



# Evidence-Based Opinions from Multidisciplinary Experts on Use of Naturopathic Herbal Remedies in Pain Management

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**Background:** Pharmacological approaches to acute and chronic pain management, including non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, are respectively associated with adverse reactions (such as gastrointestinal, cardiovascular, and renal effects) that might limit their use in patients with comorbidities and controversy related to inappropriate use. Naturopathic remedies might offer patients alternative and integrative treatments with minimal side effects.

**Objective:** To explore the regional variation in the acceptance and use of naturopathic remedies in pain management.

**Methods:** Two expert panel discussions were held by GlaxoSmithKline Consumer Healthcare (now Haleon Pte. Ltd.) over 9 and 12 hours in 2020 and 2021, respectively, and attended by multidisciplinary experts in naturopathy, Ayurvedic medicine, community pharmacy, physiotherapy, clinical pharmacy, Western medicine, academics, and naturopathic pain relief. Experts shared and discussed their experiences of naturopathic treatments and relevant clinical evidence related to different types of pain (including joint and muscle pain, migraine, sleeplessness due to pain, and general pain) and examined barriers to providing support to patients.

**Results:** Experts agreed on the potential for curcumin (2020, 71.4% [5/7]; 2021, 91.7% [11/12]) and fish oil (2020, 100% [7/7]) for management of osteoarthritic joint pain although these are not uniformly recommended in osteoarthritis treatment guidelines. In treatment of migraines, coenzyme Q10 and magnesium were favored by experts (2021, 90.9% [10/11] and 63.6% [7/11], respectively).

**Conclusion:** The need was emphasized for more and higher quality clinical studies to support naturopathic remedies, which might not be reflected in the latest treatment guidelines. The expert panel also highlighted missed opportunities for physicians and pharmacists to recommend effective naturopathic treatments.

**Keywords:** herbal remedies, naturopathy, osteoarthritis, migraine, expert panel discussion

## Introduction

Pain has been recognized as important in the primary care of patients with chronic conditions.<sup>1</sup> Similar to management of acute pain,<sup>2</sup> treatments including acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), and their combinations, are amongst the most popular medicines currently used for reducing various types of pain.<sup>3,4</sup> Acetaminophen is believed to operate by activation of descending serotonergic pathways<sup>4</sup> and NSAIDs act via inhibition of the pro-inflammatory enzyme cyclooxygenase (COX), which is involved in the generation of inflammation and biochemical recognition of pain.<sup>5</sup> However, use of NSAIDs is associated with complications of the upper gastrointestinal,<sup>6</sup> cardiovascular (CV), and renal systems.<sup>7</sup> Opioids have become increasingly used for management of chronic pain; however, these medications are associated with controversies,<sup>8</sup> owing to concerns regarding

inappropriate use and related mortality and morbidity.<sup>9</sup> Opioids account for more than 70% of 0.5 global million deaths attributable to drug use, with deaths by overdose accounting for >30% of those cases.<sup>10</sup> Increased misuse of pain medications has prompted the World Health Organization (WHO) to revise its guidance on management of pain,<sup>11</sup> motivating the need for alternative pain management solutions that avoid problems associated with NSAIDs and opioids.

Natural products and dietary supplements (hereafter referred to as naturopathic remedies/products) have relatively low side effects, which may favor their use in patients with comorbidities and represent potential alternative pain management solutions for inflammatory pain and hyperalgesia.<sup>12</sup> Many patients with both acute and chronic pain are turning to non-pharmacological therapies for additional relief and research activity, and interest in these alternative remedies have increased.<sup>13</sup> Among existing recommendations on naturopathic remedies, some treatment guidelines now incorporate recommendations on use of naturopathic remedies in conditions, including osteoarthritis,<sup>14</sup> back pain,<sup>15</sup> neuropathic pain,<sup>16</sup> and dysmenorrhea.<sup>17</sup> For example, the European League Against Rheumatism (EULAR)<sup>18</sup> and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)<sup>19</sup> have recognized the roles of naturopathic remedies. The Australian guidelines for rheumatoid arthritis also reflect evidence of the anti-inflammatory effects of curcumin.<sup>20</sup> Magnesium has been recommended for treating migraines in some countries.<sup>21,22</sup> However, there is a lack of a global consensus on the use of naturopathic remedies in clinical guidelines that address pain management.

