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INVITED REVIEW

Nutrition, endocannabinoids, and the use of cannabis: An overview for the nutrition clinician

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Abstract

The endocannabinoid system (ECs) is composed of multiple signaling compounds and receptors within the central and peripheral nervous system along with various organs, including the gut, liver, and skeletal muscle. The ECs has been implicated in metabolism, gut motility, and eating behaviors. The ECs is altered in disease states such as obesity. Recent studies have clarified the role of the gut microbiome and nutrition on the ECs. Exogenous cannabinoid (CB) use, either organic or synthetic, stimulates the ECs through CB1 and CB2 receptors. However, the role of CBs is unclear in regard to nutrition optimization or to treat disease states. This review briefly summarizes the effect of the ECs and exogenous CBs on metabolism and nutrition. With the increased legalization of cannabis, there is a corresponding increased use in the United States. Therefore, nutrition clinicians need to be aware of both the benefits and harm of cannabis use on overall nutrition status, as well as the gaps in knowledge for future research and guideline development.

KEYWORDS
cannabis, endocannabinoids, nutrition

INTRODUCTION

The endocannabinoid system (ECs) is a complex expansive signaling pathway that involves endocannabinoids and endocannabinoid-like signaling molecules, the receptors they act on, and the enzymes used in production and degradation.[1] Major ECs signaling molecules, true endocannabinoids, include *N*-arachidonoylethanolamide (anandamide [AEA]) and 2-arachidonoylgylcerol (2-AG) derived from ω-6 polyunsaturated fatty acids (PUFAs) synthesized within the phospholipid membrane on an "on-demand" basis.[2] They act on G protein–coupled receptors, cannabinoid (CB) 1 and CB2. CB1 receptors are expressed in the central nervous system and influences cognition, reward, and motor systems, whereas CB2 receptors are found mainly in peripheral immune cells.[2,3] Stimulation of CB1 receptors leads to increased eating behaviors, mediated in part by leptin levels, and overstimulation can lead to obesity.[2] The ECs has major downstream effects in skeletal muscle, the gut, and liver (summarized in Figure 1).[2–5] Other receptors within the ECs include the transient receptor potential vanilloid 1 and peroxisome proliferator-activated receptor gamma. The ECs also includes endocannabinoid-like molecules derived from dietary ω-3 PUFAs, including *N*-oleoylethanolamide (OEA) and *N*-palmitoylethanolamide (PEA), which stimulate these receptors.[2] OEA is known to suppress appetite, increase lipolysis in adipocytes, and have a key role in energy metabolism in

