

# Executive Summary of the Vulvodynia Therapeutic Research Summit

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The current treatment of provoked vestibulodynia involving neuroproliferation is often complete vestibulotomy; however, less invasive treatments are biologically plausible, yet lack study. The International Society for the Study of Women's Sexual Health, the National Vulvodynia Association, the Gynecologic Cancers Research Foundation, and Tight Lipped, a grassroots nonprofit organization that supports people with chronic vulvovaginal and pelvic pain, collectively sponsored a conference, the Vulvodynia Therapeutic Research Summit, held in April 2024. The primary objective of the Vulvodynia Therapeutic Research Summit was to identify options for further research of the treatment of provoked vestibulodynia through expert consensus. After the conference, attendees scored the presented therapeutics in rank order, leading to a hierarchy of merit. Fifteen therapeutic options were presented and ranked in order of most promising to least promising for further study on treating the neuroinflammation of provoked vestibulodynia. The top identified therapeutics for further

research were: 1) ketotifen fumarate (mast cell stabilizer with potential to prevent mast cell activation), 2) resiniferatoxin (transient receptor vanilloid 1 agonist causing chemo-inactivation of nerve terminals), 3) specialized pro-resolving mediators or strategies to boost their levels (eg, maresin 1 and 1-trifluoromethoxy-phenyl-3-(1-propionylpiperidin-4-yl) urea), 4) luteolin (flavonoid with potent anti-inflammatory, antioxidant, and neuroprotective properties), 5) alpha-lipoic acid (antioxidant with nerve-specific anti-inflammatory and mast cell stabilizing qualities), and 6) NGFR121W-SNAP IR700 trimer exposed to near-infrared light (photoablation targeting nociceptors and sparing surrounding tissue). This executive summary describes the rationale for identifying specific pharmacologic agents and medical devices as targets for research directed toward treatment of the neuroinflammatory process found in the vestibular mucosa of provoked vestibulodynia.

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Vulvodynia is the most common cause of long-lasting vulvar pain in premenopausal women and affects up to 8% of women by the age of 40.<sup>1</sup> Provoked vestibulodynia, a subtype of vulvodynia, has minimal visible signs on physical examination but carries considerable negative consequences on sexual health and quality of life.<sup>2–5</sup> The diagnosis is one of exclusion, eliminating all other potential causes such as dermatologic, hormonal, infectious, neoplastic, neurologic, traumatic, and iatrogenic (Box 1).<sup>2</sup> Previous histopathologic studies have shown neuroproliferation and activated mast cells throughout tissue samples from the vestibular mucosa in women with provoked vestibulodynia who underwent surgical removal of the vulvar vestibule with vulvar vestibulectomy.<sup>2,6–8</sup> Hyperinnervation in vestibulodynia may be related to cytokines from mast cells and other immune cells, stimulating nerve growth and leading to neuroproliferative provoked vestibulodynia.<sup>9–16</sup> Other typical features of provoked vestibulodynia are increased tension of the pelvic floor muscles<sup>17</sup> and comorbidity of other pain-related conditions, in particular conditions of mast cell aberrant activity<sup>18,19</sup> and impaired psychosocial health, which are important to address during treatment.<sup>3,20–22</sup>

A variety of medical, behavioral, and surgical therapies for the treatment of provoked vestibulodynia have been explored in clinical trials, without convincing scientific evidence of effective treatment outcomes, largely due to limitations in study design for proper analysis and synthesis of the results.<sup>20,23–25</sup> The complexity of provoked vestibulodynia often necessitates a multimodal treatment approach.<sup>23</sup> The current and definitive treatment of neuroproliferative provoked vestibulodynia remains complete vulvar vestibulectomy. Although less invasive treatments are biologically plausible, they lack sufficient study for clinical implementation. In April 2024, a summit was conducted to identify possible new treatments directed towards the neuroinflammatory process of the vestibular mucosa in provoked vestibulodynia. The primary objective of the Vulvodynia Therapeutic Research Summit was to identify options for further research study in the treatment of provoked vestibulodynia through expert consensus. This executive summary describes the rationale for identification of specific pharmacologic agents and medical devices as targets for research directed towards the treatment of provoked vestibulodynia with a neuroinflammatory basis.

## METHODS

A planning committee and advisory board for the Vulvodynia Therapeutic Research Summit was

formed in January 2023 to propose and approve experts to attend and topics to be presented at the conference. The advisory board was comprised of representatives from the International Society for the Study of Women's Sexual Health, the National Vulvodynia Association, the Gynecologic Cancers Research Foundation, and Tight Lipped, a grassroots nonprofit organization that supports people with chronic vulvovaginal and pelvic pain. In April 2024, a summit was conducted to present possible new treatments directed towards the neuroinflammatory process of the vestibular mucosa and to develop a list of promising therapeutics for future research study. Attendees included clinician and basic science research leaders who have published on vulvodynia and researchers studying therapeutics with inflammatory and neuropathic utility that could be applied to provoked vestibulodynia, as well as representatives from the sponsoring societies and foundations (individuals working in the field and patient advocates) (Appendix 1, available online at <http://links.lww.com/AOG/E410>). Appendix 2 provides specific information on the format of the meeting (available online at <http://links.lww.com/AOG/E410>). The top therapeutics were identified through majority consensus by rank order. Appendix 3 details the rank order process (available online at <http://links.lww.com/AOG/E410>). Experts were selected to coauthor a section on each identified therapeutic, which included the following criteria: summary of treatment; rationale for the therapeutic in addressing vulvodynia such as the pathophysiologic pathways targeted; a brief literature review of previous data on the therapeutic regarding vulvodynia or other related pain conditions; and a proposed plan to implement or consider the therapeutic in treatment of vulvodynia. The medical writer compiled the sections, and the paper was distributed to the group of experts for review.