Issues preventing wider recommendations of naturopathic remedies include limited and low-quality evidence of their effectiveness and/or slower onset of action compared with pharmacological treatments, as well as a lack of education and insufficient collaboration among healthcare professionals.<sup>23</sup> Standardization of naturopathic medicines also poses challenges, based on differences in preparation and plant species, which may alter the chemical profile dependent upon geographical area, seasonal variations, method of harvest, extraction procedures, and/or storage conditions.<sup>24</sup> Falling under the umbrella of complementary and alternative remedies, naturopathic remedies are not uniformly regulated across different regions, and in some cases not regulated at all.<sup>25–27</sup>

Although generally recognized as being associated with relatively few adverse drug reactions, there are risks and contraindications associated with naturopathic remedies that warrant caution.<sup>28</sup> Lower risks associated with naturopathic products depend on appropriate levels of education, and safe standards of practice and mechanisms should be enacted to ensure these standards are met. Naturopathic products are often provided as over-the-counter (OTC) medicines and are accessible for self-selection, and there is the potential for incorrect dosage and interactions with other drugs<sup>29</sup> due to a lack of clinical guidance. These features place a particular burden on pharmacists, who may be more easily accessed by the public than appointment-based naturopaths or general practitioners (GPs).<sup>30</sup> Furthermore, pharmacists are now under greater pressure to deliver frontline guidance to patients, owing to the global COVID-19 pandemic, which has led to restricted access to GPs by patients.<sup>31</sup> Patients are likely to use pharmacists as their as first point of contact, which represents an opportunity for re-education of these healthcare providers to play a more active role in advising on naturopathic remedies.

The expanding use of complementary remedies necessitates healthcare education that addresses misconceptions of the public and healthcare providers, potentially involving appropriate government oversight.<sup>32</sup> Any such measures should be supported by further clinical and basic research into complementary and alternative medicine<sup>33</sup> and studies of their cost-effectiveness and how to best integrate these options within existing public health frameworks.

In this review, we examine variation in ways of treating pain and the use of naturopathic products across different geographic regions and cultures. The panel evaluated current clinical evidence to identify evidence gaps in the use of naturopathic products for pain management. The panel also examined barriers to the uptake of naturopathic remedies, the path of patients using naturopathic treatments and potential pitfalls, as well as the scope for multidisciplinary integration of holistic approaches with existing healthcare systems. The format of these meetings provided a unique forum, bringing together experts from a range of healthcare ecosystems to discuss and share opinions on topics related to herbal remedies for consideration by industry stakeholders.

## Methods

Two online events were held over 2 days each in 2020 (9 hours total) and 2021 (12 hours total) and attended by a multidisciplinary panel of expert practitioners in naturopathy, Ayurvedic medicine, community pharmacy, pain medicine, clinical pharmacy, joint pain and osteoarthritis (OA), and naturopathic pain relief. In 2020, 7 experts joined from India, Malaysia, Singapore, and Australia. In 2021, 11 experts were in attendance from Saudi Arabia, United Arab Emirates, Finland, Italy, United Kingdom, India, Malaysia, Singapore, and Australia. The panel was selected based on a desk search of the literature, experts' affiliations in national and international organizations relevant to naturopathy, and institutional/personal websites for individuals active in the above areas of expertise and regions, who expressed an interest in participating in discussions on these topics. The duration and timing of the meetings were determined through consultation with the experts. Prior to the expert panel discussions, practicing attendees were surveyed on their current naturopathic treatment recommendations ([Supplementary Tables 1 and 2](#)). During the discussions, experts delivered presentations on naturopathic treatments for specific and relevant clinical evidence related to different types of pain, including joint and muscle pain, migraine, sleeplessness due to pain, and general pain (meeting agendas are shown in [Supplementary Tables 3–6](#)). The topics were discussed further by the panel, and consensus polling was conducted.

