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REVIEW ARTICLE

# Infant gastroesophageal reflux disease management consensus

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## Abstract

**Aim:** Infant gastroesophageal reflux is mostly benign; however, when associated with complications like failure to thrive, it may be indicative of gastroesophageal reflux disease. There are currently several unmet needs pertaining to the management of infant gastroesophageal reflux (disease). Reflux in infants is mostly composed of breast milk or formula, so this population is significantly different to older children and adults. The objective of this Delphi consensus was to establish recommendations based on published literature and the experience of clinical experts in paediatric gastroenterology in the context of infant gastroesophageal reflux (disease).

**Methods:** The Delphi methodology was used to obtain a consensus on 18 statements relating to clinical aspects of infant gastroesophageal reflux (disease).

**Results:** The expert panel comprising paediatric gastroenterology clinical specialists reached a consensus for all statements by means of an online, anonymised voting system.

**Conclusion:** It was highlighted that there is generally low awareness of or adherence to guidelines in clinical practice and that acid suppression therapy should not be indicated for non-acid reflux, which constitutes a significant proportion of total gastroesophageal reflux episodes among infants. Furthermore, it was emphasised that there is an unmet medical need for therapy for some symptomatic infants with non-acid reflux disease.

**KEYWORDS**
consensus recommendations, gastroesophageal reflux disease, infant gastroenterology, paediatrics, vomiting

## 1 | INTRODUCTION

Gastroesophageal reflux (GER) refers to the involuntary retrograde passage of gastric contents into the oesophagus and is considered a normal, benign process among the infant population.[1] Gastroesophageal reflux disease (GERD) is characterised by refluxate that results in symptoms that significantly impact quality of life for the infant and parents.[2] GER and GERD are often considered one spectrum condition as opposed to distinct conditions.[3] Common symptoms of infant GER include frequent regurgitation and vomiting, coughing, choking, hiccups, swallowing difficulties and intense crying.[4] Moreover, distinguishing between infant physiological

**Abbreviations:** ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology and Nutrition; GER, gastroesophogeal reflux; GERD, gastroesophogeal reflux disease; H2RA, histamine $H_2$ receptor antagonist; NASPGHAN, North American Society for Pediatric Gastroenterology; PPI, proton pump inhibitor.

GER and pathological GERD is often not straightforward in clinical practice.[4,5]

The global prevalence of infant GERD is not established.[1] Reported prevalence figures among paediatric populations vary widely in the literature.[3,6] However, according to epidemiological studies, regurgitation commonly occurs in around 50% of infants under 2 months of age, 60%–70% of infants aged 3–4 months and 5% of infants by 1 year of age (Figure 1).[7–9] Another systematic review reported that symptoms of GERD are present in over 25% of infants on a daily basis and show a steady decline in frequency within the first year.[1] It is noteworthy that in virtually all cases, infant reflux resolves naturally.[10] Due to the non-specific nature of symptoms in infants, GERD is often overdiagnosed, and many infants are prescribed acid suppression medications without clear evidence of acid-related disease.[11]

Gastroesophageal reflux disease induces marked infant distress, and its classical symptoms are often accompanied with inconsolable crying, irritability, difficulty sleeping and excessive regurgitation.[5,6] As such, it significantly impacts infant quality of life and is also a source of parental distress and anxiety.[12] It is thought that parental expectations may strongly influence treatment decisions in this area, as paediatricians face pressure to initiate potentially ineffective pharmacologic therapies.[13] In many cases, the optimal treatment is reassurance and/or recommending dietary modifications, such as smaller, more frequent feeds.[10] If symptoms persist, subsequent evaluation and diagnostic work-up may be warranted.

It is important to distinguish between acidic, weakly acidic and non-acidic refluxate in order to guide therapies. For infants with weakly acidic or non-acidic refluxate, acid suppression – the mainstay of infant reflux pharmacotherapy – is ineffective as the pH of reflux is already >6.0. Therefore, distinct management approaches should be considered for different reflux subtypes.[12] Additionally, acid suppression therapy, namely proton pump inhibitors (PPIs) and $H_2$-receptor antagonists (H2RAs), are associated with several adverse safety effects.[14–17] Despite this, there is an increasing trend among paediatricians to prescribe these drugs.[11,12]

**Key Notes**

- We present evidence-based consensus statements pertaining to clinical aspects of infant gastroesophageal reflux (disease) developed via the Delphi methodology.
- Eighteen statements are presented, encompassing infant gastroesophageal reflux (disease) background, diagnosis and management.
- We discuss current challenges in the management of infant gastroesophageal reflux disease and highlight the unmet medical need for therapy for some symptomatic infants with non-acid reflux disease.

