Data Pack for Healthcare Practitioners

Version 3.0

Samphire Neuroscience

Introduction

This Data Pack provides healthcare practitioners with an overview of Samphire Neuroscience's at-home transcranial direct current stimulation (tDCS) solutions - Nettle™ (UK/EU) and Lutea™ (USA/Global). It covers clinical rationale, mechanism of action, intended use, evidence, safety, and implementation advice to support clinical decision-making, patient counselling, and integration into care pathways.

How can this data pack help me improve patient outcomes and satisfaction?

- Broadens clinical understanding: Complements endocrine explanations with a neuroscience-informed view of central pain processing in pain and mood symptoms linked to the menstrual cycle.
- Integrates a new modality into practice: Provides practical, clinician-focused guidance on how Samphire's neurostimulation device works, which patients may benefit, and how to incorporate neurostimulation into existing care pathways alongside standard treatments.
- Recommend with confidence: Summarizes the current evidence base, safety profile, contraindications, and long-term use considerations to support informed, risk-aware clinical decision-making.

When should I advise a patient to consider Samphire Neuroscience's solutions?

Consider discussing Samphire Neuroscience's solutions with patients who:

- Experience menstrual pain and/or premenstrual mood symptoms (low mood, anxiety, irritability) that interfere with daily function.
- Have a menstrual-related reproductive condition or a condition that is triggered or worsened by the menstrual cycle, such as:
    - Premenstrual Syndrome
    - Primary Dysmenorrhea
    - Endometriosis
    - Premenstrual Dysphoric Disorder (PMDD)
    - Adenomyosis
    - Polycystic Ovary Syndrome (PCOS)
    - Premenstrual Exacerbation (PME)
- Are seeking an at-home, non-invasive option and/or have partial response, intolerance, or reluctance toward pharmacologic options.
- Do not have contraindications to use.

What is the intended use of Nettle™ and Lutea™ ?

Nettle™ and Lutea™ share the same underlying neurostimulation platform and are designed to stimulate the same regions of the brain. The authorized claims and described use vary by market, in line with regional regulatory frameworks.

- Nettle™ (UK & EU): CE-marked Class IIa medical device clinically validated for the management of menstrual pain and mood symptoms.
- Lutea™ (USA & Global): A wellness device using the same neurostimulation technology, designed for cycle-linked balance and focus.

Are the devices safe?

The underlying technology of Nettle™ and Lutea™ (tDCS) has been used in clinic and research for more than 30 years. It is known for its safety profile, the very low incidence of mild side effects and no reported serious adverse events in over 300,000 documented tDCS sessions. Common side effects include itching and tingling. It has been approved for consumer use in the UK and EU since 2019 and in the US since 2025.

Can the devices be used adjunctively?

Yes - they are drug and hormone free; compatible with comprehensive and standard care. There are no known, documented or expected interactions with other pharmacological or holistic options.

1. Clinical Background

For decades, conditions such as Primary Dysmenorrhea (PD) and Premenstrual Syndrome (PMS) were viewed predominantly through a gynecological lens - localized events restricted to the uterus and ovaries, driven by hormonal fluctuations and peripheral inflammation. While this framework has informed standard diagnostic criteria and treatment strategies, it has not fully explained the persistent symptom burden, variable treatment response, and high prevalence of comorbid pain and mood disorders observed in many patients.

Latest research and emerging evidence from pain science, neuroscience and psychiatry has substantially expanded this gynecological perspective. We now understand these conditions as complex, multisystem, neuroinflammatory disorders characterized by significant central nervous system (CNS) involvement, altered pain processing, maladaptive neuroplasticity, and systemic

effects that extend well beyond the reproductive organs and across the lifespan. Importantly, this integrated model complements, rather than replaces, established gynecological and endocrine mechanisms; and offers a more complete explanation for the diverse clinical presentations reported by patients.

1.1 The Need for Targeted Solutions

Across the menstrual cycle, a substantial proportion of women experience recurrent physical and affective symptoms that deeply impact quality of life, daily activities, emotional well-being, interpersonal relationships, and workforce participation (Schoep et al., 2019). Despite their prevalence and impact, current therapeutic treatments remain limited. Although NSAIDs, hormonal therapies, and SSRIs are commonly prescribed for menstrual-related pain and affective symptoms, these approaches are often associated with partial efficacy, gastrointestinal or neuropsychiatric side effects, adherence challenges, and patient resistance to ongoing pharmacologic treatment for cyclical symptoms (Marjoribanks J, et al., 2015; Schroll JB, et al., 2023; Jespersen C, et al., 2024). This therapeutic gap leaves many patients insufficiently supported and navigating care across multiple specialties without a clearly defined pathway.

There is a pressing demand for more targeted, effective, non-invasive solutions to address the neurological roots of these conditions - specifically the dysregulation of the prefrontal cortex and central pain pathways. Neurotechnology-based approaches have the potential to improve symptom control, enhance functional outcomes, and reduce the long-term burden associated with common yet undertreated (pre)menstrual conditions.

1.2 The Burden of Primary Dysmenorrhea

Women disproportionately bear the burden of chronic conditions, spending 25% more of their lives in poor health compared to men (Temkin et al., 2023; World Economic Forum, 2024). Dysmenorrhea, defined as painful menstrual cramps, is the most common gynecological complaint, impacting more than 70% of women of reproductive age (De Sanctis et al., 2024). It is classified as either primary dysmenorrhea (PD) or secondary dysmenorrhea. PD occurs in the absence of identifiable pelvic pathology, whereas secondary dysmenorrhea results from underlying gynecological conditions such as endometriosis, uterine fibroids, or adenomyosis (Burnett, 2025; De Sanctis et al., 2016).