## RESULTS

In a discussion of diagnostic criteria and terminology, experts agreed that the inflammatory and neuroproliferative processes in provoked vestibulodynia are intertwined. There was discussion about combining these associated factors and describing the condition as “neuroinflammatory vestibulodynia.” There was consensus that updated terminology is needed for this condition.

All 10 experts completed the rank order survey, for a 100% response rate. Fifteen therapeutic options were identified and ranked in order of most promising to least promising for further study in the treatment of provoked vestibulodynia (Fig. 1). In order, the

## Box 1. Diagnostic Criteria for Vulvodynia and Provoked Vestibulodynia

Vulvodynia<sup>2</sup> is defined as:

- Vulvar pain duration of at least 3 mo
- No identifiable cause
- Potential associated factors
  - Hormonal factors
  - Musculoskeletal
  - Inflammation
  - Neurologic mechanisms
    - Central
    - Peripheral
  - Psychosocial factors
  - Genetics
  - Structural defects
  - Other comorbid pain syndromes

Descriptors:

- Localized or generalized or mixed
  - Vestibulodynia-pain of the vulvar vestibule
  - Clitorodynia-pain of the clitoris
- Provoked or spontaneous or mixed
  - Provoked-insertional, with contact
- Onset
  - Primary
  - Secondary
- Temporal pattern
  - Intermittent or constant
  - Immediate or delayed

therapeutics included: ketotifen fumarate, resiniferatoxin, maresin 1, luteolin, alpha-lipoic acid (ALA), 1-trifluoromethoxy-phenyl-3-(1-propionylpiperidin-4-yl) urea (TPPU), *NGFR121W*-SNAP IR700 trimer exposed to near-infrared light (photoablation), ketamine, tropomyosin-related kinase A (TrkA) inhibitors, palmitoylethanolamide, mepyramine, 5% dextrose injection (neuraltherapy), cryoneurolysis, loperamide, and salsalate. TPPU was included with maresin 1 because both are related to the actions of specialized pro-resolving mediators; maresin 1 is a specialized pro-resolving mediator that fosters resolution of inflammation in cell and animal models of vulvodynia, and TPPU enhances the pools of specialized pro-resolving mediators by reducing their degradation. This executive review presents a summary of the six top-ranked therapeutics (Box 2). Expanded sections on the Inflammatory and Neuroproliferative Characteristics of Provoked Vestibulodynia, Top Identified Therapeutics for Further Study, and Patient Perspective of Novel Therapeutics with Complete Reference List can be found in Appendix 4 (available online at <http://links.lww.com/AOG/E410>). A table summarizing the remaining lower-ranked therapeutics presented at the summit is found

in Appendix 5 (available online at <http://links.lww.com/AOG/E410>).

## POTENTIAL THERAPEUTICS

### Ketotifen Fumarate

Ketotifen fumarate is a potent and noncompetitive antagonist of histamine (H)<sub>1</sub> receptors that functions to stabilize mast cells, inhibiting the release of allergic and inflammatory mediators such as histamine, leukotrienes C<sub>4</sub> and D<sub>4</sub>, prostaglandins, and platelet activating factor. This agent reduces chemotaxis and activation of eosinophils and has mild anticholinergic properties (see reference 41 in Appendix 4, <http://links.lww.com/AOG/E410>). The most common use of ketotifen fumarate is for treatment of allergic conjunctivitis, urticaria, mastocytosis, and mast cell activation syndrome, and as a preventative treatment for asthma and food allergy.

Ketotifen fumarate has been shown to reduce labial mechanical and thermal sensitivity thresholds in rodent models, including a yeast glycan rat model of provoked vestibulodynia and zymosan-inflammation challenges. Ketotifen fumarate administration has been associated with a reduction in nerve growth factor (NGF), mast cells, and nerve density when administered prophylactically at the time of vulvodynia induction (references 9 and 45 in Appendix 4). Ketotifen fumarate administered during vulvar inflammation reduces levels of NGF and histamine through stabilization of mast cell activity. There also is a reduction in the transcription of pro-inflammatory cytokines and regulation of the NGF pathway in the spinal cord. In this manner, ketotifen fumarate treatment during inflammation prevents mast cell accumulation, neuronal hyperinnervation, and overexpression of pain channels in the vulvar neurons, preventing the development of vulvar pain.<sup>10</sup>

Based on the studies above, ketotifen fumarate was used as a mast cell stabilizer, a “blocker” aimed at supporting the role of mast cell activation in the pathogenesis of vulvodynia. Efficacy was observed only during the prophylactic phase and not in well-established vulvodynia.<sup>10</sup> Therefore, ketotifen fumarate may have promise for prevention of vulvodynia subtypes related to candida infection or reaction to environmental triggers but is unlikely to be effective once mast cells have led to nerve proliferation. Although the bioavailability is low, a topical delivery form is advantageous due to its easy, noninvasive application, allowing for self-administration of the drug. The appeal to further study of ketotifen fumarate lies in the potential for prevention of provoked vestibulodynia.