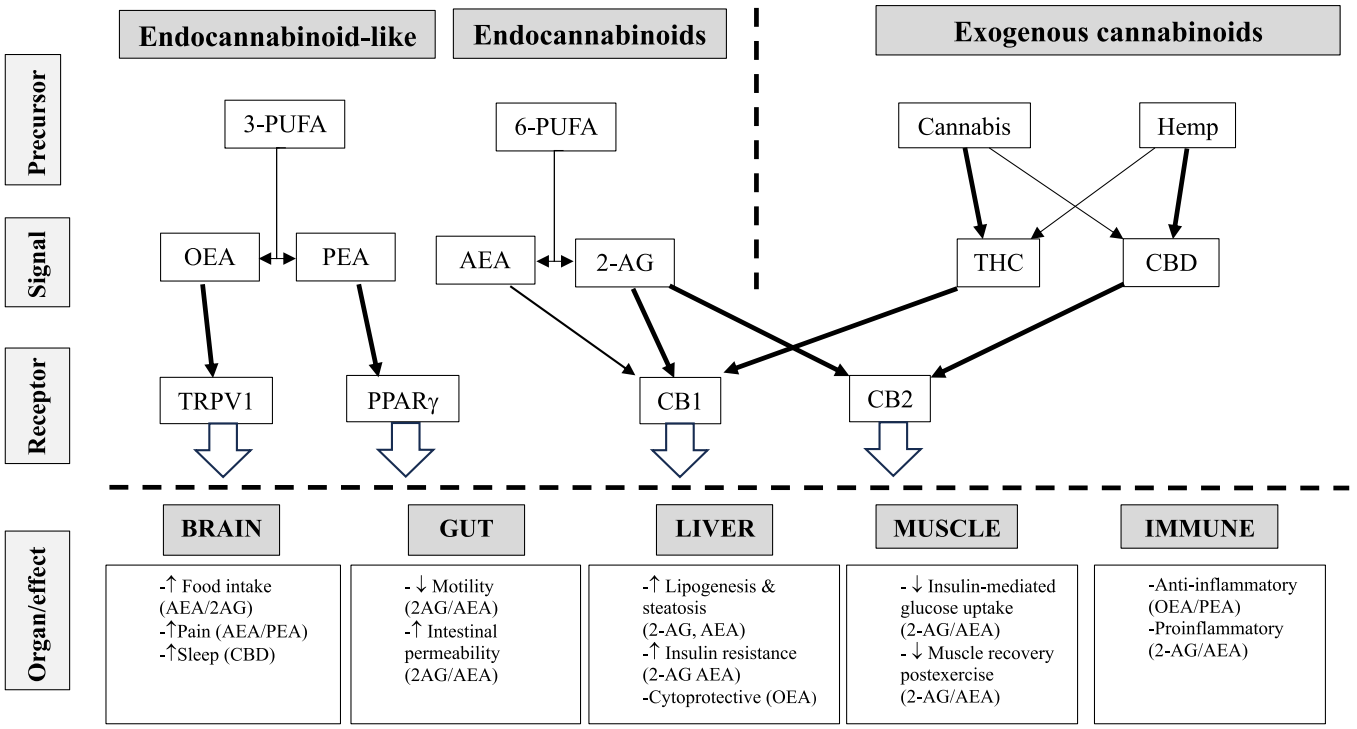

FIGURE 1 Brief summary of the common compounds within the endocannabinoid system and exogenous cannabis, including the receptors and end-organ effects.[2–5] The strength of the interaction is indicated by the thickness of the arrow. 2AG, 2-arachidonoylglycerol; AEA, anandamide; CB1, cannabinoid 1; CB2, cannabinoid 2; CBD, cannabidiol; OEA, *N*-oleoylethanolamide; PEA, *N*- palmitoylethanolamide; PPARγ, peroxisome proliferator-activated receptor gamma; PUFA, polyunsaturated fatty acid; THC, Δ9-tetrahydrocannabinol; TRPV1, transient receptor potential vanilloid 1.

both fasted and fed states.[2] PEA has robust anti-inflammatory properties and has been shown to have anxiolytic properties as well.[6] There are other ω-3 PUFA–derived compounds that influence the ECs that are reviewed elsewhere.[7] The ECs has been involved in a variety of medical conditions extensively reviewed elsewhere, including obesity,[8] metabolic syndrome,[5,9,10] eating disorders,[11–13] type 2 diabetes,[14] neurological disorders,[15] gut-brain-axis disorders,[16] intestinal health,[17] and mood disorders.[18] Overall, the manipulation of the ECs can alter metabolism, overall health, and nutrition status.

The goal of this narrative review is to briefly summarize the body of literature regarding the ECs and provide a clinical overview regarding the ECs and exogenous cannabis use in nutrition.

Exogenous Cannabinoids

Exogenous cannabinoids include both organic forms and synthetic cannabinoids. Cannabis originates from a flowering plant of the family Cannabaecae divided into three main species; *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. The plant components can be used as cannabis products (marijuana) consisting of the leaves and flowers, and the stalks/stems and sterilized seeds are classified as hemp.[19] Two main compounds include Δ9-tetrahydrocannabinol (THC), which is the main psychoactive compound, and cannabidiol (CBD). THC is a partial agonist for both CB1 and CB2 receptors, whereas CBD mainly is a noncompetitive modulator of the CB1 receptor and inverse agonist of the CB2 receptor. However, CBD interacts with other neuroreceptors, leading to different clinical effects of these compounds.[20] In general *C indica* has more of a calming effect in users as there is less THC to CBD ratio compared with *C sativa*.[20] Cannabis can be taken in a variety of forms, including ingestion through oils or edibles, smoking or vaping, and topical, such as CBD creams. Smoking cannabis leads to a higher level within the bloodstream more quickly and consistently than ingesting orally or topical use (Table 1).[21,22] The most common adverse effects of using cannabis include dizziness, nausea and dry mouth with THC-predominant formulas and diarrhea, somnolence, and nausea for CBD-predominant.[20]