The hallmark clinical feature of PD is spasmodic cramping in the lower abdomen and/or lower back. This symptom is frequently accompanied by a wide range of concomitant symptoms such as

nausea, vomiting, dizziness, headache, backache, fatigue and diarrhea, reflecting a broader inflammatory response (Iacovides et al., 2015). Onset typically occurs in adolescence, during or shortly after (6-24 months) menarche (Iacovides et al., 2015). 15% to 29% of women experience severe, incapacitating pain that necessitates absenteeism from school or work (De Sanctis et al., 2015; Burnett, 2025), underscoring the significant functional impact of this condition.

Historically, the pathophysiology of PD has been attributed to the excessive production of prostaglandins (PG) (in particular, PGF2α), causing uterine muscle ischemia and hypercontractility. While this mechanism remains a key contributor, new research indicates that it represents only part of a broader disease process.

Increasingly, PD is being characterized as a complex neuro-inflammatory disorder, involving dysregulation of the nervous system. Notably, recurrent episodes of PD induce alterations in the brain, including gray matter volume reduction in pain-modulatory regions (prefrontal cortex) and disrupted connectivity in the periaqueductal gray (PAG) (Lee et al., 2023). This state of central sensitization means the central nervous system amplifies sensory input, resulting in heightened pain perception persisting even during pain-free phases of the menstrual cycle. Clinically, this helps explain symptom severity, treatment resistance, and the progression from episodic menstrual pain to broader pain vulnerability.

If inadequately managed, this central sensitization associated with PD has longitudinal consequences. A landmark 2025 study from the ALSPAC birth cohort demonstrated that adolescents with severe dysmenorrhea had a 76% increased risk of developing chronic widespread pain (including non-pelvic pain) by adulthood (Reid-McCann et al., 2025). Collectively, these data points support a reconceptualization of PD not as a transient, localized gynecological complaint, but as an early-onset chronic pain disorder with systemic neurological implications.

1.3 The Burden of Premenstrual Disorders (PMS & PMDD)

Premenstrual disorders encompass a spectrum of cyclic physical, cognitive, and affective symptoms that typically emerge during the luteal phase of the menstrual cycle and tend to resolve with the onset of menstruation. For example, dysmenorrhea is often accompanied with a range of symptoms ranging from low mood and anxiety to irritability, impulsivity, and brain fog. These can be linked to aberrant brain activity in the prefrontal cortex during the luteal phase (Liao et al., 2017). Premenstrual Syndrome (PMS) represents the most prevalent manifestation, affecting up to 80% of women of reproductive age, and the symptoms can significantly disrupt daily activities in the

week leading up to menstruation (Branecka-Wozniak et al., 2022).
At the severe end of the spectrum lies Premenstrual Dysphoric Disorder (PMDD), a distinct and debilitating condition affecting approximately 1.2-3.2% of women of reproductive age (Reilly et al., 2024). PMDD is recognized as a neuroendocrine condition in the DSM-V and ICD-11, characterized by severe emotional disturbances that can escalate to life-threatening tendencies. Recent large-scale meta-analyses indicate that women with PMDD have a nearly 7-fold increased risk of suicide attempts and a 4-fold increased risk of suicidal ideation compared to those without the disorder (Islas-Preciado et al., 2025; Yang et al., 2024). Furthermore, a significant proportion of patients (pooled prevalence of 61%) report a history of trauma, which is believed to sensitize the stress-response systems involved in the disorder (Grewal et al., 2025).

Neuroimaging work has validated that the symptoms seen in PMDD are closely linked with the dysregulation of the Central Executive Network (CEN) and the Dorsolateral Prefrontal Cortex (DLPFC). Specifically, women with PMDD exhibit decreased functional connectivity within the CEN and a failure of the DLPFC to exert "top-down" inhibitory control over the emotional centers of the brain (such as the amygdala) during the luteal phase (Reuveni et al., 2023). This phase-specific neural collapse impairs the ability to regulate negative emotions, leading to the characteristic irritability, anxiety, and mood lability of the disorder.

Both PMS and PMDD are believed to stem from a negative cognitive network reaction to otherwise normal hormonal fluctuations during the menstrual cycle, with symptoms often worsening around significant reproductive events (Le et al., 2020; Hantsoo et al., 2015). Importantly, PMDD is a strong predictor and likely trigger of postpartum depression (PPD) and increased lifetime risk of major depressive disorder (MDD) (Yang et al., 2024), highlighting its significance as an early marker of vulnerability to chronic mood disorders.

2. About Samphire Neuroscience

2.1 Technical Details

Samphire Neuroscience's solutions are wearable, Bluetooth-controlled, non-invasive transcranial direct current stimulation (tDCS) devices worn on top of a user's head. This form of electrotherapy is mature and has been researched for over ~30 years, with 8,000+ peer-reviewed papers published since the year 2000 (Lewis et. al., 2025). At-home use of this technology has been approved for consumers in the UK and EU since 2019 and in the US since 2025.

The devices consist of a flexible headband made from hard and soft plastics with electronics, including a rechargeable battery, integrated inside the mechanical shell. The bottom frame of the headband, which faces the surface of the head, has four integrated, conductive surface electrodes (see Figure 1). These electrodes are made of medical-grade conductive silicone and covered by a saline-soaked sponge (electrode cover) prior to use. The sponges are single-use only, where each use is defined as a single session of neurostimulation. Prior to each session, the user is instructed to insert the sponges and hydrate them. After each session, the user is instructed to remove the sponges and dispose of them alongside household waste.