Considering that the majority of reflux episodes in infants are weakly acidic or non-acidic, there is a significant unmet need in the management of infant GER(D). The rationale for this Delphi consensus is to contextualise the unmet needs within the framework of existing treatment guidelines and expert recommendations and to gain an understanding of potential areas of opportunity as they relate to diagnosis and disease management.

## 2 | METHODS

The Delphi technique was used to reach a consensus on statements relating to clinical aspects of infant GER(D). The expert panel consisted of six distinguished paediatric gastroenterologists representing clinical practice from around the world (Asia, Europe, North America and South America). A comprehensive review of the published literature surrounding the disease area, existing guidelines, and unmet needs was conducted, and consensus statements were subsequently developed based on findings from the literature.

The consensus statements were discussed at a virtual meeting on 8 December 2022, and amendments to the statements were made

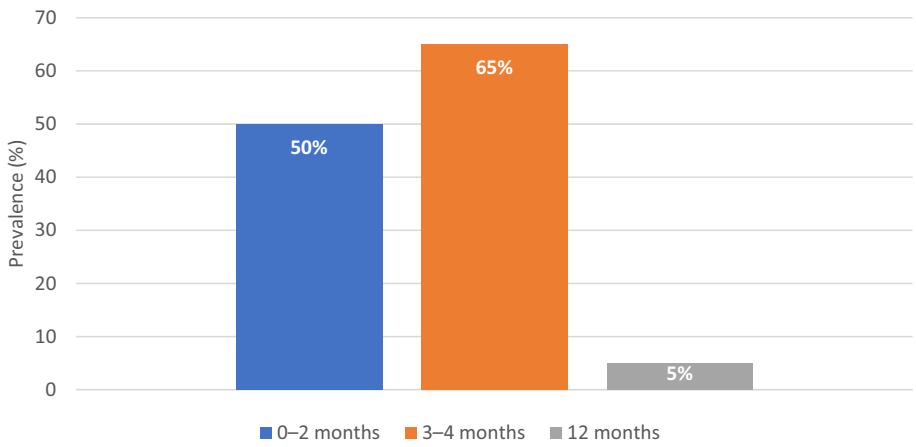


FIGURE 1 Prevalence of regurgitation among infants from 0 to 12 months of age.[7–9]

based on recommendations from the voting participants. Following the meeting, the expert panel anonymously voted on each of the 18 Delphi statements. Voting options were 'strongly agree', 'agree', 'disagree', 'strongly disagree' and 'abstain/unable to answer'. A consensus was considered when ≥80% of experts chose to 'strongly agree' or 'agree' with a particular statement. Note that ethical approval is not applicable for this consensus manuscript.

## 3 | RESULTS

The finalised Delphi statements were divided into three categories: infant GER(D) background, diagnosis of infant GERD and management of infant GERD. A consensus was reached for all statements.

### 3.1 | Infant GER(D) background

The expert panel fully agreed with the statements listed in Table 1. A distinction was made between GER and GERD, and it was established that infant reflux is not an appropriate reason to stop breastfeeding.

### 3.2 | Diagnosis of infant GERD

The voting participants also fully agreed with all statements in Table 2. These statements highlight that refluxate can be categorised based on pH and that distinguishing between acidic, weakly acidic and non-acidic reflux can be determined by combined pH/impedance studies, but as these tests are not widely available, distinction between GER and GERD clinically is challenging. In addition, the panel agreed that there is generally low awareness of the clinical relevance of weakly acidic and non-acidic refluxate among healthcare providers.

### 3.3 | Management of infant GERD

A consensus was reached for all statements pertaining to the management of infant GER(D) listed in Table 3. These statements refer to PPIs, H2RAs, prokinetic agents, feed thickeners and alginate. Crucially, there was unanimous agreement that there is an unmet need for therapies for some symptomatic, breastfed infants with weakly acidic or non-acid reflux disease.