## Results and Discussion

### Joint and Muscle Pain

Osteoarthritis is the leading cause of disability and joint pain worldwide.<sup>34</sup> As a complex and multifactorial degenerative joint disease, osteoarthritis is primarily a disease of the articular cartilage that causes local inflammation and mechanical changes. Nutrition and dietary supplementation have been shown to have meaningful effects on the disease.<sup>35,36</sup>

Curcumin is a popular treatment option for joint pain/muscle pain due to its strong antioxidant and anti-inflammatory effects.<sup>37</sup> These effects are well supported by clinical evidence including a 2016 systematic review and meta-analysis, which, although based on a small number of RCTs, concluded that turmeric extract is effective in managing pain from osteoarthritis.<sup>38</sup> Boswellia has been investigated in a few recent clinical trials that have reported conflicting results.<sup>39,40</sup> A recent meta-analysis<sup>41</sup> found that boswellia and its extracts may be an effective and safe treatment option for patients with osteoarthritis. Use of fish oils in osteoarthritis has been widely studied; however, a meta-analysis has noted the low-to-moderate quality of current supporting evidence.<sup>42</sup>

Experts who attended the 2021 panel discussion reported that 5–30% of their patients were seeking non-medicated pain relief from osteoarthritic joint pain. A higher percentage of patients reportedly sought non-medicated solutions for joint and muscle pain in the Middle East (50–90%) compared with Singapore/Malaysia (10–20%) and Australia (5–10%).

In 2020 experts responded to a pre-meeting survey question on their top 3 naturopathic solutions used to treat joint pain. Curcumin and fish oil were both strongly recommended, with each receiving 7 votes, followed by magnesium and boswellia (2 votes each). Glucosamine, palmitoylethanolamide with nattokinase, and ginger root also received 1 vote each. During the meeting, the experts voted for curcumin (5 of 7 experts) and ginger root (1 of 7 experts) as their preferred naturopathic remedies for joint pain.

In a consensus discussion on the use of curcumin complex, the 2021 panel agreed (11 of 12 experts with 1 abstention) that the complex offered benefits in treating joint pain. Common factors that motivate the selection of treatment options were safety and efficacy of the natural compounds, as supported by naturopaths, pharmacists, and researchers (9 votes); personal experience/observation (5 votes); and access to high-quality products (2 votes).

In a roundtable discussion, the experts considered the importance of communicating the effects of different ingredients for different types of pain, the role of oral versus topical use, and the holistic effects of therapies in terms of the gut microbiome. Integration of naturopaths and pharmacists, who often advise patients, was also discussed as a means of promoting the role of naturopathic remedies in the healthcare system.

## Sleeplessness Due to Pain

Population-based studies have found that up to a third of people may report sleep disorders;<sup>43</sup> however, sleep complaints are more prevalent in people with chronic pain disorders (50–88%).<sup>44</sup> Furthermore, a bidirectional relationship between sleep and pain exists, whereby pain reduces sleep quality<sup>45</sup> and poor sleep quality amplifies pain perception.<sup>46</sup> Sleeplessness due to pain can increase a patient's risk for depression and anxiety, reduce functional ability,<sup>45</sup> and increase systemic/widespread pain.<sup>47</sup>

Among naturopathic treatments for sleeplessness, the use of *Valeriana officinalis* is widely supported in the literature.<sup>48–50</sup> In 2021, experts from most regions, except Europe, concurred that *V. officinalis* has a role in managing sleeplessness due to pain, although there were some differing practices. Australia experts also recommended magnesium and St John's Wort/Ziziphus (2 votes each). Experts from Europe (ie, UK, Finland, and Italy) preferred magnesium, boswellia, and melatonin (1 vote each). Singapore/Malaysia experts preferred ashwagandha (*Withania somnifera*) (2 votes) and passiflora (1 vote). Saudi Arabia/UAE experts preferred passiflora and melatonin (1 vote each).

A consensus discussion focused on the use of ashwagandha to promote sleep in patients with associated chronic pain. While experts reported positive feedback from patients using ashwagandha for this purpose, the experts were divided on the use of ashwagandha for this specific novel combination of indications (6 of 12 in favor) but concluded that ashwagandha might be useful in managing sleeplessness with pain.

Use of melatonin and its combination with other nutrients are supported for use in sleeplessness; however, long-term use of OTC products can have adverse effects on regulation of endogenous melatonin production and release by the pineal glands.<sup>51</sup> Experts across different specialties concurred that the most convincing evidence for treating sleeplessness due to pain was in melatonin. In Saudi Arabia and Italy, fewer patients sought naturopathic solutions (0% and 3%, respectively) for sleeplessness compared with 50% of patients in Australia, which might reflect the status of melatonin as a prescription drug in the former regions. Consumers from these countries may be more likely to seek medicated solutions for sleeplessness (eg, prescription melatonin and potentially other pharmacological treatments) rather than natural options.