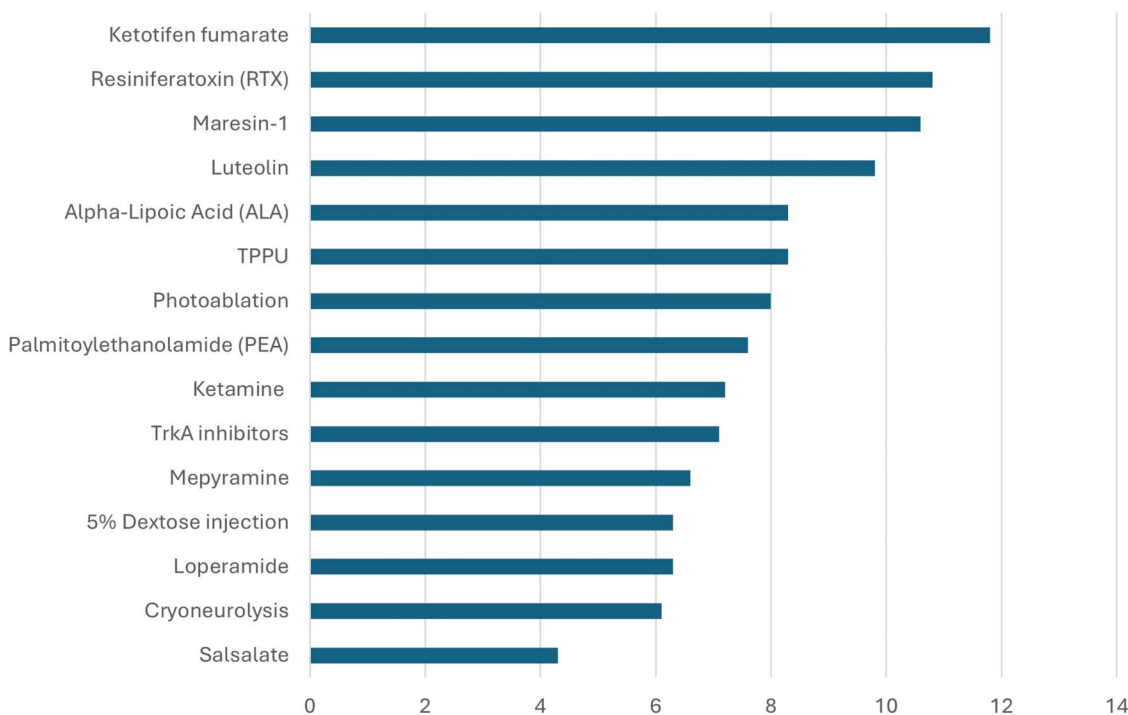
## Resiniferatoxin

Resiniferatoxin is a small polycyclic molecule extracted from *Euphorbia resinifera* that is a potent agonist of the transient receptor vanilloid 1 cation channel protein (TRPV1) (reference 46 in Appendix 4). Binding of resiniferatoxin to TRPV1 is pseudo-irreversible and causes a large transmembrane  $\text{Ca}^{++}$  flux into nerves in the skin (references 46–48 in Appendix 4). Subcutaneous injections will cause a  $\text{Ca}^{++}$  mediated chemo-inactivation of TRPV1-containing nerve terminals that is of long duration (reference 49 in Appendix 4).

Provoked vestibulodynia can be characterized as a peripheral nociceptive nerve terminal hyperexcitability state. Hyperexcitable nerve endings are present in models of experimental inflammation, surgical incision, and osteoarthritis. Highly effective analgesia can be obtained in these models or in clinical conditions with local administration of resiniferatoxin. The list of indications encompasses resiniferatoxin injection into a rat hind paw for carrageenan inflammation and surgical incision, perineural injection in rats and horses, intraarticular injection for osteoarthritis in canine and human patients, subcutaneous injection to treat burn pain in a rat model, intrathecal

administration in goats for arthritis, intratrigeminal injections in rats and rhesus monkeys for corneal pain, and intrathecal injection in dogs and humans for pain from advanced cancer (references 50–55 in Appendix 4). Aggregate data indicate that local administration of resiniferatoxin is safe and effective. At the present time a clinical trial of resiniferatoxin for neuropathic pain in patients with Morton neuroma is underway (NCT05695339).

In the patients with provoked vestibulodynia, a potential experimental treatment approach could consist of injections of resiniferatoxin subcutaneously in the vulvar vestibule. Hypothetically, resiniferatoxin will ablate the peripheral endings of the neuroproliferative C-afferent nociceptors in the vulvar vestibular endoderm. It is hypothesized that resiniferatoxin-induced chemodenervation of the hyperexcitable nerve endings will yield relief from the severe allodynia and hyperpathia originating at the vulvar vestibule. It is further hypothesized that, after resiniferatoxin chemoablation, the nerve endings will regenerate as normal nerve terminals, rather than hyperactive endings, and normal sensation might be reinstated permanently. There are plans underway for further study.



