ST Genesis™

Percutaneous Nerve Field Stimulator

MONOGRAPH

SPERANZA THERAPEUTICS

Bridging the gap between hope and healing

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1.0 EXECUTIVE SUMMARY

S.T. Genesis Percutaneous Nerve Field Stimulator (PNFS)

Device Name	S.T. Genesis
Manufacturer	Speranza Therapeutics
FDA Approved	May 2, 2018
Summary	S.T. Genesis is a Percutaneous Nerve Field Stimulator (PNFS) that supports reduction of opioid withdrawal symptoms through application to branches of cranial nerves V, VII, IX, and X as well as the occipital nerves
OVERVIEW OF DISEASE STATE	
Disease State	Opioid use disorder (OUD) is the condition in which an individual continues persistent use of opioids despite the harmful consequences of its use. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), defines OUD as “a problematic pattern of opioid use leading to clinically significant impairment or distress.”
Diagnosis	The diagnosis of OUD is made using the International Classification of Diseases 11th revision or Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria (DSM-5). Clinicians also evaluate the OUD severity using the DSM-5; presence of 2–3 criteria is considered mild, 4–5 moderate, and 6 or more is severe on the OUD spectrum.
Treatment	There are effective psychosocial and pharmacological interventions for opioid use disorders. Psychosocial therapies such as cognitive behavioral therapies, relapse prevention, contingency management and motivational enhancement therapy can be used by themselves or in combination with a pharmacotherapy. Pharmacotherapy options include opioid agonists, partial agonists and antagonists, as well as alpha-2-adrenergic agonists, which are used to manage symptoms of opioid withdrawal syndrome. Medication-assisted treatment (MAT) is the use of medications with counseling and behavioral therapies to treat opioid use disorders and prevent overdose. Conventional MAT includes the medications methadone, buprenorphine, Naloxone and Naltrexone, and Lofexidine (Lucemyra).
Monitoring	

2.0 DISEASE STATE OVERVIEW:
OPIOID USE DISORDER/OPIOID WITHDRAWAL SYNDROME

2.1 DISEASE BACKGROUND

The misuse of and addiction to opioids (e.g. prescription pain relievers, heroin, and synthetic opioids such as fentanyl) has reached epidemic proportions in the United States, affecting both public health as well as social and economic welfare. ***Opioid use disorder (OUD)*** is the condition in which an individual continues persistent use of opioids despite the harmful consequences of its use. The disorder is characterized by a pattern of opioid use associated with a variety of physical, mental, social, and legal difficulties, leading to clinically significant impairment or distress.

INTERNATIONAL CLASSIFICATION OF DISEASES 11TH REVISION CRITERIA FOR OPIOID USE DISORDER
Hazardous pattern of use of opioids • *A pattern that has caused impairment to physical or mental health or resulted in behavior leading to harm to the health of others.* • *Opioid use is considered hazardous if episodic over a period of at least 12 months or continuous (i.e., daily, or almost daily) for at least 1 month.* • *Harm to the individual occurs due to: behavior related to intoxication; direct or secondary toxic effects on body organs and systems; or a harmful route of administration.* • *A hazardous pattern also includes physical harm, trauma, or mental disorder of individuals that is directly attributable to the opioid-related behavior of the person to whom the diagnosis of harmful pattern of use of opioids applies.*
Opioid dependence • *A disorder arising from repeated or continuous use of opioids in which an individual's ability to control opioid use is impaired, and opioid use is persistent despite harm or negative effects.* • *The disorder is characterized by a strong internal drive to use opioids, increasing priority given to use over other activities, and are often accompanied by a subjective sensation of an urge or craving to use opioids.* • *Physiological features include: tolerance to the effects of opioids, withdrawal symptoms following cessation or reduction in use of opioids, or repeated use of opioids or pharmacologically similar substances to prevent or alleviate withdrawal symptoms.* • *The features of opioid dependence are usually evident over a period of at least 12 months, but the diagnosis might be made if opioid use is continuous (daily or almost daily) for at least 1 month.*

The types of opioids used by individuals with OUD include both prescription and illicit opioids and the non-medical use of pharmaceutical opioids is of substantial concern for both law enforcement authorities and public health professionals. The first wave of the OUD epidemic in the United States began in the 1990s with increased prescribing of opioids; overdose deaths involving prescription opioids (natural and semi-synthetic opioids and methadone) have been rising since 1999. This was followed by a second wave (2010) where rapid increases in overdose deaths involving heroin were reported, followed by a third wave (2013), in which significant increases

occurred in overdose deaths involving synthetic opioids, particularly those involving illicitly sourced fentanyl mixed with heroin or other drugs.

OUD is associated with a range of mental and general medical comorbid disorders and is also associated with increased mortality. While genetics play a role in the risk of developing OUD, the risk is increased among individuals of younger age, male sex, and lower educational level and income as well as among those with psychiatric disorders such as other substance use disorders and mood disorders.

Opioid Withdrawal is an obstacle to treatment among individuals with OUD. Abrupt cessation of opioids after repeated use leads to opioid withdrawal symptoms, which are frequently severe, and may prompt patients to restart opioids in the early days after opioid discontinuation or prevent them from attempting to stop discontinue use of opioids at all. These symptoms can also lead to opioid seeking in pain patients in whom acute opioid withdrawal is not effectively managed.