## 4 | DISCUSSION

### 4.1 | Infant GER(D) background

Gastroesophageal reflux and regurgitation are common processes in infants that usually resolve without the need for intervention.[1] In fact, regurgitation has been shown to occur daily in up to 70% of healthy infants[18] and this resolves naturally by 12 months of age in 95% of cases.[4,10] GERD is characterised by GER accompanied by troublesome symptoms and/or complications such as failure to thrive and esophagitis.[2,10]

Distinguishing between physiological GER and pathological GERD is not straightforward in clinical practice, especially in infants due to the non-specificity of classical symptoms and variability in presentations.[5,6] As such, there is a 'grey zone' between GER and GERD defined subjectively by parents and healthcare providers.[19] However,

**TABLE 1** Consensus statements pertaining to GER(D) background.

| Statement | | Consensus (%) |
|---|---|---|
| 1 | Infant GER is a highly prevalent, benign physiological process. | 100 |
| 2 | GERD occurs when GER is associated with symptoms and/or complications that negatively impact quality of life. | 100 |
| 3 | Infant GER/GERD is a common reason for visits to paediatric primary care providers and specialists. | 100 |
| 4 | Symptoms suggestive of GER/GERD often cause significant parental distress. | 100 |
| 5 | Reflux symptoms in breastfed infants are not an appropriate reason to stop breastfeeding. | 100 |

**TABLE 2** Consensus statements pertaining to the diagnosis of infant GERD.

| Statement | | Consensus (%) |
|---|---|---|
| 6 | Refluxate can be characterised as acidic, weakly acidic or non-acidic, and therapies should be tailored to the predominant reflux type. | 100 |
| 7 | Investigations to determine if reflux is acidic, weakly acidic or non-acidic are relatively invasive, not universally available and require expert interpretation and should, therefore, only be undertaken if clarification of the diagnosis is required. | 100 |
| 8 | Among parents and healthcare providers, there is inadequate awareness of weakly acidic and non-acidic refluxate and their role in symptom generation. | 100 |

**TABLE 3** Consensus statements pertaining to the management of infant GERD.

| Statement | | Consensus (%) |
|---|---|---|
| 9 | There is generally low awareness/adherence to relevant guidelines in routine clinical practice across paediatric specialties, leading to inconsistent management approaches. | 100 |
| 10 | Healthcare providers are often asked by caregivers to prescribe acid suppression therapy even when the condition is not acid-related. | 100 |
| 11 | The efficacy and safety profiles of PPIs and H2RAs do not warrant their use in non-acid reflux. | 100 |
| 12 | PPIs can be used as part of a short diagnostic trial (<8 weeks) at an appropriate dose (1–3 mg/kg/day) if acid reflux is suspected. | 100 |
| 13 | If long-term (>8 weeks) acid suppression is ineffective and a definitive diagnosis of acid-related GERD is not established, reconsideration of the treatment choice is warranted. | 100 |
| 14 | The evidence supporting the use of prokinetic agents in treating infant reflux is low, and there are potential adverse events associated with these drugs. | 100 |
| 15 | There is an unmet medical need for therapies for some symptomatic infants with non-acid reflux disease, especially in breastfed infants. | 100 |
| 16 | In non-breastfed infants, feed thickeners are an appropriate line of treatment for symptomatic non-acid reflux as they have a demonstrated, strong efficacy profile and are not associated with serious adverse safety effects. | 100 |
| 17 | Adding a feed thickener to pumped breast milk is preferred to stopping breastfeeding. | 100 |
| 18 | Alginate represents a potential treatment option for weakly acidic or non-acid infant reflux, independent of feeding mode (breastfed or bottle-fed). | 100 |

while infant GER resolves in the majority of infants naturally without the need for pharmacotherapy, GERD management necessitates lifestyle adaptations, pharmacotherapy and rarely, surgery. Therefore, correctly diagnosing and distinguishing between these two conditions is crucial to target treatment and prevent unnecessary use of medications, which is a major concern in this disease area.[4]