**Fig. 1.** Average ranked scores of therapeutics for provoked vestibulodynia after presentation at the Vulvodynia Therapeutic Research Summit. TPPU, 1-trifluoromethoxy-phenyl-3-(1-propionylpiperidin-4-yl) urea; TrkA, tropomyosin-related kinase A. *Krapf. Executive Summary of the Vulvodynia Therapeutic Research Summit. Obstet Gynecol 2026.*

## Box 2. Top-Ranked Potential Therapeutics for Provoked Vestibulodynia

### KF

- Antagonist of H1 histamine receptors stabilizes mast cells
- Currently used for allergic conjunctivitis, urticaria, mastocytosis, and preventively for asthma and food allergy
- Animal models: use of KF in yeast glycan rat model of provoked vestibulodynia reduced sensitivity thresholds, as well as NGF and nerve density
- Available orally as well as topically
- Proposal: RCT involving topical KF vs placebo cream or vs topical lidocaine

### RTX

- Local injection of RTX can block neural impulses from hyper-responsive nerve endings.
- Extracted from *Euphorbia resinifera*, agonist of TRPV1 leads to calcium flux into cells (chemo-inactivation of nerve terminals)
- Local administration of RTX achieves analgesia in animal and human models of inflammation, surgical incision, osteoarthritis, and cancer.
- Proposal: NIH Clinical Center open-label phase 1 dose-escalation design of injections of RTX along the vulvar vestibule to ablate peripheral nerve endings in the endoderm (similar doses to treatment for Morton neuroma) under propofol anesthesia

### Specialized Pro-Resolving Mediators

- Lipids that act on immune cells to reduce inflammation
  - Maresin 1 is a specialized pro-resolving mediator.
  - TPPU prevents specialized pro-resolving mediator degradation.
- Specialized pro-resolving mediators are deficient in vulvodynia tissues corresponding to areas of pain.
- Maresin 1 significantly reduces pain in validated mouse models of vulvodynia. It could be applied topically, but chemical modification is needed to extend shelf life and safety trials are needed.
- Another strategy: Extend the life of specialized pro-resolving mediators by preventing breakdown. Two synthetic compounds are undergoing safety trials but have not been studied in vulvodynia. TPPU reduced pain in mouse models and may complement or be used in place of specialized pro-resolving mediator supplementation in provoked vestibulodynia.

### Luteolin

- Flavonoid, mast cell stabilizer → anti-inflammatory, antioxidant with neuroprotective properties
- Vulvodynia involves chronic neuroinflammation through mast cell activation and oxidative stress.
- Animal studies show that luteolin inhibits TRPV1 receptors to reduce pain perception (analgesic).
- Luteolin has high lipid solubility, which makes it a good candidate for topical application. Studies confirm effective transdermal drug delivery. Animal studies support topical luteolin in models of irritant and allergic contact dermatitis and skin wound healing.
- Luteolin is widely used as an over-the-counter oral supplement with excellent safety profile. There are no clinical trials in vulvodynia
- Proposal: study of oral luteolin in vulvodynia and further development of topical luteolin to be tested in animal models of vulvodynia

### ALA

- Antioxidant that works against free radicals to increase natural immunologic process in the tissue
- Readily available oral supplement for healthy nerve function and to reduce inflammation
- Animal studies show decreased oxidative stress, improved nerve blood flow and conduction in diabetes.
- Clinical trials in diabetic neuropathy, approved in Germany. Well studied treatment in burning mouth syndrome (parallels to provoked vestibulodynia). Evaluated in vulvodynia and painful bladder syndrome in a small, randomized trial with ALA or amitriptyline vs amitriptyline alone with improvement
- May have utility as adjunct to established medication targeting neuropathic genitopelvic pain, such as amitriptyline or gabapentin, in setting of vulvodynia due to pudendal neuralgia

### Photoablation

- *NGFR121W*-SNAP IR700 trimer exposed to NIR (photoablation)—involves tagging SNAP to photosensitizer dye, which reacts to red light therapy → binds to TrkA-positive cells and achieves selective ablation of targeted nerve receptors while leaving surrounding tissue unharmed
- Only affects nociception not other sensation, but nociceptor density returns to baseline after 28 days
- Proposal: Study photoablation based on Nocchi et al [reference 169 in Appendix 4, available online at <http://links.lww.com/AOG/E410>] protocol in the rodent model of vulvodynia

KF, ketotifen fumarate; NGF, nerve growth factor; RCT, randomized controlled trial; RTX, resiniferatoxin; TRPV1, transient receptor vanilloid 1 cation channel protein; NIH, National Institutes of Health; TPPU, 1-trifluoromethoxy-phenyl-3-(1-propionylpiperidin-4-yl) urea; ALA, alpha-lipoic acid; NIR, near-infrared; TrkA, tropomyosin-related kinase A.

## Specialized Pro-Resolving Mediators

The vestibule of provoked vestibulodynia patients shows an overall reduced abundance of polyunsaturated dietary omega fatty acid-derived lipids that resolve inflammation and, instead, an increased abundance of lipids that cause and perpetuate inflammation, such as agonists of pain signaling channels, namely the transient receptor potential cation subfamily V member 4 (TRPV4) channel (references 11 and 63 in Appendix 4). When TRPV4 is activated, inflammatory mediator production further increases, further exacerbating the underlying lipid dysbiosis and pain signaling, leading to a vicious neuroinflammatory cycle (Fig. 2). Over the past few decades, specialized pro-resolving mediators have become increasingly recognized for their roles in inflammatory resolution, wound healing, and analgesia (references 56, 96, and 97 in Appendix 4). Specialized pro-resolving mediators are noted to be deficient in vestibular tissue and fibroblasts derived from painful areas (references 11, 62–63, and 65 in Appendix 4).