Opioid withdrawal symptoms include those that appear with early (acute) withdrawal and those evident as patients progresses to fully developed withdrawal; the duration depends on the severity of the physical dependence on opioids as well as the specific opioid. Withdrawal symptoms for short-acting opioids generally last 7–10 days, while symptoms from long-acting opioids can persist for 14 days or more. Standardized instruments such as the ***Clinical Opiate Withdrawal Scale (COWS)*** and the ***Subjective Opiated Withdrawal Scale (SOWS)*** are used to assess symptoms of acute withdrawal. Once the acute withdrawal phase is complete, many patients experience a prolonged ***Opioid Withdrawal Syndrome,*** characterized by dysphoria, craving, insomnia, and hyperalgesia (i.e. heightened sensitivity to pain) that reflects brain circuitry neuroadaptations associated with addiction. A major physiologic driver of these symptoms is central noradrenergic hyperactivity that occurs as a result of abrupt opioid discontinuation in opioid-tolerant individuals.

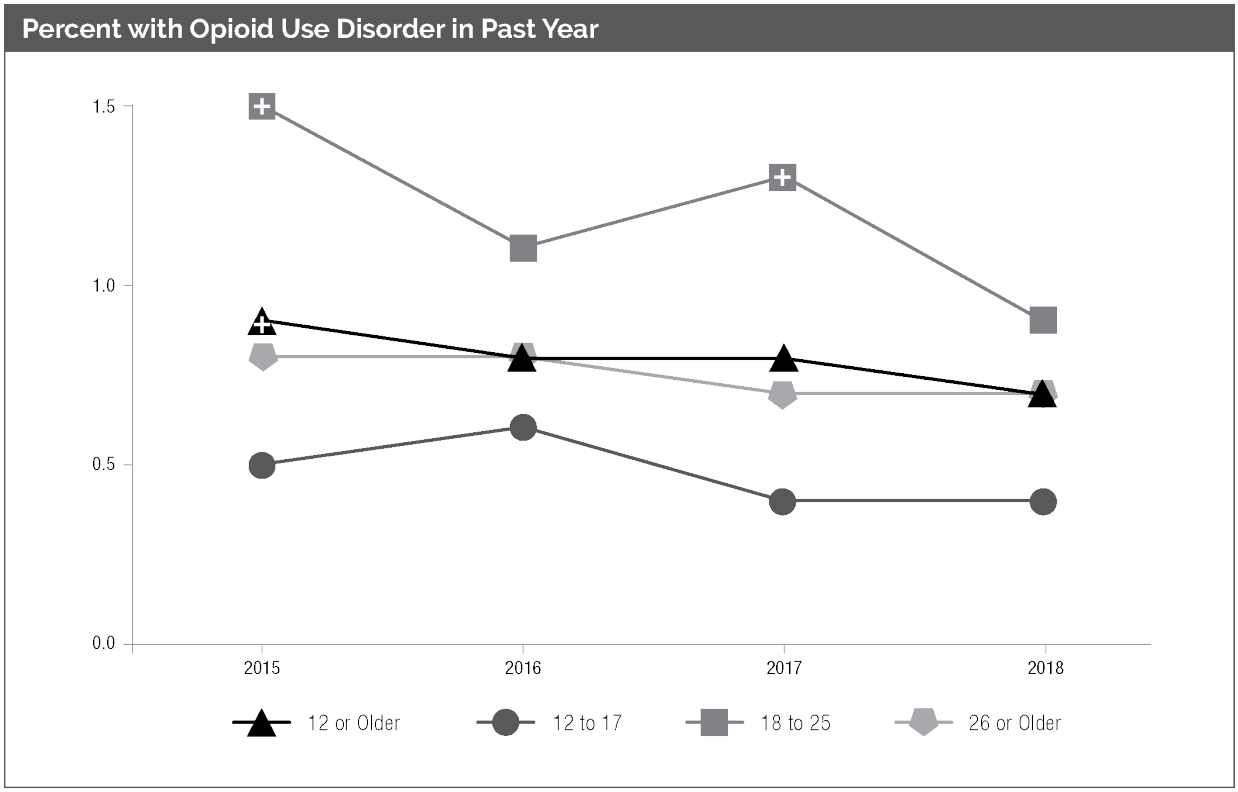
Opioid withdrawal symptoms

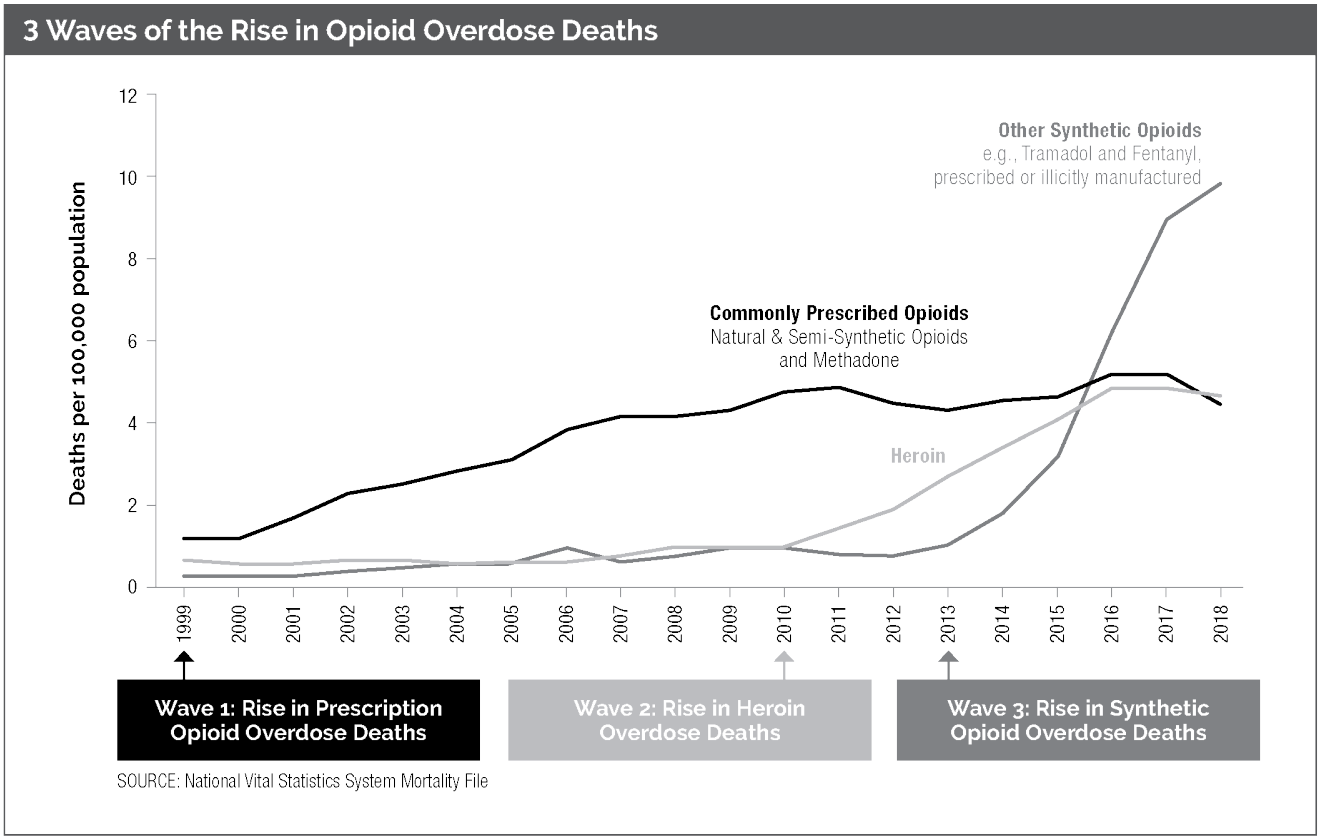
	TIME AFTER LAST USE	SIGNS	SYMPTOMS
Early withdrawal	Short-acting opioids: 8–24 h; long-acting opioids: up to 36 h	Mydriasis (pupillary dilatation), piloerection (gooseflesh), muscle twitching	Lacrimation, rhinorrhea, diaphoresis (sweating), yawning, tremor, insomnia, restlessness, myalgia, arthralgia, abdominal pain, nausea, vomiting
Fully developed withdrawal	Short-acting opioids: 24–72 h; long-acting opioids: 72–96 h	Tachycardia, tachypnoea, hypertension or hypotension, dehydration, hyperglycemia	Fever, anorexia, nausea, vomiting, diarrhea