## Headache/Migraine

Acute and chronic pain from migraine and headache may derive from a variety of diseases<sup>52</sup> and can negatively affect many important aspects of life.<sup>53</sup> Naturopathic therapies are likely to have an important role in managing migraine, owing to their fewer associated adverse effects.<sup>54</sup>

For feverfew (*Tanacetum parthenium*), there is clinical evidence to support its use in treating headache; however, a need for further and higher quality studies is noted.<sup>55</sup> Feverfew is indicated for migraines in some treatment guidelines.<sup>56–58</sup>

Magnesium has a more established role in treating migraine. Although a 2019 systematic review found insufficient evidence for magnesium in combination with coenzyme Q10 (vitamin B) for migraine prophylaxis,<sup>59</sup> a later 2020 systematic review of reviews<sup>60</sup> found support for its effects in reducing the intensity/frequency of migraines. Magnesium is currently recommended in several guidelines for treatment of migraines.<sup>21,22,56–58,61–63</sup>

There is also evidence to support the effectiveness of coenzyme Q10 in reducing the frequency and duration of migraines,<sup>62</sup> and a number of guidelines include this recommendation.<sup>21,58,61,62,64,65</sup>

Experts were asked for their top 3 naturopathic therapies for migraine. Coenzyme Q10 (vitamin B) received the greatest number of recommendations (10 votes) followed by magnesium (3 votes). Feverfew also received 1 mention, in addition to *Ginkgo biloba*, calcium, curcumin/turmeric, and probiotics. During the meeting, 7 experts voted magnesium as the top treatment option for migraine. Pre-meeting survey results from the 2021 meeting indicated a similar preference for magnesium, with some regional differences: Australian and European experts preferred feverfew (4 votes), magnesium (3 votes) and willow bark (2 votes). Singapore/Malaysia experts preferred magnesium (1 vote), boswellia (1 vote), and palmitoylethanolamide (1 vote). Saudi Arabia/UAE experts preferred feverfew (1 vote) and menthol (1 vote).

Following a consensus discussion, experts were divided on the use of feverfew, with 6 of 12 agreeing that it might be effective for migraine prophylaxis (preventive care) or for episodic relief of migraine.

## General Pain

General pain includes both chronic and acute pain resulting from conditions such as back pain,<sup>66</sup> menstrual pain,<sup>67</sup> abdominal pain,<sup>68</sup> and musculoskeletal pain.<sup>69</sup>

Meta-analyses have indicated the effectiveness of magnesium for various types of pain,<sup>70</sup> and specifically in dysmenorrhea.<sup>71</sup> Although magnesium is recommended for different types of pain (including aforementioned migraines) few treatment guidelines currently recommend use of magnesium for dysmenorrhea.<sup>72</sup>

Although widely recommended for general pain, boswellia has not been extensively studied outside of the indication for osteoarthritis. Potential anti-oxidative, anti-inflammatory, anti-amyloidogenic, and anti-apoptotic properties have been recognized; however, there is a need for further clinical evidence to support use of boswellia for different pain types.<sup>73</sup>

Curcumin/turmeric received the most recommendations for treatment of general pain from experts who indicated their top 3 preferred solutions prior to the 2020 expert panel discussion (3 votes). Omega-3 fatty acids and resveratrol also received 2 mentions each, and magnesium, willow bark, Jamaican dogwood received 1 vote each. During the meeting, experts voted for curcumin/turmeric (4 of 7 experts) and omega-3 fatty acids (3 of 7 experts) as their preferred naturopathic solutions for general pain.

In 2021, the top 3 naturopathic ingredients recommended to treat general pain included magnesium (7 votes), curcumin (6 votes), and boswellia (6 votes). In Australia, curcumin (2 votes), magnesium (2 votes) and boswellia (2 votes) were preferred. European (UK/Finland/Italy) experts preferred curcumin (2 votes), willow bark extract (2 votes), and boswellia (1 votes). In Singapore/Malaysia, magnesium (1 vote) and boswellia (1 vote) were preferred. Usage in Saudi Arabia/UAE included *Arnica montana* extract (1 vote), *Vitis vinifera* leaf extract (1 vote) and menthol (1 vote).

