.

Moharic et al. Transcutaneous electrical nerve stimulation, pregabalin, and their combination in patients with painful diabetic neuropathy: effects on pain and quality of life. Zdrav Vestin. 2009.

Moharic and colleagues conducted a prospective, randomized, comparative, single site study of the efficacy of TENS, pregablin, or both in 65 subjects with painful diabetic neuropathy.[56] High frequency TENS at a strong but comfortable intensity was self-administered at home for 3 consecutive hours daily for three weeks. Statistically significant pain reduction was seen in all 3 treatment groups with the decrease in pain intensity in the nerve stimulation group comparable to that seen in the pregabalin group. Subjects treated with nerve stimulation only were also evaluated for temperature thresholds, cold and heat pain thresholds, vibration perception thresholds and touch perception thresholds. No changes were found in any of these thresholds consistent with a central mechanism of action.[57]

Clinical Relevance: Intensive (3 hours every day) high frequency TENS reduces pain caused by PDN comparably to pregablin.

Carbonario et al. Effectiveness of high-frequency transcutaneous electrical nerve stimulation at tender points as adjuvant therapy for patients with fibromyalgia. Eur J Phys Rehabil Med. 2013.

Carbonario and colleagues conducted a prospective, controlled study of the efficacy of transcutaneous electrical nerve stimulation in fibromyalgia.[58] A total of 28 female subjects were enrolled and allocated to an 8-week program of exercise and nerve stimulation or just nerve stimulation. Subjects in the nerve stimulation group received high frequency stimulation at a strong but comfortable intensity for 30 minutes twice a week during the same clinic session as their exercise program. Pain was assessed at baseline and at the end of the study by a 10 cm visual analog scale. Pain intensity improved by 2±2.9 cm in the nerve stimulation and exercise group and 0.7±3.7 in the exercise only group, which was a statistically significant difference. Subjects in the nerve stimulation and exercise group had clinically relevant improvement in work

performance, fatigue, stiffness, anxiety and depression. Those in the exercise group only had clinical improvement in morning tiredness and depression.

Clinical Relevance: Infrequent (twice per week) high frequency nerve stimulation may improve symptoms and overall function in subjects with fibromyalgia. It is possible that these results were due to a short-term reduction in pain that enabled more aggressive exercise in the nerve stimulation group. Daily nerve stimulation for several hours may have had a great clinical benefit.

QUANTIFY Registry

The gold standard for obtaining clinical data on the efficacy of a medical intervention is a blinded randomized clinical trial (RCT). However these studies provide data on a very limited subset of subjects. Although the results may be conclusive in demonstrating that the intervention has a biological effect distinct from placebo, the generalizability of the data is severely limited by the sample size and the narrow characteristics of the subject pool.[59] Moreover, blinded studies of physical interventions such as TENS are difficult because it is challenging to blind subjects to the sensation of stimulation.

A post-market registry is a clinical study where data is collected on users of an intervention within an open label observational framework. The strength of a data registry is the ability to collect a large sample size of real-world use.[59] The QUANTIFY ("QUell ANalgesia Tracking Investigation For Year") registry is a prospective, open label, single-arm, observational post market study of Quell use in patients with chronic pain. All Quell users using the mobile app are invited to opt-in to the registry. Enrolled subjects are followed for at least a year. The primary endpoint is improvement in health status as indicated by the Patient Global Impression of Change (PGIC)[60] at 4, 12, and 52 weeks post therapy onset. Secondary endpoints include changes in pain and pain interference as assessed by the BPI-SF[61,62] and changes in pain medication use at 4, 12, and 52 weeks post therapy onset. Additional analyses include dose-response relationships and changes in objective sleep metrics. The registry enables demonstration of clinical improvement using Quell in many different chronic pain syndromes. The registry also identifies demographic, clinical, and utilization markers for response to therapy.

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