Two million people (0.7 % of the population) had an OUD in the United States in 2018 and according to the 2019 National Survey on Drug Use and Health. Prescription opioid abuse has increased substantially over the past two decades in the United States and non-medical use of pharmaceutical opioids has reached epidemic proportions. In the United States, opioid prescriptions increased from 76 million in 1991 to 219 million in 2011, with associated increases in opioid-related emergency room visits, treatment admissions, and overdose deaths. An estimated 25 million people initiated nonmedical use of pain relievers between 2002 and 2011 and in 2018 alone, 10.3 million people misused prescription opioids, as reported by the 2019 National Survey on Drug Use and Health.

In 2018, approximately 1.6 million adults aged 26 or older had an OUD in the past year, representing 0.7 percent of adults in this age group while 0.9 percent (N=312,000) of young adults aged 18 to 25 had an opioid use disorder in the same time period.

Despite extensive research regarding the addictive properties of opioid medications, there is an opioid overdose epidemic in the United States and opioid overdose-related deaths continue to rise. From 1999–2018, nearly 450,000 people died due to an overdose involving an opioid, including both prescription and illicit opioids. Overdose deaths involving opioids, including prescription opioids, heroin, and synthetic opioids such as fentanyl, have increased almost 6 times since 1999. In 2015 and 2016, life expectancy in the United States declined for two consecutive years for the first time in half a century, and the increase in unintentional injuries, including overdose deaths, was a key factor. In 2018, overdoses involving opioids killed 46,802 (69.5% of all drug overdose deaths); 32% of those deaths involved prescription opioids and 2 out of 3 (67.0%) opioid-related overdose deaths involved synthetic opioids.