In a study assessing the CANNUSE database of traditional cannabis use from an ethnopharmacologic perspective, 75.4% was reportedly for medicinal purposes for treatment of nutrition disorders, nervous system and mental health disorders, and pain and inflammatory conditions.[23] In a North American study, 27% of

TABLE 1 Different formulations for exogenous cannabis and pharmacokinetics.[21,22]

Formulation	Time of onset	Duration of effect	Uses	Downfalls
Inhalation	3–10 mins	2–4 h	Pain, anxiety, nausea, insomnia	Lung irritation, cough
Oral	1–3 h	4–12 h	Pain, anxiety, nausea, insomnia	Dry mouth, diarrhea
Sublingual	15–60 mins	4–6 h		Lower bioavailability due to first pass liver metabolism
Topical	5–120 min	Variable	Pain	Skin irritation

self-reported cannabis users claimed use for medicinal purposes; the most common physical ailment was pain (53%) and mental health ailment was anxiety (52%).[24] The proportion of cannabis users were higher in US legal recreational states as compared with US legal for medicinal use only.[24] A recent systematic review demonstrated the most robust evidence for the use of exogenous cannabis as a treatment was for chemotherapy-induced nausea and vomiting, neurological conditions, and non-diabetic neuropathic pain.[25]

There are currently three US Food and Drug Administration (FDA)–approved synthetic cannabinoids for medical use: dronabinol, nabilone, and an oral cannabidiol solution (Epidiolex).[25] Nabiximols, which are oral mucosal sprays of 1:1 ratio of THC to CBD, are approved in other countries for the management of pain and spasticity in multiple sclerosis.[26] A recent comprehensive systematic review highlights the clinical data on these medications.[25] Nabilone, a synthetic THC cannabinoid, is currently FDA approved for treating nausea and vomiting associated with cytotoxic chemotherapy.[27] Nabilone is classified as a schedule II drug with high potential for abuse/addiction; therefore, careful monitoring of use is advised.[28] Dronabinol is approved for use in nausea and vomiting associated with chemotherapy and for anorexia with weight loss in patients with AIDS- or HIV-associated wasting syndrome.[29,30] Studies have found increase in total body weight in patients with HIV taking dronabinol compared with placebo; however, the effect was modest.[29] Other benefits include increase in reported appetite and quality of life metrics.[27,29] Dronabinol is considered a schedule III medication with a low to moderate risk of abuse and/or addiction.[30] There have been other studies assessing the use of nabilone and dronabinol in other disease states, such as mental health disorders or pain with mixed benefits.[25,27] Epidiolex is a synthetic CBD oil that is approved for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome.[31] Common adverse events reported in taking synthetic cannabinoids include somnolence, decrease appetite, dry mouth, diarrhea, nausea, paranoid reaction, concentration difficulties, malaise, drowsiness, and abdominal pain.[25,27,28,30,31] A prior meta-analysis assessing adverse events with cannabinoid medication found lack of studies assessing long-term adverse events and the most common were neurological side effects, dizziness, euphoria, disorientation, and confusion on cannabis.[27]