Two of the electrodes are designed to be placed bilaterally over the motor cortex (M1), while the other two electrodes are designed to be placed bilaterally over the dorsolateral prefrontal cortex (DLPFC) regions of the brain linked to pain and mood regulation, respectively.

An accompanying Samphire mobile application, available on the Apple App store and Android Google Play Store, controls and monitors the use of the device, guides users through these process steps and helps troubleshoot any technical issues that may come up. It also helps users track their health data, participate in wellness activities like meditation and mental exercises and provides a PDF export detailing their cycle and symptom data (when available) and record of completed and planned neurostimulation for clinician review.

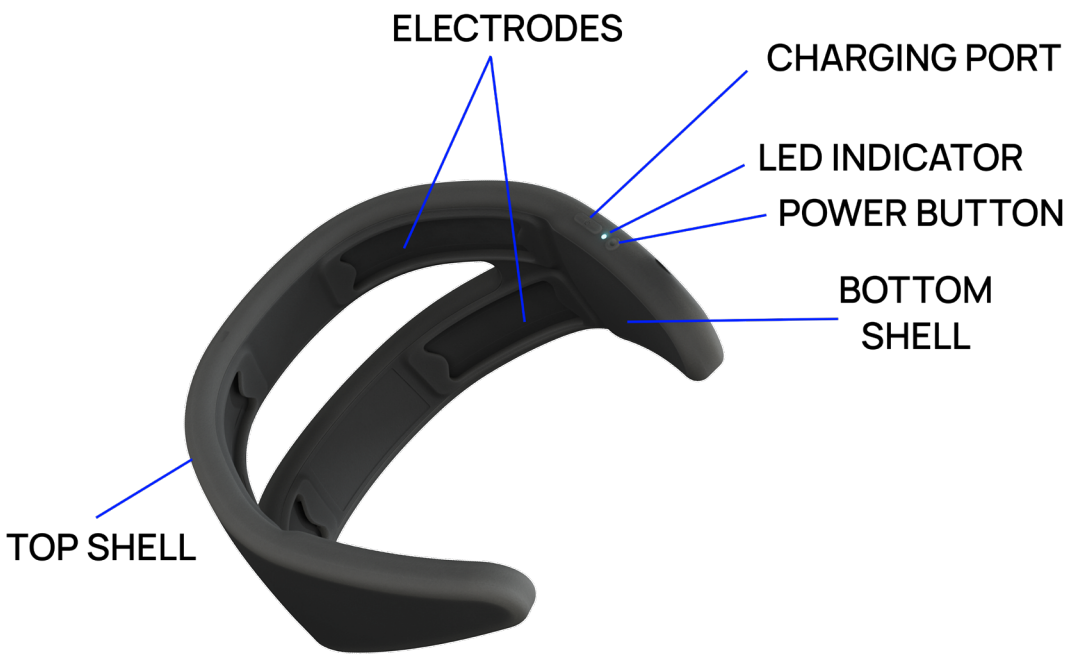

Figure 1. Illustration of the Samphire Devices.

2.2 Mechanism of Action

2.2.1 Targeting the motor cortex (M1) for pain relief

The back band of Samphire's neurostimulation device targets the motor cortex (M1). This is because the M1 has inputs to the posterior insula, which is a brain region known to be associated with perceiving and processing pain sensitivity (Lu et al., 2016), and has impaired functional connectivity in pain syndromes (Kim et al., 2019).

There have been significant effects in reducing menstrual pain shown in real vs sham controlled studies using tDCS over the M1, such as in Pegado et al., 2020 (primary dysmenorrhea) and Mechsner et al., 2023 (secondary dysmenorrhea due to endometriosis), with the latter phase II trial reporting clinically meaningful and in some cases long-lasting reductions in chronic pelvic pain without serious adverse events (Mechsner et al., 2023).

Converging evidence from structural and functional neuroimaging has long shown strong anatomical and functional connectivity between the posterior insula and the primary motor cortex (M1) (Uddin et al., 2017; Dionisio et al., 2019). More recently, tract-tracing and connectomic studies have further characterized dense posterior insula projections to brainstem nuclei within the descending pain-modulatory system, as well as extensive connectivity with primary sensorimotor regions (Liang & Labrakakis, 2024; Labrakakis, 2023).

This connectivity is particularly important because the posterior insula, responsible for pain perception and regulation, lies too deep within subcortical regions to be directly targeted using non-invasive neuromodulation techniques. As a result, non-invasive stimulation of M1 as a functional relay to the posterior insula has emerged as a viable alternative approach. Indeed, multiple studies have shown that M1 stimulation can increase pain perception thresholds, leading to reduced subjective pain experience (Pegado et al., 2020; Meeker et al., 2019; Vaseghi et al., 2015; Gan et al., 2022). Supporting this mechanism, recent mechanistic reviews of motor-cortex–mediated analgesia indicate that M1 stimulation recruits insula-centred and brainstem pain-modulatory circuits, providing a coherent neurobiological basis for these effects (Pacheco-Barrios et al., 2024).

2.2.2 Targeting the dorsolateral prefrontal cortex (DLPFC) for mood improvement

The front band of Samphire's neurostimulation device targets the dorsolateral prefrontal cortex (DLPFC). This is because the DLPFC is a well-known node for processing interpretation of low mood

and anxiety symptoms from the limbic system (White et al., 2023; Nejati et al., 2021; Clarke et al., 2020) and there is a substantial body of evidence showing its efficacy in reducing depression and anxiety symptoms.