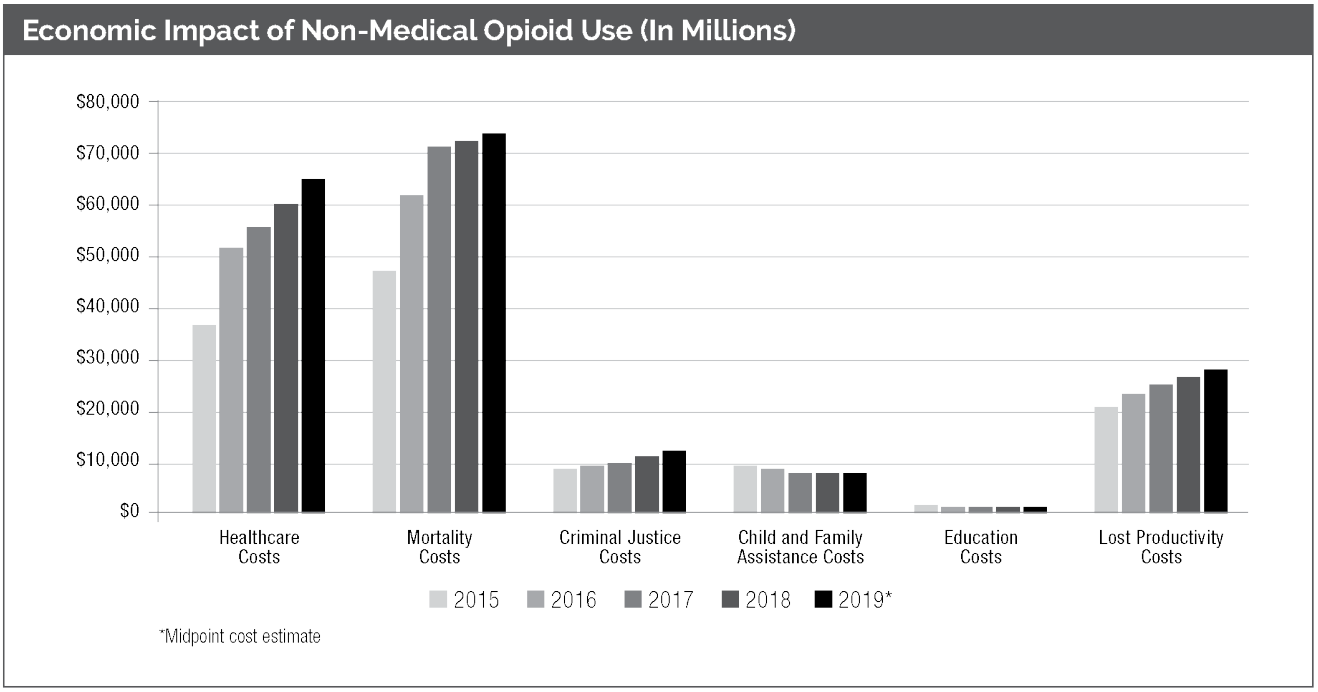




Numerous studies have shown that while OUD is associated with elevated mortality primarily due to drug overdose, cardiovascular diseases, cancer, and infectious diseases are also among the leading causes of death for individuals with OUD and both hepatitis C virus and alcohol use disorder are clinically important indicators of overall mortality risk in this population. All-cause crude mortality rate has been reported at 20.9 per 1000 person-years with a pooled standardized mortality ratio of 14.7 per 1000 person-years.

2.2 BURDEN OF ILLNESS

The economic burden of the opioid addiction epidemic is substantial. A report by the Council of Economic Advisers estimates the total costs to be $504.0 billion in 2015, with a low range estimate of $293.9 billion to a high of $622.1 billion. The Society of Actuaries (SOA) estimated that the cost of this epidemic to the United States economy was at least $631 billion from 2015 to 2018. Mortality was the largest cost category ($253 billion), accounting for 40% of the estimated economic impact, primarily due to lost lifetime earnings because of premature death from drug overdoses involving opioids. Nearly one-third of the estimated economic burden was attributable to excess healthcare spending ($205 billion) related to OUD, as well as neonatal abstinence syndrome or neonatal opioid withdrawal syndrome. Lost productivity costs associated with absenteeism, reduced labor force participation, incarceration for opioid-related crimes and employer costs for disability and workers' compensation benefits to employees with opioid use disorder totaled $96 billion from 2015 through 2018.



Compared with patients who do not struggle with OUD, those with an OUD utilize significantly more healthcare resources, including emergency department visits, physician outpatient visits, and inpatient hospital stays. A recent study of the U.S National inpatient sample (NIS) demonstrated that almost half a million hospitalizations annually were associated with OUD while the rate of OUD hospitalizations has increased from 59.8 /100,000 in 1998–2000 to 190.7/100,000 in 2015–16. Greater usage of healthcare resources impacts not only cost, but may lead to longer wait times, fewer appointment options, and increased staff workload. Healthcare resource utilization related to treatment programs is also high. Approximately 400,000 people aged 12 or older in 2018 with an OUD received illicit drug use treatment at a specialty facility in the past year, representing 19.7% of those with an OUD.

The opioid epidemic also carries a heavy burden due to diminished quality of life for those with OUD. Several studies have found that patients with OUD have significantly worse physical and mental quality of life compared with the general population ($P < .001$), with high rates of sleep disturbances. Family members of individuals with OUD also experience diminished quality of life from OUD. Caregivers have reported moderate to severe burdens related to burden on finances, disruption of family routine, disruption of family leisure, and disruption of family interaction.

The clinical burden of OUD is also high. Patients with OUD have higher levels of comorbid conditions, resulting in an increased burden of illness for this population. Individuals with OUD, particularly those who inject drugs, are at increased risk of transmissible diseases, particularly HIV/AIDS, hepatitis C, syphilis, and tuberculosis as well as other infections such as bacterial endocarditis, cellulitis, endophthalmitis, wound botulism, necrotizing fasciitis and brain, spleen, or myocardial abscesses and emboli. Diseases related to heavy tobacco use, such as chronic obstructive pulmonary disease, hypertension, and coronary artery disease are also more prevalent than in the general population. Furthermore, individuals with OUD often do not receive regular health care, and these comorbid conditions may be underdiagnosed and undertreated. Conditions resulting from intoxication or criminal activity, such as head trauma or gunshot wounds, may also be more prevalent in individuals with OUD.

2.3 DIAGNOSIS

Individuals with opioid use disorder may seek treatment for other disorders or symptoms, such as infections or pain, screening for opioid misuse and opioid use disorder in psychiatric and general medical settings is likely to be an effective way to identify individuals whose disorder would otherwise be missed. When opioid misuse or opioid use disorder is identified through screening instruments, a more in-depth evaluation of the severity of the disorder is warranted. Several screening instruments can help to identify patients who use drugs, but most do not specify the types of drug being used.

The diagnosis of OUD is made using the International Classification of Diseases 11th revision or Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria (DSM-5). Clinicians also evaluate the OUD severity using the DSM-5; presence of 2–3 criteria is considered mild, 4–5 moderate, and 6 or more is severe on the OUD spectrum. An assessment of other comorbid conditions is necessary to determined other diseases that may need to be treated. Drug testing may be used to determine the use of other substances and can help to monitor progress.