The panel noted that, particularly for acute pain, naturopathic products may be administered at higher doses or used as an adjunct to pharmaceutical pain killers to reduce doses required by the patient. Naturopathic products may also allow for gradual tapering from strong painkillers once a patient's pain has improved.

## Barriers to the Use of Naturopathic Products

Many consumers seek rapid solutions for their pain, particularly in the case of acute pain, which might result in the underlying causes for their symptoms going undiagnosed. This treatment-seeking behavior may be at odds with naturopathic approaches to pain management, which consider patient symptoms from a holistic context. For acute pain, naturopathic approaches may be effective in use alongside conventional pharmaceutical therapies; however, naturopathic remedies together with holistic lifestyle changes could offer preventative and greater longer-term benefits to patients and reduce reliance on pharmaceutical pain killers. There remains a lack of high-quality evidence to demonstrate the broader efficacy of naturopathic consultations. However, the 2021 panel unanimously agreed (11/11) that natural pain medications have a role in both symptomatic and preventative care.

The panels identified gaps in the training of healthcare professionals. Those trained in Western medicine may have misconceptions about naturopathic treatment and prevent or discourage patients from using naturopathic treatments. Hence, referrals to naturopaths from healthcare practitioners (HCPs) were noted to be rare across all regions. HCPs and researchers often consult treatment guidelines, many of which exclude naturopathic solutions because of poor quality evidence. Hence, there is also a need to both improve the quality and the volume of studies supporting naturopathic remedies, including non-inferiority trials.

As an additional barrier, many naturopathic products are more expensive than regular pharmaceutical products. Hence, there is a need to improve affordability and accessibility of naturopathic remedies to realize their full value in treatment as primary medicines.

Patients often seek naturopathic options owing to mistrust of medical doctors and concern about side effects of standard medications. Pre-conceptions about naturopathic therapies, unrealistic expectations for immediate effects and the differences between effectiveness towards acute and chronic pain may lead to low trust in the products. In self-administering naturopathic remedies, patients might not be aware of the time required for response and fail to complete their full treatment course. Use of naturopathic products is not without risk, and there is a need to provide more information to consumers about contraindications and drug interactions. There may also be perceptions among general

consumers that naturopathic remedies are poor quality, high in cost, and/or ineffective compared with pharmaceuticals. Therefore, to establish patient trust, production methods and quality assurance approaches to naturopathic remedies should mirror requirements of the pharmaceutical industry. Standardization of active ingredients should help to build greater trust in naturopathic products among both healthcare professionals and patients.

## Importance of Pharmacy Education and Labelling

The patient journey to consult with a naturopathic practitioner typically starts with a desire to avoid starting a course of pharmaceutical treatment or to substitute or decrease reliance on their current medication. Amid growing interest in alternative therapies among patients and the absence of guidance from GPs and pharmacists, patients are likely to seek alternative sources of information.

Social influencers in this space have raised awareness of alternative therapies, but provision of unreliable information could potentially lower trust in naturopathic remedies. When regional agencies seek to revise their guidelines through the consensus approach, it may be useful to engage with a trusted spokesperson from the naturopathic community to raise awareness of naturopathic treatments among experts. There may also be benefits from developing national and international networks of naturopathic practitioners to align on delivery of treatment and consistent patient messaging.<sup>32</sup>

A large proportion of patients who experience pain are likely to first approach a pharmacist for an OTC solution. Pharmacy visits represent an important opportunity for providing patients with information about effectiveness, safety, dosage, and duration of naturopathic therapies. Product labelling is also crucial, and packaging information on indications treated and specific doses for symptomatic and preventive care might benefit patients. The use of online resources accessed through QR codes on packages could provide more information on the product and about naturopathy. Regardless of the source and delivery method, patient information about naturopathic products should avoid over-promising treatment benefits and emphasize the holistic context in which these products best serve patients.<sup>74,75</sup>

There is a clear long-term need for inclusion of content on naturopathic medicine in the curriculum for medical students and pharmacists. This might be achieved by further research into course design in collaboration with instructors, collecting evaluations and reflections from participating students. Incorporating naturopathic medicine within existing healthcare systems may improve the rate of appropriate referrals from GPs to naturopaths. This may in turn help to address misconceptions among the public and build trust in naturopathic remedies and an understanding of their role alongside pharmaceuticals.