Non-invasive stimulation of the dorsolateral prefrontal cortex (DLPFC) has consistently been shown to improve low mood and reduce anxiety, most robustly demonstrated in studies of FDA-cleared conventional and accelerated (high-dose) transcranial magnetic stimulation (TMS) for depression (Rossi et al., 2021; McClintock et al., 2018). Converging network-level evidence suggests that therapeutic effects are not limited to local cortical excitation, but instead arise from modulation of fronto-limbic circuits: effective DLPFC targets show functional connectivity with key affective regions, including the subgenual anterior cingulate cortex and the amygdala (Siddiqi et al., 2024; Bramson et al., 2024). Through this network engagement, DLPFC stimulation is thought to enhance top-down cognitive and emotional regulation over limbic reactivity.

Samphire's devices use transcranial direct current stimulation (tDCS) to non-invasively engage these same DLPFC-centred mechanisms, offering a safe, portable, at-home alternative to TMS, which requires in-clinic administration. tDCS delivers low-intensity electrical current that modulates cortical excitability and plasticity in targeted regions, facilitating downstream network effects rather than inducing action potentials directly. Recent randomized controlled trials demonstrate that remotely supervised, home-use DLPFC tDCS is feasible, well tolerated, and associated with significant improvements in depressive symptoms and cognitive function (Woodham et al., 2025; Aktürk et al., 2025), supporting its use outside traditional clinical settings. These findings align with broader regulatory progress, including EU clearance in 2019 and FDA clearance in 2025 for DLPFC-targeted tDCS systems.

The evidence base for tDCS targeting the DLPFC in affective disorders is now substantial. International evidence-based guidelines have upgraded tDCS for major depressive disorder to Level A ("definitely effective") (Fregni et al., 2021). Meta-analyses show that prefrontal tDCS is significantly superior to sham stimulation in acute depressive episodes, with higher response and remission rates (Razza et al., 2020). More recently, a large JAMA Network Open meta-analysis of 88 randomized trials of transcranial electrical stimulation found that both tDCS and tACS are associated with overall reductions in depressive symptoms, with particularly robust effects in patients with psychiatric or medical comorbidities and when used alongside pharmacotherapy; importantly, anodal left-DLPFC montages, like those used by Samphire, were consistently linked to better clinical outcomes (Ren et al., 2025).

In the context of premenstrual syndrome (PMS), low mood and anxiety are increasingly understood as arising from heightened sensitivity of fronto-limbic circuits to cyclical hormonal fluctuations, rather than from abnormal hormone levels per se (Schmidt et al., 2017). Across the late luteal phase, changes in ovarian steroids and their neuroactive metabolites (notably allopregnanolone) are known to alter GABAergic and glutamatergic signalling, increasing limbic reactivity and reducing prefrontal regulatory control (Turkmen et al., 2011). Neuroimaging and behavioural studies indicate that this state is associated with reduced DLPFC engagement during emotional regulation tasks and increased amygdala responsivity, mirroring circuit-level patterns observed in affective disorders.

By modulating excitability in the left DLPFC and strengthening top-down regulation over limbic regions, DLPFC-targeted tDCS offers a mechanistically coherent intervention for PMS-related low mood and anxiety (Dutra et al., 2020). Importantly, because tDCS does not alter systemic hormone levels, it provides a non-hormonal approach that directly targets the neural expression of cyclical mood symptoms, making it well suited for time-limited, phase-specific, and home-based use in individuals whose affective symptoms reliably track the menstrual cycle (Radyte et al., 2023; Rodrigues et al., 2024).

2.3 Nettle™ (UK & EU)

Nettle™ is a Class IIa medical device designed, clinically validated and regulated to reliably deliver tDCS to the motor cortex and dorsolateral prefrontal cortex to alleviate pain and mood associated with menstruation. Samphire Neuroscience is its official and exclusive manufacturer.

2.3.1 Clinical Outcomes Assessed in Trials

The WIND (At-home Treatment of Primary Dysmenorrhea using a Wearable IoT Neurostimulation Device: A Triple-Blind, Randomized Sham-Controlled Trial) study was able to show that after a single month's use of Nettle™:

1. 72% of users reported clinically significant pain relief and the average pain symptoms reduced by 53% within the first month of use. This kept decreasing over time, and the overall highest reduction is expected after 3 months of consistent use due to neuroplastic effects. Over 44% of women reported negligible period pain (pain reported as under 2/10) after a single month's use.

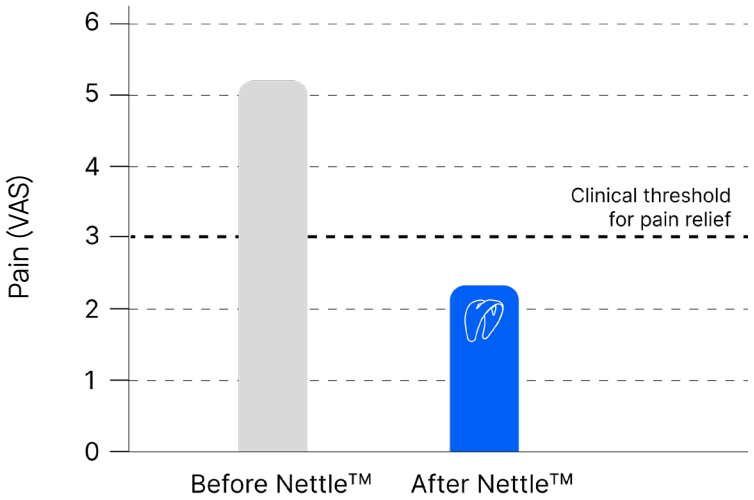

Figure 2. The average period pain decreased by 53% after a single month's use of Nettle™

2. **67% of users reported a clinically significant improvement in low mood and the average low mood symptoms in the PMS period improved by 34% within the first month of use.** 100% of users with extremely severe low mood symptoms (PANAS score above 25) improved to moderate or mild low mood symptoms after a single month's use of Nettle™. Low mood symptoms also showed neuroplastic effects (symptom relief maintained for one more month after stopping the use of Nettle™, and is likely to improve with longer-term use).