DSM-5 CRITERIA FOR OPIOID USE DISORDER

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. *Opioids are often taken in larger amounts or over a longer period of time than was intended.*
2. *There is a persistent desire or unsuccessful efforts to cut down or control opioid use.*
3. *A lot of time is spent in activities to obtain the opioid, use the opioid, or recover from its effects.*
4. *Craving, or a strong desire or urge to use opioids.*
5. *Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.*
6. *Continued opioid use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of opioids.*
7. *Important social, occupational, or recreational activities are given up or reduced because of opioid use.*
8. *Recurrent opioid use in situations in which it is physically hazardous.*
9. *Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.*
10. *Tolerance[a] as defined by either of the following: (a) A need for markedly increased amounts of opioids to achieve intoxication or desired effect. (b) A markedly diminished effect with continued use of the same amount of an opioid.*
11. *Withdrawal[a]*

[a]This criterion is not met for individuals taking opioids solely under appropriate medical supervision.

2.4 TREATMENT LANDSCAPE

2.4.1 Overview

There are effective psychosocial and pharmacological interventions for opioid use disorders. Psychosocial therapies such as cognitive behavioral therapies, relapse prevention, contingency management and motivational enhancement therapy can be used by themselves or in combination with a pharmacotherapy. Pharmacotherapy options include opioid agonists, partial agonists, and antagonists, as well as alpha-2-adrenergic agonists, which are used to manage symptoms of opioid withdrawal syndrome.

Medication-assisted treatment (MAT) is the use of medications with counseling and behavioral therapies to treat opioid use disorders and prevent overdose. Conventional (MAT) include the medications methadone (a full

agonist) and buprenorphine (a partial agonist) and can also be used to assist with short-term detoxification. Opioid antagonists, medications that block the opioid receptors, include Naloxone and Naltrexone which are non-narcotic and non-addictive but may lead to withdrawal symptoms in individuals physically dependent on opioids since these medications block the opioid receptors. Lofexidine (Lucemyra) is a non-opioid medication (alpha-2-adrenergic agonist) that suppresses noradrenergic hyperactivity.

2.4.2 Current Treatments

Below is a chart summarizing the existing treatments for opioid withdrawal syndrome.

Summary of Existing MAT

OPIOID USE DISORDER TREATMENTS	DESCRIPTION	PERCEIVED ADVANTAGES	LIMITATIONS
S.T. Genesis	Non-opioid/ Percutaneous Neurostimulator (Non-Invasive)	Effects seen within 20 minutes; 5-10 days to complete. No adverse reactions other than minimal skin reactions at application site.	
Buprenophrine	Opioid-based/Tablet	High availability for office use.	Risk for addiction dependence/abuse. Dose adjustment for patients with severe hepatic impairment; multiple adverse effects.
Buprenorphine and Naloxone	Opioid-based/ Sublingual Film; Buccal Film; Sublingual Tablets		Risk for addiction dependence/abuse. May not be appropriate for patients with moderate hepatic impairment; should be avoided in patients with severe hepatic impairment; multiple adverse effects.
Lucemyra	Non-opioid/Tablet	No risk for addiction dependence/abuse.	Dose adjustment for patients with renal and hepatic impairment; multiple cardiac adverse effects.
Methadone	Opioid-based/Tablet	Effective treatment with long-term data supporting its use.	Risk for addiction dependence/abuse. Requires REMS program. High risk of relapse with discontinuation of methadone maintenance treatment. Lower starting doses and slow titrations for patients with renal and hepatic impairment; multiple adverse effects.

2.4.3 Treatment Trends

Currently, there are three approved medications for treatment of OUD as part of MAT—methadone, buprenorphine, and naltrexone—that are considered the standard of care for most patients with opioid use disorder. Of these, methadone has been available the longest and has the largest evidence base on efficacy.

There are substantial barriers for persons seeking MAT and treatment trends reflect this. A limited number of MAT providers treat OUD and in recent years, federal initiatives have been launched to improve access to and extend use of MAT. However, recent survey data show that few providers report confidence in treating OUD (19 %) or managing opioid tapering (24 %). Most providers prefer to refer patients for OUD (89 %), but few report that appropriate services are readily available (22 %).

The efficacy of these medications for opioid use disorder is well accepted, there is an unmet need for new therapies that will increase adherence and retention, and that can be provided as options to current treatments. Many patients are unable to adhere to medications for opioid use disorder for sufficiently long periods of time, some cannot be inducted onto them, and some may stop responding after a period of benefit.

2.4.4 Monitoring

Monitoring recommendations from the American Society of Addiction Medicine vary depending on the medication used for MAT. In general, patients are seen frequently at the beginning of their treatment, with weekly or more frequent visits recommended until patients are determined to be stable. Stable patients can be seen less often but should be monitored at least monthly. Use of other prescription medications is often monitored through access to PDMP data. Urine drug testing or other reliable biological tests are used to test for use of illicit drugs (e.g. heroin and marijuana, and prescription medications including benzodiazepines, prescription opioids, and amphetamines). Drug testing has served as both an objective measure of treatment efficacy as well as a method to monitor patient progress during medication-assisted treatment for opioid addiction.