Possible GERD is one of the most common reasons for outpatient paediatric gastroenterology consultation visits.[20] Paediatric GERD has been shown to adversely impact health-related quality of life across domains including physical, emotional and social. Furthermore, it has been demonstrated that parents of paediatric GERD patients miss significantly more workdays than on average.[21] This is indicative of the high level of parental distress caused by the condition. Indeed, infant GERD is thought to induce heightened parental anxiety and impair quality of life for parents as well, and the degree of anxiety caused can often be a driving factor in diagnostic and management decisions.[6,7]

The voting participants emphasised that the presence of GERD symptoms in infants is not an appropriate reason to stop breastfeeding. Studies have demonstrated that breastfed infants are at lower risk of reflux compared with formula-fed infants, and breastfeeding is also associated with faster resolution of GERD symptoms.[7,22] Overall, breastfeeding should be encouraged and is considered the optimal mode of infant feeding, as it offers numerous protective effects in terms of immunity, healthy development, cognition and maternal bonding.[23]

## 4.2 | Diagnosis of infant GERD

There is no gold standard diagnostic test for infant GERD. Infants can exhibit a wide range of non-specific symptoms that can be misinterpreted as symptoms of GERD. However, it is not always clear whether these clinical manifestations are a direct result of GERD, and this can result in over- and underdiagnosis and treatment.[13] A thorough medical history and the use of reflux questionnaires can play important roles in ascertaining the severity of symptoms and the overall health of the infant. Validated questionnaires specifically designed for GER(D) provide standardised tools to assess the severity and frequency of symptoms such as regurgitation, vomiting and irritability.[24]

The pH of refluxate is considered an important factor in determining the severity and clinical features of GERD. Acidic refluxate (i.e. pH < 4) has traditionally been considered the most important subtype of reflux in the pathogenesis of GERD. However, recent studies have demonstrated that weakly acidic (i.e. pH 4–7) and non-acidic (i.e. pH > 7) refluxate are also important subtypes that play a significant role in pathophysiology of symptoms in the postprandial period. Weakly acidic or non-acid reflux comprise a significant proportion of total reflux episodes in infants. Studies report the proportion of weakly acidic or non-acid reflux episodes to the total number of episodes in infants is 53%–56%.[25–29] In addition, weakly acidic and non-acid reflux have been shown to relate more closely to infant distress than acid reflux.[30] It has also been suggested that volume of reflux is more strongly associated with infant distress than pH.[12] Characterisation of refluxate subtype based on pH is important and can have clinical implications, as this may influence management decisions and choice of therapy.

While characterisation of refluxate as acidic, weakly acidic or non-acidic may have clinical implications, investigations to determine refluxate subtype are relatively invasive and not universally available. The primary test for acid GERD is 24-h oesophageal pH monitoring, which involves the placement of a pH probe in

the distal oesophagus to measure refluxate pH. This procedure can be invasive and uncomfortable for infants and cannot measure non-acidic refluxate, the most common type in infants.[31] Consequently, pH monitoring should be reserved for selected infants with suspected acid-related symptoms for whom clarification of the diagnosis is required. On the other hand, combined pH/impedance monitoring tests have been developed that are capable of measuring directionality of bolus flow and composition of refluxate and may provide additional information about refluxate subtype. However, impedance monitoring is not widely available, is associated with interpretation issues and is equally invasive to pH monitoring.[32]

There is generally inadequate awareness of weakly acidic and non-acidic refluxate and their roles in symptom generation. Parents and healthcare providers may erroneously believe that acid reflux is the only type capable of causing GERD symptoms; however, studies have demonstrated that weakly acidic and non-acidic refluxate may be responsible for a significant proportion of symptoms in infants with GERD. In a study of infant reflux in 30 subjects, weakly acidic or non-acidic refluxate comprised 49% of total reflux episodes and were associated with similar frequencies of adverse respiratory, sensory and movement symptoms compared with acidic refluxate.[30,33]

Lack of awareness of weakly acidic and non-acidic reflux may lead to delayed diagnosis and treatment, as well as inappropriate use of acid-suppressing medications in cases of non-acidic reflux. Therefore, it is important to promote awareness of the different types of refluxate and their potential impacts on symptom generation in infants. Education and awareness campaigns targeted at healthcare providers and parents may help to increase knowledge and understanding of refluxate subtypes and their roles in GERD. Additionally, further research is needed to identify the optimal diagnostic and therapeutic approaches for infants with weakly acidic and non-acidic refluxate.