Conversations with pharmacists and consumers should also be promoted. Surveys to evaluate pharmacist knowledge and engagement with naturopathic remedies might offer useful insights. This might enable the development of factsheets to be shared by pharmacists and could be a useful tool for delivering dependable and accessible product information. Pharmacy assistants could be educated through bite-sized engaging materials to increase their confidence in recommending naturopathic medicine in the OTC setting and ensure that doses are tailored to the patient.

## Strengths and Limitations

There are some limitations to insights obtained from these expert panel discussions. Notably, no formal consensus or qualitative research methodology was applied to either meeting; furthermore, expert views are not supported by a comprehensive review and quality assessment of the clinical literature. Nevertheless, the independent insights from this large panel of international experts serves to highlight regional differences and similarities in provision of naturopathic remedies for pain management. There was a potential risk of selection bias in deciding the panel. Panel members may also have felt compelled to vote in line with the majority during the meetings. However, both pre-meeting voting and voting following discussions in the meetings demonstrated strong alignment among experts on the effectiveness of specific ingredients and on qualitative steps for integrating naturopathic practices with conventional healthcare systems. Although not all the same experts were able to attend both meetings, there was overall agreement of several key experts between the meetings. Furthermore, although the panels agreed that naturopathic remedies may be safer than conventional pharmaceuticals, there remains a risk of adverse reactions by individuals to certain ingredients and a need for caution in combining natural remedies with other therapies. Further exploration of appropriate dosages and contraindications of the ingredients are warranted.

## Conclusions

Notable regional variation was observed in the use of naturopathic products by patients with pain across this multi-disciplinary and geographically diverse panel. For example, views differed on the benefits of ashwagandha for sleeplessness due to pain. However, the panels agreed on the benefits of certain therapies, including curcumin and fish oil for osteoarthritic joint pain and coenzyme Q10 and magnesium for migraines. Here, we try to integrate differing views from a range of practitioners representing these regions and develop integration of naturopathic products with conventional pain management solutions. However, further studies should seek to identify appropriate dosages and consider potential safety issues associated with specific naturopathic products.

Consumers and patients may not be aware of the effects of the ingredients in naturopathic medicine. Hence, there is a need to ensure that naturopathic products for pain are marketed based on the indication they treat rather than the ingredients. Labelling on products should also clearly indicate dosage and the treatment period to ensure that patients have realistic expectations and maintain compliance with naturopathic products. Any important safety considerations in using the medicine should also be clearly highlighted on labels. Labelling could be augmented with digital media, through QR codes, to provide more information on products.

A key barrier to recommending naturopathic remedies in treatment guidelines is the lack of quality evidence. Thus, new clinical trials with larger populations are required, to generate high-quality evidence related to effectiveness and safety of naturopathic products. There are inconsistencies across regional recommending bodies regarding naturopathic treatments, which are based on existing evidence of effectiveness. Involvement of the naturopathic community in medical expert panel discussions and consensus meetings could help to ensure that naturopathic products are fairly evaluated and recommended where appropriate.

Pharmacy assistants in most countries may be the first point of contact within a pharmacy and there is a need to add content on naturopathic products to the curriculum of pharmacists to improve awareness among the profession and to provide consumers with trustworthy information on the effectiveness of the products and their safety. Provision of information brochures and factsheets with products that may also be shared with consumers could help to improve acceptance of the products among experienced pharmacists and pharmacy assistants and support staff.

## Ethics Approval

Our study is a narrative review/commentary based on a consensus discussion of professionals who gave written consent to participate in the meetings and signed standard agreements, which assigned Haleon full rights to the content generated, including consent for scientific publication. There was no intervention, and no human subjects were involved in the study. On this basis, the study is not subject to the Declaration of Helsinki and exempt from institutional review board ethical review.

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## Disclosure

VS is a current employee of Haleon (formerly GSK Consumer Healthcare); AM has consulted for and received honoraria from Haleon. AS-C, FCG, JM, and MG have all received honoraria from Haleon. The authors report no other conflicts of interest in this work.

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