Topical vulvar application of docosahexaenoic acid, Lipinova (purified docosahexaenoic acid naturally enriched for specialized pro-resolving mediator precursors) or maresin 1 significantly reduces pain in a validated mouse model of vulvodynia (references 63 and 65 in Appendix 4). Most mice (more than 90%) receiving any of these treatments once to twice daily recover to their baseline sensitivity thresholds within 4 weeks, with at least a quarter of the mice recovering as early as 2–3 weeks (references 63 and 65 in Appendix 4) (Fig. 2). Thresholds are maintained even after treatment is withdrawn, so the effects may be long lived, although this is yet to be tested in humans (references 63 and 65 in Appendix 4). The data are strongest for maresin 1, making it a leading candidate for new therapeutics (references 63 and 65 in Appendix 4).

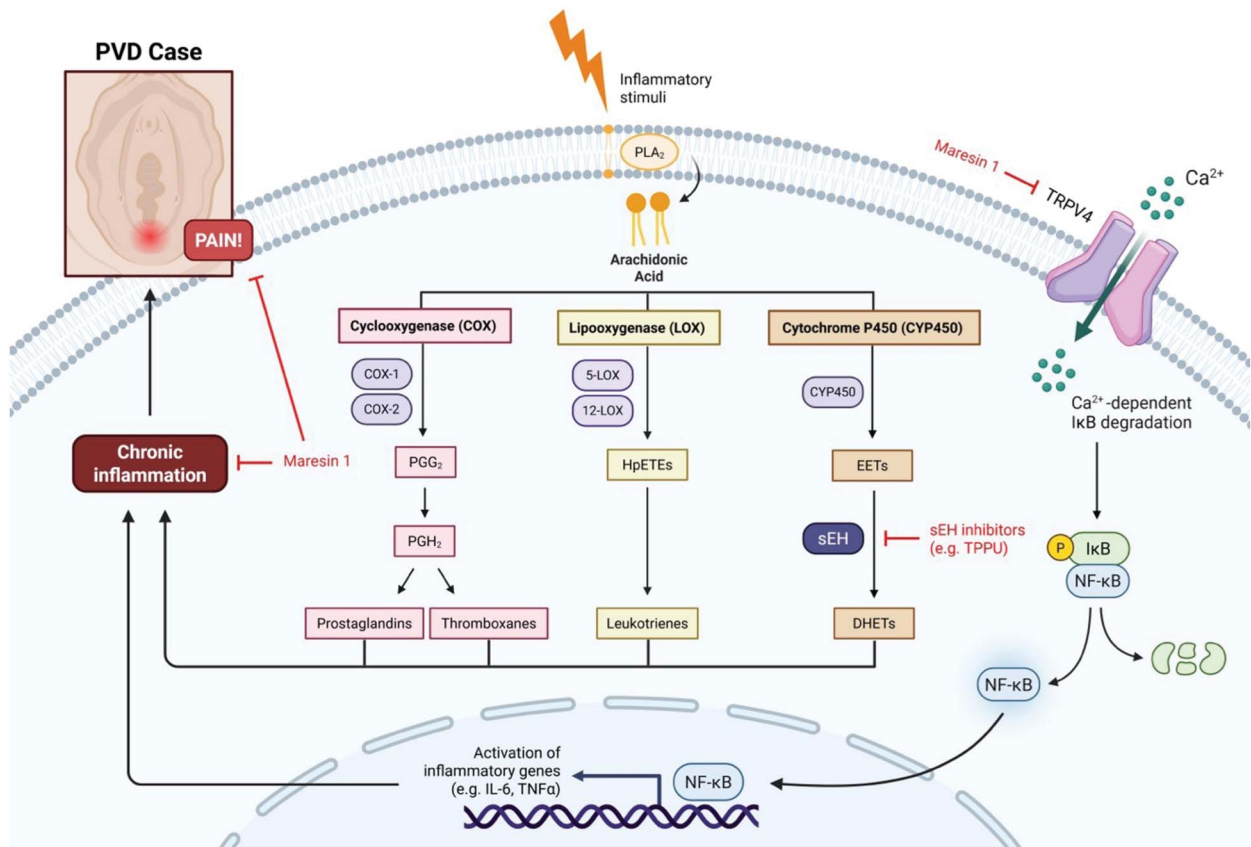
Because maresin 1 is naturally produced by the human body from dietary unsaturated fatty acids, it is generally regarded as safe (references 11, 56, 57, 65, and 98 in Appendix 4). However, it cannot be purified from dietary sources and is sensitive to oxygen, heat, and light, making this lipid often short-lived in vivo (references 11 and 98–100 in Appendix 4). Therefore, chemical modification is necessary to extend the shelf life of a potential maresin 1 product to make it suitable for human pharmaceutical use. Maresin 1 is effective at low (nanomolar) tissue concentrations making it feasible to chemically synthesize. Although the low doses needed limit the likelihood of off-target effects, there is some degree of systemic absorption (referen-

ces 11, 65, 96, and 98 in Appendix 4). As such, animal toxicology studies or Phase 1 safety trials will be required before larger scale efficacy trials. As an example, another specialized pro-resolving mediator topical lipoxin A4 has been tested in infants with eczema, successfully resolving symptoms with no observed side effects (reference 101 in Appendix 4).