### 4.3 | Management of infant GERD and adherence to guidelines

The expert panel of voting participants indicated that there is generally low awareness of or adherence to relevant guidelines in routine clinical practice, which leads to inconsistent management approaches. A survey of 100 paediatricians aimed to illustrate approaches to management of GER(D) among infants and children.[34] The survey revealed that only 2% of paediatricians showed complete adherence to guidelines published by the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).[35] Moreover, results of the survey indicated that 57% of paediatricians diagnose GERD based exclusively on clinical symptoms, even though published guidelines consider symptom description as unreliable and non-specific in infants and children. Another survey of 149 pharmacists with inpatient paediatric experience reinforced that adherence to clinical guidelines was low, with many infants receiving treatment that was not consistent with NASPGHAN/ESPGHAN guidelines.[36] Specifically, there was excessive use of acid-suppressing medications. These findings highlight the importance of enhancing education and training for healthcare providers in this disease area. A 2014 study by Quitadamo et al.[37] demonstrated that providing training on clinical guidelines for infant GER(D) management improved adherence among paediatricians. Ongoing education and reinforcement of guidelines are, therefore, crucial for better adherence in routine clinical practice and ultimately, superior patient outcomes.

One factor that may possibly contribute to low adherence to clinical guidelines is parental expectations. Infant GER, especially when associated with other signs like inconsolable crying, can induce significant parental anxiety and adversely impact quality of life for the entire family. As such, parents may strongly request initiation of specific therapies that contradict clinical guidelines. It has been suggested that this factor may promote inappropriate prescription of acid suppression medications. It is, therefore, important for healthcare providers to communicate effectively with parents and provide appropriate education on the risks and benefits of different treatment options for infant reflux.

Proton pump inhibitors are the most frequently prescribed medications for the treatment of GERD.[38] There are several different PPIs with comparable efficacy and safety profiles, though omeprazole, esomeprazole and lansoprazole have been the most widely studied in infants and children.[39] Compared with adults, infants and children require considerably larger relative doses of PPIs per kilogram, and this is thought to relate to altered drug metabolic processes in these age groups.[7] Rather than reducing reflux, PPIs inhibit gastric acid secretion.[12] It is also thought that PPIs are no more effective than placebo in decreasing crying, coughing, back arching and regurgitation in infants with GER.[6] However, it is noteworthy that these findings are based on studies that may have utilised inappropriate doses, especially considering the significant hepatic metabolism activity of PPIs in infants.

Proton pump inhibitor use in paediatric patients is associated with risks of infections, such as *Clostridium difficile*, pneumonia and viral gastroenteritis.[17,40,41] PPIs are also linked to changes in bone density and increased risks of developing allergic diseases and asthma in infants and children.[14,42,43] Furthermore, a recent review that aimed to reveal the effects of PPIs on the microbiome concluded that PPIs modify microbial diversity of the mouth, gut and lungs in young children, creating dysbiosis that may have unintended health consequences.[15] Given the risks, it is important that PPIs are only prescribed in cases of acid-related disease in infants. PPIs may also be used as part of a short diagnostic trial (<8 weeks) at an appropriate dose (1–2 mg/kg/day) if acid reflux is suspected.[44]

$H_2$-receptor antagonists reduce acid secretion by reversibly inhibiting histamine $H_2$ receptors of gastric parietal cells. Ranitidine, though no longer available, was the most used drug in this class, which includes cimetidine, famotidine and nizatidine.[38] While they are demonstrably more effective than placebos in reducing gastric

acid secretion, studies have shown that they are less effective than PPIs in terms of healing rates and symptom relief.[7,45,46] Like PPIs, H2RAs do not reduce the frequency of reflux and are, therefore, not recommended for the treatment of non-acid reflux in infants.