3.0 PRODUCT INFORMATION

S.T. GENESIS PRODUCT INFORMATION

3.1 DESCRIPTION

- S.T. Genesis™ is the latest generation of auricular Percutaneous Electrical Neural Field Stimulators (PNFS) and is FDA cleared for use in opioid withdrawal
- The S.T. Genesis administers an auricular neurostimulation treatment through electrodes applied to specific cutaneous branches on the ear. Stimulation is performed by sending subtle electrical pulses through the electrodes. Each patient's treatment is determined by frequent measurement of Clinical Opiate Withdrawal Scale (COWS) feedback until the opiate cravings have subsided
- The therapeutic effect of PNFS is long-lasting, and has been shown to last for weeks, even months, after the treatment has ended. The S.T. Genesis helps reduce the duration and intensity of withdrawal symptoms, giving patients the opportunity to continue with a recovery program through additional medication-assisted therapy and cognitive behavioral therapy
- The S.T. Genesis achieves its therapeutic effects through multiple ***non-pharmacologic mechanisms of action*** that target specific areas in the central nervous system (CNS)
- PNFS is a low-risk, non-invasive therapy that has shown to reduce opioid withdrawal symptoms and associated COWS scores
- S.T. Genesis neurostimulation techniques are safe, well-tolerated, and avoid the systemic side effects of conventional drug therapies
- S.T. Genesis has few adverse effects - occasional local irritation and local bleeding occur in less than 1/2 of 1% of cases
- S.T. Genesis can be removed at any time without the lingering metabolic consequences of drugs that must be excreted from the body

S.T. GENESIS™ MECHANISMS OF ACTION

The S.T. Genesis™ mechanism of action reshapes the neuronal and synaptic properties of CNS neurons and the neurotransmitters that they release by modifying intrinsic neuronal membrane properties, thereby altering the neuron's response to synaptic events. Electrical neuromodulation has been shown to influence the development of new neuronal circuits in the brain as well as to reshape the outputs of existing circuits. This process exploits neuroplasticity to, in essence, rewire and reprogram the brain to achieve specific therapeutic goals. Neuromodulation's exploitation of central nervous system plasticity can loosely be characterized as a manipulation of the balance between different brain networks resulting in specific therapeutic effects when applied correctly and in the appropriate context. Even short durations of neurostimulation have been shown to exert long-term inhibition on brain stem interneurons consistent with neuroplastic changes within these circuits.

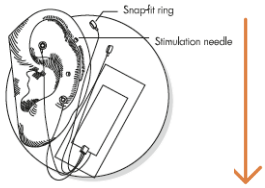
3.2 INDICATIONS

S.T. Genesis is an FDA-cleared Percutaneous Nerve Field Stimulator (PNFS) that can be used as an aid to reduce the symptoms of opioid withdrawal, through application to branches of cranial nerves V, VII, IX, and X and the occipital nerves identified by transillumination.

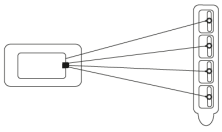
3.3 DOSAGE AND ADMINISTRATION

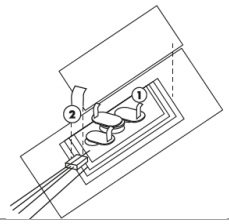
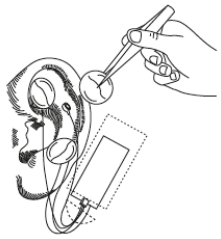
S.T. Genesis™ PNFS is designed to administer auricular neurostimulation treatment while offering the patient a high degree of comfort and mobility. Stimulation is performed by sending electrical pulses emitted through needles strategically positioned in the ear. Once the device is applied, the therapy begins and continues for a maximum of 12 hours. Each patient's treatment is determined by frequent measurement of Clinical Opiate Withdrawal Scale (COWS) feedback until the opiate cravings have subsided.

HOW IT WORKS



1. Clean and disinfect surface of ear and skin behind the ear
2. Locate and mark stimulation point for cranial nerve branches V, VII, IX and X
3. Fix the stimulation needle with the S.T. Genesis Device
4. Activate the S.T. Genesis device
5. Apply S.T. Genesis device behind ear and apply needles to stimulation points
6. Add additional adhesive

INSTRUCTIONS FOR USE OF THE S.T. GENESIS PERCUTANEOUS NERVE FIELD STIMULATOR	
1. Clean and disinfect	Clean and dry the surface of the ear chosen for stimulation. Clean and dry the skin behind the ear where the S.T. Genesis device will be placed.
2. Locate and mark the stimulation point	A transilluminator is used to locate the auricular stimulation point from the cranial nerve branches V, VII, IX and X. Project the transilluminator (Pen Type) on the ear to identify the stimulation points and mark the point against the surface of the skin with a surgical marker. Do not touch the marked points with your hand. Repeat the procedure for the other two stimulation points and to the ground.
3. Fix the stimulation needle with the S.T. Genesis Device 	Remove the protective cover from the sterile pack of needles. Take the S.T. Genesis device out of the pack, pick up one of the snap-fit rings with the help of a tweezer and fix it onto the stimulation needle placed inside the blister pack. Repeat to connect the snap-fit ring to other three needles.

4. Activate the S.T. Genesis device 	Once after fixing all the stimulation needles to the device peel off the battery foil and press the battery slightly and then slide the top cover on the devise. The cover will snap into pace only if the recess on the cover is at the lead.
5. Apply the S.T. Genesis device 	Peel off the protective file from the electrode on the rear side of the S.T. Genesis device and place the device behind the ear. Gently take out one Stimulation Needle from the blister by holding the wing sticker with the help of the tweezer. Apply the needle to the center of the marked stimulation point and repeat for other three needles. Press the holder stickers above each needle on the ear to fix the needle in place.
6. Add additional adhesive	Place the adhesive over the S.T. Genesis device control module and wire for additional strength.

3.4 PHARMACOKINETICS

Not applicable.