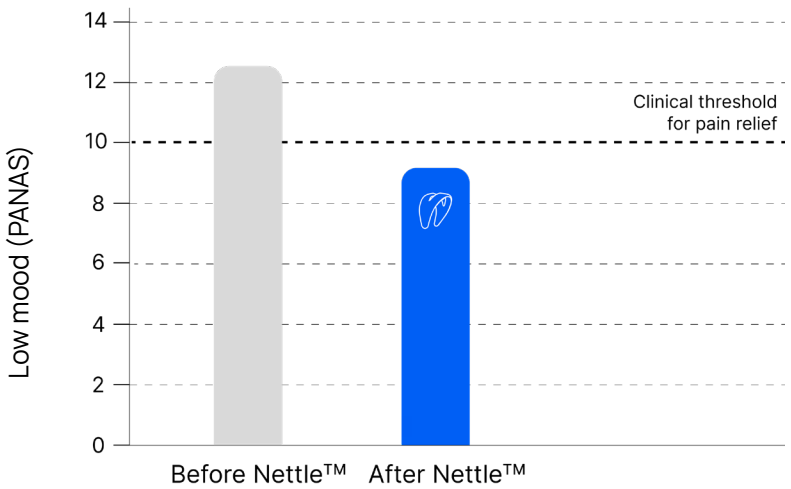

Figure 3. The average low mood symptoms in the PMS period improved by 34% after a single month's use of Nettle™.

3. **67% of users reported a clinically significant improvement in their average functionality, or fitness status, which improved by 11% within the first month of use.** This is believed to be primarily linked to the reductions in pain and anxiety, as well as improvements in mood, which lead to the ability to be more active. These improvements were directly linked to the use of Nettle™ and disappeared in the follow-up period, suggesting that it is not directly a brain-based effect (but rather a secondary effect of the improvements in the cycle-brain axis) which would be subject to neuroplasticity.

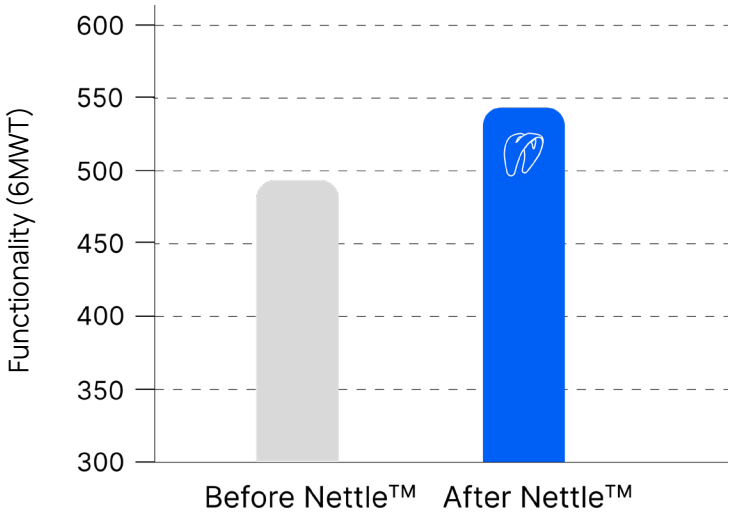

Figure 4. The average functionality, or fitness status, improved by 11% after a single month's use of Nettle™.

2.3.2 Treatment Protocol

To achieve the intended clinical outcome, the average user must complete at least 5 therapy sessions (at least once daily, and at most twice daily) in their premenstrual period (10 days before the first day of the menstrual cycle). This is the most evidence-based protocol effective for managing menstrual pain and PMS symptoms that was shown in Pegado et al., 2020 and Dutra et al., 2020; and the WIND trial.

One therapy session consists of a 20-minute active stimulation, and the required pre- and post-session patient inputs, for a total of 30 minutes per session. The user can engage in other activities during the 20-minute active stimulation session. If a session is paused, it should be resumed within 5 minutes to ensure the intended clinical effects. Users have the flexibility to pause or terminate the session either by using a clearly marked virtual button on the app or by simply taking off the device. After the session concludes, users are guided through a feedback process and are then instructed, both on the app and in the instructions for use (IFU), on how to properly clean the device.

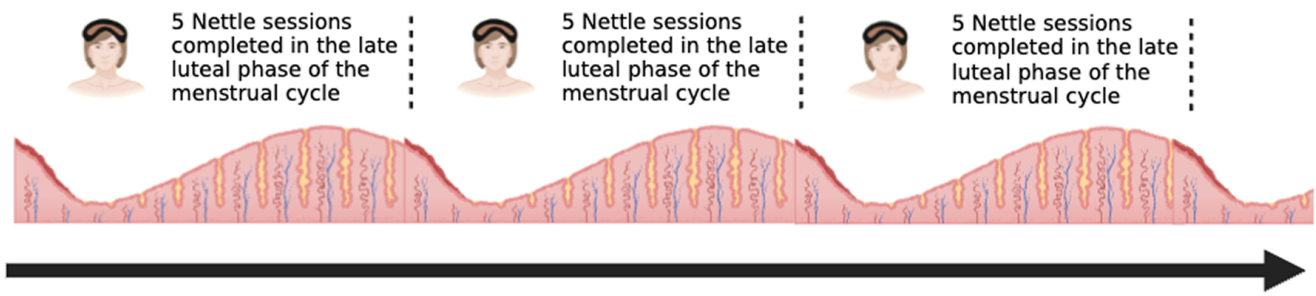

Figure 5. Illustration of the Nettle treatment protocol for PMS and dysmenorrhea.