Another strategy to boost pro-resolving mediator levels, thus limiting inflammation and subsequently pain, would be to extend the life of pro-resolving mediators by using soluble epoxide hydrolase enzyme inhibitors (reference 102 in Appendix 4). There are two compounds already in the clinical pipeline (GSK2256294 and EC5026) that are undergoing safety trials for nonvulvar indications related to inflammation and spinal cord injury (references 104–107, NCT06438471 in Appendix 4). Preclinical trials for vulvodynia have been completed using a similar soluble epoxide hydrolase inhibitor, 1-trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl) urea (TPPU), that is widely available for laboratory use (reference 108 in Appendix 4). As with maresin 1, mice recovered to their starting baseline as early as 2 weeks; nearly all mice had recovered after 4 weeks. No significant side effects were noted, even with oral delivery. Therefore, decreasing the breakdown of pro-resolving lipids is another promising option that could complement or be used in place of specialized pro-resolving mediator supplementation in provoked vestibulodynia patients. Local topical application to the vulva would help limit systemic absorption and perhaps enhance their safety profile, thereby increasing the probability that trials for vulvodynia could move directly to phase II.

## Luteolin

Luteolin, a naturally occurring flavonoid with potent anti-inflammatory, antioxidant, and neuroprotective properties, has been extensively studied for its therapeutic potential in pain and inflammatory conditions (reference 109 in Appendix 4). The chronic neuroinflammation of provoked vestibulodynia is characterized by increased levels of the pro-inflammatory cytokines tumor necrosis factor- $\alpha$ , interleukin-6, and interleukin-1 $\beta$  (reference 69 in Appendix 4). Luteolin suppressed production of each of these cytokines in multiple models of inflammation (Fig. 3) (references 115 and 116 in Appendix 4). Luteolin also inhibits the activation of the NLRP3 inflammasome, a key mediator in inflammatory pain, which may have direct implications in vulvodynia (reference 120 in Appendix 4). Luteolin suppresses anti-inflammatory cytokines primarily by inhibiting the master second



**Fig. 2.** Inflammatory mechanism of provoked vestibulodynia and treatment strategies. The vestibule of provoked vestibulodynia patients exhibits a heightened response to inflammatory stimuli, leading to changes in the vulvar lipidome that favor production of pro-inflammatory lipids and not pro-resolving lipids. This results in chronic inflammation and transient receptor potential vanilloid type 4 (TRPV4) activation. TRPV4 channel opening further elevates pro-inflammatory mediator production as a result of calcium-dependent NFκB activation, thus creating a feed-forward loop of inflammation that culminates in pain. Maresin-1 supplementation disrupts this cycle by reducing inflammation and pain and directly inhibiting TRPV4 channels. Similarly, treatment with soluble epoxide hydrolase inhibitors, such as 1-trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl) urea, increases the levels of pro-resolving lipids, thereby limiting inflammation and promoting resolution. PVD, provoked vestibulodynia; PLA2, phospholipase A2; PGG2, prostaglandin G2; PGH2, prostaglandin H2; HpETE, hydroperoxyeicosatetraenoic acid; EET, epoxyeicosatrienoic acids; DHET, dihydroxyethersatrienoic acids; NF-κB, nuclear factor kappa B; IκB, inhibitor of nuclear factor kappa B. Created with BioRender.com.

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messenger signaling molecule NF-κB (reference 121 in Appendix 4). Luteolin's multiple hydroxyl groups convey potent antioxidant and free radical scavenging properties while upregulating endogenous antioxidant enzymes such as superoxide dismutase and catalase, which can protect tissues from oxidative damage, a process implicated in nerve injury and hyperalgesia of provoked vestibulodynia (references 122 and 123 in Appendix 4).

Chronic pain conditions such as vulvodynia often involve altered neural signaling and central sensitization. Luteolin has shown neuroprotective effects in various studies, demonstrating the ability to modulate pain pathways through inhibition of ion channels and

signaling pathways associated with pain perception, such as the MAPK-ERK pathway (references 117 and 124 in Appendix 4). Additionally, luteolin has been shown to inhibit mast cell activation (reference 125 in Appendix 4), a known contributor to neuroinflammation in chronic pain conditions, including vulvodynia (references 10, 31, and 66 in Appendix 4). Luteolin's analgesic potential is supported by its modulation of pain-related pathways. Studies have shown that luteolin can modulate TRPV1 receptors, which are often upregulated in chronic pain states (reference 126 in Appendix 4). In rodent models of inflammatory pain, luteolin administration significantly reduced pain behaviors, decreased cytokine levels, and reduced