3.5 SAFETY CONSIDERATIONS

3.5.1 Contraindications

S.T. Genesis is contraindicated:

- In patients with cardiac pacemakers or similar biomedical implants
- During pregnancy (unless medical advised)
- In patients with hemophilia
- In patients with psoriasis vulgaris, an intact skin surface is essential for the use of the S.T Genesis device
- In patients with diminished mental capacity or physical competence about the handling of the devices
- On anesthetized or desensitized skin
- When driving a vehicle or operating potentially dangerous equipment

3.5.2 Warnings and Precautions

- For the device to be properly operated and applied, it is necessary for the S.T. Genesis device to be used as described in the instructions. Non-observance of the warnings and safety instructions may lead to injuries and infection to the user and others
- Patients on long-term blood-thinning medication must be place under medical observation during treatment

- S.T. Genesis device may only be applied under the supervision of a doctor
- The sterile stimulation needles are only intended for single use and should not be re-sterilized. The repeated usage of single-use product represents a possible risk of infection for the patient.
- S.T. Genesis device should only be used on clean, intact skin
- If the device and/or needles become detached, they must not be refastened by the patient under any circumstances. The patient should visit their doctor as soon as possible in order to have the puncture point disinfected
- When removing the device, it is important that care be taken to avoid contact with the needles. The needles can be separated from the S.T. Genesis device by carefully cutting through the connection leads.
- It is important that all contaminated tips or sharp objects in medical are handled with extreme care and disposed of according to local regulations
- Direct contact with water may destroy components of the S.T. Genesis device. When showering, the device must not be allowed to come into direct contact with water
- The use of the S.T. Genesis device in a potentially explosive area is not permitted
- Use of the device in the vicinity (~ 1 meter/3 feet) of short wave, microwave, or any radio frequency emitting device may cause interference and therefore must be avoided

3.5.3 Adverse Effects

S.T. Genesis neurostimulation techniques are assuredly safe, well-tolerated, and avoid the systemic side effects of conventional drug therapies. The only complications with this procedure are occasional local irritation and local bleeding (occurring in less than 1/2 of 1% of cases).

No adverse events were recorded in any subject during the entire study of neurostimulation with the percutaneous nerve field stimulator.

3.5.4 Drug Interactions

Not applicable.

3.5.5 Use in Special Populations

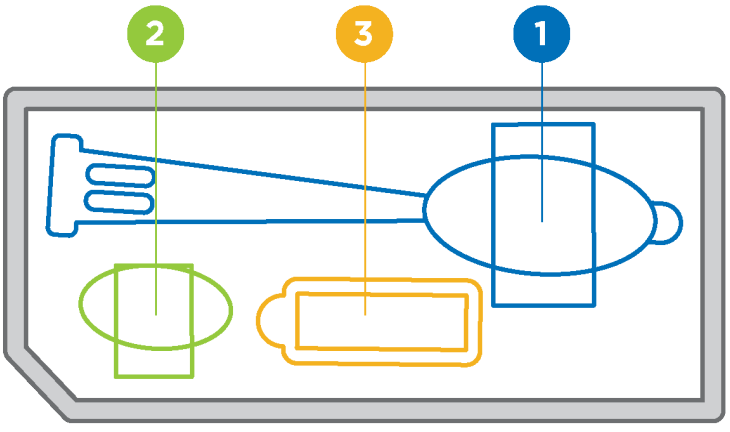
Not applicable.

3.6 DETAILED DEVICE DESCRIPTION

S.T. Genesis is provided as a device with inserted but non-activated batteries, wires and snap-fit ring, sterile pack of three single-use needles, adhesive for device and needles and cover for device.

Before use, each device pack should be visually inspected. If any defects are discovered, the complete unit including all components must be returned to the manufacturer's local representative. Do not refrigerate or freeze. Store at temperatures of 5°C to 40°C, relative humidity of 40-80% and ambient air pressures of 800-12000 millibars. (68°F -77°F). The product has a limited shelf life of six months from the date of manufacture. Device should be kept away from sunlight and kept away from rain.

Items Supplied



- S.T. Genesis Device with inserted, but not activated batteries, wires and snap-fit ring. **(1)**
- Cover of the S.T. Genesis Device **(2)**
- Sterile pack of needles for use with the S.T. Genesis Device **(3)**
- Adhesive to fasten the needle and snap-fit
- Adhesive for the S.T. Genesis Device
- Instructions for use

Please check the contents when you open the package. S.T. Genesis Device and its accessories are for single use only. The application of S.T. Genesis Device is supported by a transillumination device. Please purchase separately.

4.0 SUPPORTING CLINICAL EVIDENCE

SUPPORTING CLINICAL EVIDENCE

4.1 KEY CLINICAL STUDY

A clinical trial was performed utilizing a device that functions similarly to the S.T. Genesis device to stimulate peripheral cranial neurovascular bundles in the external ear. The trial data shows that nearly all adult patients included in the study successfully transitioned from the use of the device during detoxification (medically supervised opioid withdrawal) to medication assisted therapy (MAT). A reduction in COWS scores was noticeable within 20 minutes of device placement, with scores continuing to drop over the five-day duration of opioid withdrawal treatment. This effective approach has been shown to allow patients to progress with recovery with the support of physician follow-up along with MAT.

Adult patients (≥18 years old) who met DSM-IV criteria for opioid dependence and voluntarily presented to outpatient drug treatment clinics (June 2015 - July 2016) were included in this retrospective study. In order to be included patients needed to have a history of dependence on heroin or other opioids including prescription narcotics, methadone, and buprenorphine/naloxone. Patients were excluded if they reported a history of dependence on alcohol, pregnancy, or inability to consent to the treatment.