The Samphire mobile application, as well as the IFUs (instructions for use) provided to each patient, will guide users through running the first session, as well as future sessions, and will help personalize the schedule to the individual user's needs.The manufacturer makes no additional claims outside of the intended use and intended clinical benefits.

2.3.3 Adjustments to the Standard Treatment Plan with Nettle™

Endometriosis

People living with endometriosis, a chronic condition in which tissue similar to the lining of the uterus grows outside the uterus, often experience moderate to severe chronic pelvic and menstrual pain (dysmenorrhea). As of 2024, it takes over 10 years for people with endometriosis to receive an accurate diagnosis (De Corte et al., 2025) in developed countries, which means that many people living with endometriosis spend a large proportion of their reproductive lives experiencing moderate to severe menstrual pain.

Samphire Neuroscience is actively investigating endometriosis-specific pain relief associated with the use of Nettle in its ongoing trials:

- ENHANCE: Studying Nettle™ 's effect on chronic pelvic pain in endometriosis patients (double blind, sham-controlled, in collaboration with the NHS).
- HOPE: Investigating Nettle™ for pain, fatigue, and quality of life among endometriosis patients (double blind, sham-controlled, in collaboration with UFRN).
- RELIEF: Focusing on chronic pelvic pain and wellbeing in women with endometriosis (US-based, decentralized, double blind, sham-controlled).

There are no known risks or contraindications associated with the use of Nettle™ for the management of pain relating to menstruation and mood symptoms relating to premenstrual syndrome in women with endometriosis.

Previous research (Mechsner et al., 2023) has shown that an adjustment to a mildly more intensive (10-20 tDCS sessions) protocol may be beneficial for people experiencing endometriosis-related pain, and is within the approved appropriate range (up to 20 sessions) of monthly use of Nettle™. Many current users with endometriosis report successful pain alleviation with use 5 days/week.

Premenstrual dysphoric disorder (PMDD)

It takes over 12 years to receive an accurate diagnosis of PMDD, as it is often comorbid with other psychiatric disorders such as major depressive disorder (MDD), attention deficit-hyperactivity disorder (ADHD), and autism. This means that most women living with PMDD are likely unaware of their diagnosis, and believed to be experiencing moderate to severe mood symptoms associated with premenstrual syndrome.

Samphire Neuroscience is actively investigating PMDD-specific symptom relief associated with the use of Nettle™ in its ongoing trial with Queen Mary University London (QMUL). Participants use the device from ovulation to menstruation (or 14 days prior to predicted onset if ovulation is unknown). Preliminary results indicate that Nettle™ use significantly reduced anxiety, improved emotion regulation, decreased emotional reactivity, and reduced pain/discomfort.

There are no known risks or contraindications associated with the use of Nettle™ for the management of pain relating to menstruation and mood symptoms relating to premenstrual syndrome in women with (undiagnosed) PMDD who may not have access to alternative options (or may not be eligible to use them). Ongoing research and current users seeing successful symptom relief have shown that an adjustment to a mildly more intensive (approximately 14 tDCS sessions, from ovulation to period) protocol may be beneficial for people experiencing mood symptoms related to menstruation that may involve undiagnosed cases of PMDD, and is within the approved appropriate range (up to 20 sessions) of monthly use of Nettle™.

Other Conditions

Should a physician or clinic choose to use Nettle™ to treat any other condition, this would be classified as “off-label” use with the accompanying risks.

To date, there is level A (definitely effective) evidence for the use of tDCS targeting the DLPFC in the treatment of Major Depressive Disorder (MDD); and level B (probably effective) evidence for the use of tDCS targeting the motor cortex in the treatment of neuropathic pain, cancer-related pain, migraines, fibromyalgia and stroke rehabilitation. There is also rapidly emerging evidence around the use of tDCS in the management of obsessive-compulsive disorder (OCD) and attention deficit-hyperactivity disorders (ADHD). These evidence guidelines were last revised in 2017 and are expected to be upgraded to level A evidence for the above conditions in 2026/27 based on data that has emerged since 2017.

2.4 Lutea™ (USA & Global)

Lutea™ is a wellness device using the same underlying neurostimulation technology as Nettle™ , and also stimulating the DLPFC and M1. It is designed to support balance, focus and resilience across the natural ups and downs of the menstrual cycle.

It is positioned to support:

- Emotional Balance: Supporting a positive mood and relaxation, particularly during the luteal phase of the cycle.
- Physical Comfort: Promoting general physical comfort and wellbeing during menstruation.
- Daily Functioning: helping individuals maintain their daily activities and quality of life throughout the menstrual cycle.

2.5 Safety Profile of Nettle™ and Lutea™

tDCS' safety profile is well documented with a very low incidence of mild side effects and no reported serious adverse events in over 300,000 documented sessions (Antal et al., 2025).

Common Adverse Effects (Mild & Transient):

- Skin sensations: Itching, tingling, and warming under the electrodes (reported in ~20-40% of sessions).
- Skin reaction: Mild erythema (redness) is common but typically resolves within minutes to hours. Nettle™ and Lutea™ work across the hair, meaning redening is not visible.
- Systemic: Transient mild headache, fatigue, or dizziness occur less frequently, dissipate within half an hour, and are often indistinguishable from "sham" (placebo) groups in blinded trials.
- No withdrawal or dependency effects have been reported with the use of tDCS.
- Nettle™'s clinical trials have confirmed that the type and the number of adverse events reported with Nettle™ are no more severe than those seen in relation to comparable alternatives in state of the art.