$H_2$-receptor antagonists are also associated with adverse safety effects. Like PPIs, they may be associated with increased risks of *Clostridium difficile* infection, pneumonia and viral gastroenteritis.[47,48] A retrospective cohort study of 274 very low birth weight infants reported a 5.5-fold increase in infection risk and a significantly higher mortality rate in subjects exposed to ranitidine.[49]

Prokinetic agents promote gastric emptying and oesophageal acid clearance via different mechanisms of action on the gastrointestinal tract.[11,39] Examples of such drugs include prucalopride, metoclopramide, erythromycin, domperidone, cisapride and baclofen.[6,7] Several large-scale studies and meta-analyses have demonstrated that prokinetics offer little or no benefit for the treatment of GER(D) in infants and children.[50–52] Additionally, prokinetic agents are associated with significant adverse effects in paediatric patients, including dizziness, drowsiness, restlessness, seizures and QT interval prolongation.[4,6,7,13,53] As such, current NASPGHAN/ESPGHAN guidelines do not recommend their routine use for the management of infant GER(D).[13]

The panel of voting participants highlighted that in non-breastfed infants, feed thickeners are an appropriate line of treatment for symptomatic non-acid reflux as they have a demonstrated, strong efficacy profile and are not associated with serious adverse safety effects.[54,55] A variety of different thickeners can be used to reduce regurgitation and/or vomiting in infants. Although generally considered safe, there are some concerns regarding the use of feed thickeners for infant reflux, including arsenic exposure, microbiome alterations and malabsorption of micronutrients.[12,56–58] Furthermore, thickeners can be added to breast milk, and this is strongly recommended over stopping breastfeeding for patients with non-acid-related symptoms. As such, there is an unmet medical need for therapies for some symptomatic infants with non-acid reflux disease, especially in breastfed infants.

Alginate represents a potential treatment option for weakly acidic or non-acid infant reflux, independent of feeding mode (i.e. breastfed or bottle-fed). It has a fast onset of action and can safely and effectively relieve symptoms within minutes, with effects lasting for approximately 4 h.[39,59,60] Studies in infants and children have demonstrated that alginates can significantly reduce reflux episodes and improve symptoms.[60–62] However, it has also been shown that while alginate can produce a significant improvement in average reflux height in infants, the difference is marginal compared with placebo.[60] Therefore, further research is warranted to investigate the promising clinical utility of alginate.

## 5 | CONCLUSION

There are several unmet needs that hinder the optimal management of infant GER(D), such as inadequate adherence to clinical guidelines and potential overuse of acid suppression medications. The panel of experts in paediatric gastroenterology reached a consensus on 18 statements regarding the diagnosis of GER(D) and pharmacotherapeutic options. The efficacies and contexts of appropriate use of different medications are discussed with consideration to safety, tolerability and infant feeding mode.

### AUTHOR CONTRIBUTIONS

**Yvan Vandenplas:** Conceptualization; methodology; writing – review and editing; investigation; validation; project administration. **Marina Orsi:** Conceptualization; methodology; investigation; validation; writing – review and editing. **Marc Benninga:** Conceptualization; methodology; investigation; validation; writing – review and editing. **Felizardo Gatcheco:** Conceptualization; methodology; investigation; validation; writing – review and editing. **Rachel Rosen:** Conceptualization; methodology; investigation; validation; writing – review and editing. **Mike Thomson:** Conceptualization; methodology; investigation; validation; writing – review and editing.

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### CONFLICT OF INTEREST STATEMENT

Yvan Vandenplas, Marina Orsi, Marc Benninga, Felizardo Gatcheco, Rachel Rosen and Mike Thomson received honoraria fees from Reckitt Benckiser as advisory board members. Yvan Vandenplas has also participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott Nutrition, Alba Health, Ausnutria, Biogaia, By Heart, CHR Hansen, Danone, ELSE Nutrition, Friesland Campina, Nestlé Health Science, Nestlé Nutrition Institute, Nutricia, Mead Johnson Nutrition, Pileje, Sanulac, United Pharmaceuticals (Novalac), Yakult and Wyeth. Marina Orsi has also participated as a speaker for Abbvie, Nestlé and Nutricia. Marc Benninga has also participated as a consultant and/or speaker for Abbott, Allergan, Coloplast, Wellspect, Menarini, Mallinckrodt, Danone, FrieslandCampina, HIPP, United Pharmaceuticals and Sensus. Rachel Rosen has also participated as a consultant for Neuraxis.

### ETHICS STATEMENT

Ethical approval is not applicable as this work does not describe any new studies with human participants or animals performed by any of the authors.

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