Patient demographics and drug use characteristics (n=73)

Age in years (SD)	32.9 (9.4)
Gender (%)	
Male	48 (65%)
Female	25 (35%)
Duration of Drug Use in Months (SD)	70 (55)
Opioids Used (%)	
Heroin	50 (68%)
Prescription Narcotics	23 (31%)
Buprenorphine/naloxone	24 (33%)
Methadone	7 (9%)
Presence of Poly-drug Use (%)	
Marijuana	15 (21%)
Benzodiazepines	13 (18%)
Cocaine	2 (3%)
Alcohol	0 (0)

Providers received training regarding the PNFS device placement via an online module followed by a clinic site visit from the training representatives. The device was packaged with all the necessary supplies for proper placement and the device was placed as per standard protocol. Baseline Clinical Opioid Withdrawal Scale

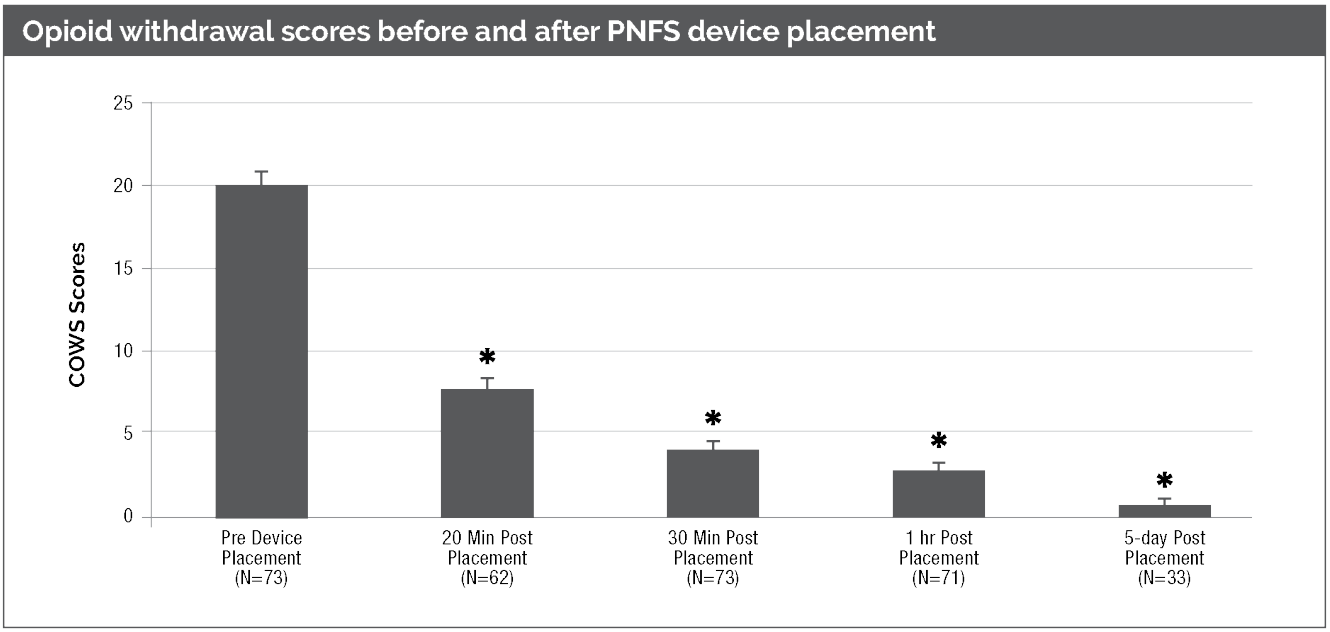
(COWS) scores were recorded and again at three other time intervals (20, 30, and 60 minutes) in all patients. These scores were extracted from the medical chart along with scores recorded at 5-day following device placement. The scores ranged from 0 to 48 and were rated as mild (5–12), moderate (13–24), moderately severe (25–36) or severe (>36).

Patients were observed after device placement and sent home once symptoms of withdrawal were relieved, typically after the first hour. The use of any rescue medications was recorded for the first hour of neurostimulation with the device, including antipsychotics, narcotics, or benzodiazepines. Patients received discharge instructions emphasizing that the device was not a cure, but rather a tool to alleviate the symptoms associated with opiate withdrawal. Patients were also instructed to wear the device for 5 days and then follow-up at the clinic within 1–5 days depending on the clinic.

The primary outcome was reduction in withdrawal scores as determined by the COWS score. A secondary outcome examined successful transition to MAT in the subset of patients who returned to the clinic on day 5 and received their first dose of maintenance medication with naltrexone.

4.2 EFFICACY OF S.T. GENESIS

- The PNFS device decreased scores to a mean of 7.5 (±5.9) by 20 minutes (62.7% reduction $P < .001$), 4.0 (±4.4) by 30 minutes (80% reduction, $P < .001$), and 3.1 (±3.4) after 60 minutes (84.6% reduction, $P < .001$)
- Overall, 73/73 (100%) subjects had a reduction in COWS scores by 60 minutes with a minimum decrease in at least 36.4%
- At 60 minutes 57/73 (78.0%) had withdrawal scores of ≤3
- No rescue medications were used in any subject during the first 60 minutes after device placement
- A significant decrease in scores was seen after just 20 minutes with an 84.6% reduction from baseline by 60 minutes and 97% after 5 days (*$P < .001$ vs. baseline scores)



- In subset of patients who had withdrawal scores recorded 5 days after PNFS device placement and prior to transitioning to MAT (n=33), the average withdrawal score prior to receiving the first dose of naltrexone was 0.6 (97.1% reduction)
- In the entire cohort of 73 patients, 64 (88.8%) successfully transitioned to MAT after device placement

4.3 SAFETY RESULTS

No adverse events were recorded in any subject during the entire study of neurostimulation with the percutaneous nerve field stimulator.

4.4 BENEFIT RISK ANALYSIS

Not Applicable

4.5 IMPORTANT SAFETY INFORMATION

Not Applicable

4.6 REFERENCES

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