2.6 Certification and Quality Control

Nettle™ is available across the European Union and United Kingdom as a CE-marked, class IIa medical device, approved for the alleviation of pain and mood associated with menstruation. Samphire Neuroscience Ltd is certified under ISO13485 as the legal manufacturer of Nettle™.

Lutea™ is available across the United States, Canada, and globally as a wellness device.
If you have any questions about whether Nettle™ or Lutea™ is available in your country of practice, please contact support@samphireneuro.com.

2.7 How to get started working with Nettle™ and Lutea™

1. Reach out to Samphire's clinical partnerships team: Email us at partnerships@samphireneuro.com to express interest in partnering with Samphire to explore whether our neurostimulation products would be the right fit for your patients and/or clients.
2. Clinical onboarding: We will share further details about our partnership program and identify the best fit for you. If applicable, we will provide a 1-on-1 call with a clinical expert on our team , for you to gain a deeper understanding of tDCS in the context of your patients' and/or clients' profiles, and determine if this care pathway aligns with you and your practice needs. .
3. Training and support: After onboarding, you will be provided access to a 1-hour training session designed to equip clinicians with the knowledge to educate patients about Nettle™ or Lutea™'s use and benefits.
4. Implementation: Start recommending Nettle™ or Lutea™ to patients.
5. Results: Observe real-life impact of your patients using Nettle™ or Lutea™.
6. Ongoing Support: Access continued training and clinical support from the Samphire team as needed. The Samphire team will also be available on-call to support any questions you may have around recommending our products or supporting patients already using our products under your care.

2.8 Samphire App

The Samphire app serves as the central command center for the Samphire ecosystem. It is the primary interface used to pair, control, and monitor sessions for both Nettle™ and Lutea™ devices.

The app is a software companion designed to facilitate device usage, track user data, and provide educational support. It does not provide automated diagnoses or replace professional medical advice.

The Samphire app integrates three key pillars of cycle management into a single interface:

- Device Control: The app is required to operate the device. It connects via Bluetooth to unlock the device, select the appropriate treatment or wellness session, monitor electrode contact quality, and time the 20-minute stimulation period. The app also provides notifications to ensure that users stay on track with their neurostimulation sessions for best benefits.
- Comprehensive Tracking: Users can log daily symptoms, including pain levels, mood fluctuations, energy, and flow, or create custom trackables. It also features dedicated medication tracking, allowing patients to both record and get reminders for pharmacotherapy use alongside their neurostimulation sessions, providing a holistic view of their management plan. Tracking data is available for clinician review as a PDF export at any time.
- Cycle Predictions & Insights: Using entered data, the app predicts upcoming cycle phases (e.g., Luteal Phase, Menstruation) to remind users when their neurostimulation sessions would be most effective. Personalized scheduling maximizes flexibility, with an algorithm that automatically reduces sessions when symptoms are well controlled and increases them when needed.

Beyond functional control, the app acts as a psycho-educational resource. It hosts a library of evidence-based content explaining the neuroscience of the menstrual cycle, helping patients understand the "cycle-brain" connection. You can dive deeper into this by reviewing the "Cycle-Brain Guide" on the samphireneuro.com website. This feature supports clinician goals by improving patient health literacy and adherence to the recommended protocol. In addition, the app delivers structured, guided meditative sessions designed to support autonomic regulation, stress reduction, and emotional self-regulation; complementing the broader therapeutic approach.

The Samphire app is available for free download on both iOS (Apple App Store) and Android (Google Play Store). It is fully compatible with both Nettle™ and Lutea™ devices.

3. Contraindications

If any of the below contraindications apply to the patient, they should not use Nettle™ or Lutea™:

- Persons who are under 18 years old.
- Persons with a history of seizures or epilepsy.
- Persons who are pregnant or may be pregnant.
- Persons experiencing active suicidal thoughts.

- Persons with a pre-existing neurological condition.
- Persons with a lesion, tumour or other defect in your skull (cranium) or brain.
- Persons with an implant inside their skull, cochlear implant or implanted hearing aid.
- Persons with implanted medical devices, such as a cardiac pacemaker or neurostimulation
- Devices, such as spinal cord stimulators, vagal nerve stimulators, auricular stimulators, or deep-brain stimulating electrodes.

4. Long-Term Use

tDCS technology, which underlies both Nettle™ and Lutea™ devices, is safe for long-term use. tDCS has now been a standard part of clinical practice since 2019 in the EU and since 2025 in the US.

Highlighted below are some studies indicating the safety and efficacy of long-term tDCS use:

- Bikson et al., 2016: Safety of Transcranial Direct Current Stimulation: Evidence Based Consensus Update 2016: Consensus study confirming no long-term adverse events or change in safety profile with extended use of tDCS.
- Woodham et al., 2022: An open-label, single-arm feasibility study with long term (6-month) follow-up, showing 91.3% users maintaining clinical response outcomes and no increase in treatment side effects.
- Navarro-Lopez et al., 2022: A systematic review of randomized sham-controlled trials, showing no increase in the odds ratio of adverse events following longer-term tDCS use.
- Aparicio et al., 2019: A clinical trial with long-term (6-month) follow-up, showing no increase in side effects over time.

5. Frequently Asked Questions (FAQs)

Can I recommend Nettle™ or Lutea™ to my patients with PMDD?