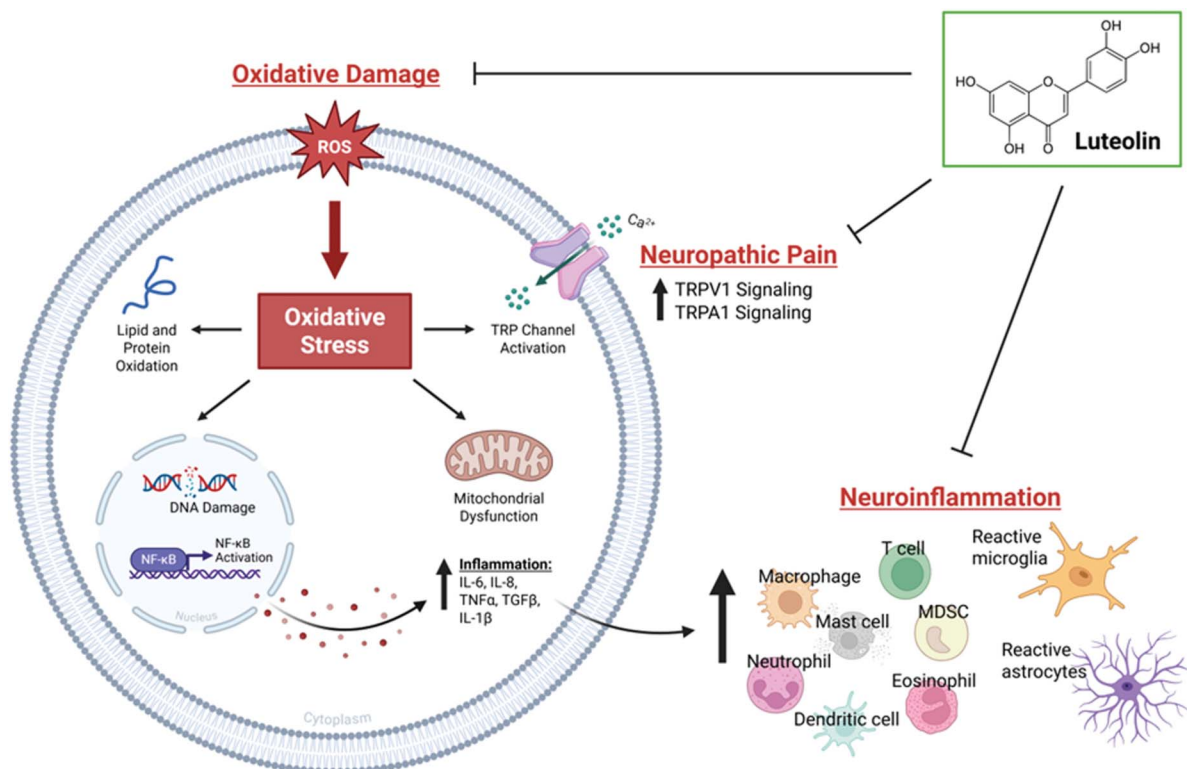
oxidative stress markers (reference 127 in Appendix 4). These findings indicate luteolin's ability to modulate pain through multiple mechanisms that may be relevant to vulvodynia, where both inflammatory and neuropathic pain components are present.

Although luteolin can be orally absorbed, the compound's high lipid solubility makes it a good candidate for topical application (reference 130 in Appendix 4). Studies that evaluated various luteolin-loaded nanovesicles for optimal drug content, drug release, delivery, pharmacologic activity and toxicity for topical applications showed effective transdermal drug delivery (reference 131 in Appendix 4). Effectiveness of topical application of luteolin has been demonstrated in mouse models of induced irritant and allergic contact dermatitis (reference 132 in Appendix 4). The antipruritic effect of luteolin was attributed to inhibition of mast cell activation and antagonism of released chemokines. A derivative of luteolin, tetramethoxyluteolin, also has been evaluated for topical administration, because it is more lipid soluble and, therefore, thought to be more potent (reference 134 in Appendix 4). Although spe-

cific clinical trials that investigate luteolin's effects on vulvodynia are lacking, luteolin's safety profile has been well-documented in clinical trials for conditions such as allergic inflammation and neurodegenerative diseases, demonstrating high tolerability and minimal side effects (references 125 and 135 in Appendix 4).

### Alpha-Lipoic Acid

Alpha-lipoic acid, a caprylic acid-derived antioxidant involved in glucose and lipid metabolism, metabolized to dihydrolipoic acid within cells (reference 137 in Appendix 4). Both ALA and dihydrolipoic acid neutralize free radicals and play a role in the regeneration of vitamins C and E. These actions reduce oxidative stress-related inflammation through chelation of heavy metals, which has a protective effect on nerves (references 137–139 in Appendix 4). In addition, ALA inhibits tumor necrosis factor- $\alpha$  induced expression of fractalkine, leading to reduced inflammation (references 138, 140, and 141 in Appendix 4). Fractalkine has been implicated in neuropathic pain, as well as burning mouth syndrome, interstitial



**Fig. 3.** Actions of luteolin. Luteolin suppresses pro-inflammatory and pro-apoptotic gene expression leading to decreased oxidative damage, neuroinflammation, and neuropathic pain. TRP, transient receptor potential; IL-6, interleukin-6; IL-8, interleukin-8; TNF $\alpha$ , tumor necrosis factor; TGF $\beta$ , transforming growth factor-beta; IL-1 $\beta$ , interleukin-1 beta; TRPV1, transient receptor potential vanilloid 1; MDSC, myeloid-derived suppressor cell. Created with BioRender.com.

Krapf. Executive Summary of the Vulvodynia Therapeutic Research Summit. Obstet Gynecol 2026.

cystitis, and painful bladder syndrome, and the vaginal microbiome in the setting of genital inflammation and chronic pelvic pain (references 139 and 142–144 in Appendix 4). Alpha-lipoic acid also has been shown to stabilize mast cell activity (reference 145 in Appendix 4). In animal studies, ALA has been found to decrease oxidative stress, as well as improve nerve blood flow and conduction in distal, sensory, and motor nerves in animals with diabetes (reference 146 in Appendix 4). There have been several clinical trials indicating benefit of ALA in reducing neuropathic symptoms of diabetic neuropathy (references 146 and 148 in Appendix 4).

Alpha-lipoic acid is the most studied treatment in the management of burning mouth syndrome, a condition associated with mastocytosis and mast cell activation syndrome (reference 137 in Appendix 4), which holds many parallels to provoked vestibulodynia. Alpha-lipoic acid has been evaluated in gynecologic conditions associated with oxidative stress such as polycystic ovarian syndrome, infertility, endometriosis, and vulvodynia, as well as interstitial cystitis or painful bladder syndrome (references 138 and 162 in Appendix 4). In a randomized trial of 84 women with vulvodynia and painful bladder syndrome receiving either amitriptyline alone or amitriptyline (average dose, 22 mg) with a commercially available preparation containing ALA 600 mg with omega-3 polyunsaturated fatty acids (n-3 polyunsaturated dietary omega fatty acid-derived lipids), docosahexaenoic acid 250 mg, and eicosapentaenic acid 16.67 mg, the group receiving ALA/n-3 polyunsaturated dietary omega fatty acid-derived lipids showed greater pain reduction, less dyspareunia, and improved pelvic floor muscle tone. The treatment was well tolerated, with minimal adverse events of sedation, constipation, and dry mouth (reference 165 in Appendix 4). This antioxidant may have utility as an adjunct treatment for provoked vestibulodynia.

### Photoablation

Provoked vestibulodynia is characterized by an increased density of nociceptors in the vestibular mucosa, and the excision of this tissue with vulvar vestibulectomy is believed to be due to removal of these nociceptors confirmed with surgical pathology (references 31 and 40 in Appendix 4). Conceptually, if it were possible to remove or inactivate these nociceptors without having to remove the surrounding tissue, it is plausible that the allodynia would resolve. In the peripheral nervous system, TrkA is expressed predominantly on peptidergic nocicep-

tors, and NGF signaling plays an important role in dictating pain sensitivity (reference 169 in Appendix 4). The recognition that NGF has a critical role in the generation and potentiation of pain was the rationale for developing methods that interfere with its signaling. One approach was the development of anti-NGF antibodies, which advanced to phase III trials for hip and knee osteoarthritis, but safety issues due to rapidly progressive osteoarthritis stopped these trials and newer monoclonal agents are currently being studied (reference 168 in Appendix 4).

Accessing nociceptive neurons through their TrkA receptors using ligand-guided delivery of a phototoxic agent to silence their activity may avoid the complications of inhibiting NGF signaling (reference 170 in Appendix 4). Nocchi et al tested this hypothesis by generating a SNAP-tagged NGF that was conjugated to the photosensitizer IRDye700DX phthalocyanine (IR700) (reference 169 in Appendix 4). Injection of NGF-SNAP-IR700 trimer and subsequent illumination with near-infrared light reduced nociceptive behavior in sensitized mice. In addition, there was a parallel retraction of nerve fibers from the epidermis. They chose a “painless” derivative NGF p.R121W, which binds to TrkA-positive receptors but does not elicit TrkA-mediated signaling. Through ligand-guided delivery of a small molecule photosensitizer, they were able to achieve selective disruption of nociceptor input and substantially reduce pain (reference 169 in Appendix 4).

In an inflammatory rodent model of pain-causing mechanical and thermal allodynia demonstrated through Von Frey testing, mice were locally treated with a trimer composed of NGF p.R121W conjugated to the photosensitizer IRDye700DX phthalocyanine (IR700) using a SNAP-tag (a commercially available protein tag). The mice were then exposed to near infrared light on three consecutive days. Within two days of the last light exposure, there was a complete reversal of pain sensitivity and a corresponding retraction of nociceptors innervating the epidermis. Additionally, although there was a destruction of the superficial nociceptors, other adjacent cellular types were preserved. However, there was a reinnervation of the epidermis and return to mechanical hypersensitivity within 28 days (reference 169 in Appendix 4). If these promising results can be reproduced in an animal model of provoked vestibulodynia, repeated treatments could possibly result in a longer-term reduction in nociceptor density and allodynia. There is currently an initiative to raise funding to support further research in this area.

## Additional Therapeutics

Eight treatment options discussed at the Vulvodynia Therapeutic Research Summit received lower rank order scores and are summarized in Appendix 4 (<http://links.lww.com/AOG/E410>). Additional therapeutics include ketamine, TrkA inhibitors, palmitoylethanolamide, mepyrmine, dextrose injection neuraltherapy, cryoneurolysis and cryoanalgesia, loperamide, and salsalate (references 172–202 in Appendix 4).

## CONCLUSION

As evidenced by the findings of the Vulvodynia Therapeutic Research Summit, there are many therapeutic targets that hold promise in the treatment of provoked vestibulodynia with a neuroinflammatory or idiopathic basis. These treatments have been used in adjacent conditions with similar pathophysiology. Research funding is necessary to promote the study and implementation of these promising therapeutics to provide safe and effective nonsurgical treatment options for provoked vestibulodynia. In addition, patient advocacy is essential in studying and adopting novel therapies. Breaking down silos between basic scientists and clinical researchers as well as between different areas of research and medical specialties will be additional challenges in advancing further study of these neuroinflammatory targeted therapeutics. Multidisciplinary efforts such as the Vulvodynia Therapeutic Research Summit highlight the novel and exciting areas for future exploration.

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