Nettle™ is currently undergoing dedicated clinical validation in individuals with premenstrual dysphoric disorder (PMDD). Given that its existing certification covers mood symptoms associated with menstruation more broadly, a substantial proportion of users with PMDD (often undiagnosed)

are already using Nettle™ in real-world settings and reporting meaningful symptom relief. Consistent with this, 38% of participants in the validation study for Nettle™, WIND, had a clinical diagnosis of PMDD, supporting its relevance to this higher-severity population.

Given that PMDD remains substantially underdiagnosed, Nettle™ may offer important clinical value. As it has no known interactions with pharmacological treatments, it is well suited for use as an adjunct therapy within a comprehensive care plan that may include psychotherapy, medication, and lifestyle interventions.

Nettle™ can be considered a safe, non-invasive addition to a holistic treatment strategy. The most common observed use is for the 14 days preceding menstruation, or throughout the full luteal phase when cycle timing is known.

Lutea™ is based on the same technology as Nettle™ but is available outside of the EU and the UK.

Can I recommend Nettle™ or Lutea™ to my patients with endometriosis?

Nettle™ is currently undergoing dedicated clinical validation in individuals with endometriosis across multiple jurisdictions. Given that its existing certification covers pain symptoms associated with menstruation more broadly, a substantial proportion of users with endometriosis are already using Nettle™ in real-world settings and reporting meaningful improvements in endometriosis-associated chronic pelvic pain. This real-world use supports the relevance of Nettle™ for this higher-burden pain population while formal clinical validation and claim expansion is ongoing.

Given the chronic and often treatment-refractory nature of endometriosis-associated pain, Nettle™ may offer important clinical value. As it has no known interactions with pharmacological treatments, it is well suited for use as an adjunct therapy within a comprehensive care plan that may include medical, surgical, and lifestyle-based interventions. Nettle™ can be considered a safe, non-invasive addition to a holistic treatment strategy. The most common observed use among endometriosis patients finding relief is five days per week (20 sessions per month).

Lutea™ is based on the same technology as Nettle™ but is available outside of the EU and the UK.

How is Nettle™ different from Flow Neuroscience?

From a technical and scientific standpoint, Nettle™ stimulates two regions of the brain - the DLPFC, associated with mood improvement, and the M1, associated with pain relief - while Flow Neuroscience's device only stimulates the DLPFC.

From an intended use perspective, Flow Neuroscience's device is approved for the treatment of Major Depressive Disorder (MDD) only. Nettle™ is approved for the alleviation of pain and mood symptoms associated with menstruation.

Therefore, if your patients are interested in managing mood and pain symptoms associated with menstruation, Nettle™ is a better fit. If your patients are interested in managing MDD only, Flow Neuroscience's device is a better fit.

How is Nettle™ different from Lutea™?

Nettle™ and Lutea™ use tDCS to stimulate two regions of the brain – the DLPFC and M1.

Nettle™ is a regulated medical device approved in the UK and EU for the treatment of pain relating to menstruation and mood symptoms relating to PMS. Lutea™ is a general wellness device available in the US and globally, intended to support focus, calm, and mental clarity during the menstrual cycle.

Therefore, if your patients are located in the UK or EU, Nettle™ would be best for them. If your clients are located in the US or outside of the EU/UK, Lutea™ is available.

Can I recommend Nettle™ or Lutea™ for chronic pain that is not of menstrual origin to patients?

Nettle™ has been verified to offer promising benefits in managing menstruation-related pain. Its efficacy for chronic pain not of menstrual origin is considered off-label. As it acts on the central sensitization that many conditions can stem from, many users have reported benefits with fibromyalgia, hypermobility type Ehlers-Danlos Syndrome (hEDS), MS-related pain, cancer-related pain, migraine and more. Large-scale meta-reviews have determined that there is level B (probably effective) evidence for the use of tDCS targeting the motor cortex in the treatment of neuropathic pain, migraines, fibromyalgia and stroke rehabilitation, and more research continues to emerge. This evidence level is likely to be updated to level A in 2026/27.

Lutea™ is based on the same technology as Nettle™ but is available outside of the EU and the UK.

Can I recommend Nettle™ or Lutea™ for depression that is not of menstrual origin?

Though Nettle™ has been verified to offer promising benefits in managing mood symptoms associated with premenstrual syndrome (PMS), its efficacy for the treatment of major depressive disor-

der (MDD) specifically has not been tested. However, large-scale meta-reviews have determined that there is level A (definitely effective) evidence for the use of tDCS targeting the dorsolateral prefrontal cortex in the treatment of MDD, and more research continues to emerge. The use of Nettle™ for MDD treatment should be technically similar to the use of any other tDCS equipment targeting the DLPFC, but would be considered to be "off label" in the context of Nettle™'s intended use.

Lutea™ is based on the same technology as Nettle™ and Flow Neuroscience's approved tDCS device for MDD, but is available outside of the EU and the UK.

Have you tested Nettle™ or Lutea™ on women of colour?

Yes. Designing and testing on a diverse population has been at Samphire Neuroscience's core from the outset; 47.1% of participants in our clinical trials self-identified as women of colour. 67.6% of participants had wavy, curly or coily hair, and trial participants had a BMI range from 19 to 29. In the real-world, we have a diverse community of users benefitting from neurostimulation every day; you can find some of their testimonials here.

Can Nettle™ or Lutea™ be used as an in-clinic treatment?

Yes. However, neurostimulation for most users needs to be applied for 20 minute-sessions daily during the late luteal phase, which makes it a high-intensity in-clinic treatment, so we recommend using Samphire's neurostimulation devices in at-home settings for convenience and flexibility.

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