Hemp is classified as containing <0.3% of THC and is available as seeds, oils, other food products, textiles, clothing, animal feed, and biofuel.[19,32] Hemp is generally recognized as safe by the FDA; therefore, is not under regulation like recreational and medicinal cannabis.[32] A recent study demonstrated that ingestion of various hemp oral products led to detection of cannabinoid metabolites in urine, suggesting influences on the ECs.[33] It is unclear if there are any lasting effects on the ECs with the use of hemp products. From a nutritional value, hemp seeds and oil have a high composition of fatty acids in an ideal ratio for ω-6 to ω3 PUFAs.[32] Prior human and animal studies found that hempseed oils led to a reduction in fat profiles and anti-inflammatory cytokines.[32] However, there are no current guidelines supporting the regular use of hemp seeds or hempseed oil as a nutritional supplement to prevent cardiovascular diseases or for its anti-inflammatory properties.[19] Longitudinal data may be helpful to assess for long-term effects of use of hemp products and the influence on the ECs through dietary PUFAs.[19]

With the increasing legalization of cannabis products across the United States, including 33 states plus the District of Columbia,[34] there is an increase in recreational and medicinal cannabis users.[35–37] There has also been an increase in marketed hemp products as well as CBD-containing foods products that are not currently regulated by the FDA.[19,32]

CANNABIS AND NUTRITION

Endocannabinoids and nutrition

It is known that CB1stimulation and increased endocannabinoid concentrations leads to lipogenesis and adipogenesis.[3,5] Centrally, it is related in the control of hedonic eating,

or eating based on pleasure and reward network,[11] which can influence dietary intake. A prior study found a positive correlation between intuitive eating, defined as eating behaviors based on physical or physiological signaling, and other ω-3 PUFA compounds independent of body mass index, age, or oral fatty acid intake.[38] However, there were no significant changes in AEA, 2-AG, OEA, and PEA in a healthy population.[38] It is unclear what the long-term changes associated with eating behaviors in relation to changes in the ECs will look like for disease prevention and/or treatment.

In terms of dietary composition, levels of AEA and 2-AG alone in food are clinically insignificant.[39] Other endocannabinoid-like molecules are mainly derived from ω-3 and ω-6 PUFAs, which can be optimized in the diet.[7] Preclinical mouse research demonstrated that a diet deficient in ω-3 PUFAs led to an increase in 2-AG levels in the brain that resolved with supplementation.[40] Other studies have shown that dietary changes with high ω-3 PUFAs and low ω-6 PUFAs led to decreased 2AG levels compared with a low ω-6 PUFAs diet alone.[41] Other studies found the Mediterranean diet led to a lower ratio of ω-6 to ω-3 PUFAs that can influence the levels of ECs in the bloodstream.[42] A recent randomized clinical trial in individuals with obesity found that 8 weeks of the Mediterranean diet led to increased ratios of both OEA/AEA and OEA/PEA while decreasing AEA plasma concentrations.[43] Another study assessed long-term effects of the Mediterranean diet and found a persistent decrease in 2-AG concentrations and increase in OEA/PEA ratio after 3 years.[44] They also found sex difference in ECs, in which OEA/AEA ratios in women and OEA/PEA ratios in men were associated with >8% weight loss.[44] It is unclear the duration of adherence to make long-term changes, as even a 3-day Mediterranean diet intervention led to altered plasma endocannabinoid levels in healthy controls.[45]

Intravenous lipid emulsions within parenteral nutrition contain different concentrations of ω-3 and ω-6 PUFAs depending on the formulation.[46] Preclinical data demonstrated that ω-3–enriched parenteral nutrition in mice and in vitro studies altered endocannabinoids levels and subsequent inflammatory cytokines.[47] Two meta-analyses demonstrated that ω-3–enriched parenteral nutrition led to significant risk reduction in infection and reduction in mean days in the critical care unit and hospital days in both hospitalized and critical care patients.[48,49] A more recent randomized control trial on combination of ω-3–enriched enteral with supplemental parental nutrition led to increase in catecholamine-free days in critically ill patients in the intensive care unit.[50] It is unclear if the clinical benefit derives from manipulation of the ECs through ω-3 metabolites.[7] Future studies incorporating the measurement of both clinical data and biochemical metabolites related to the ECs may provide mechanistic insight.

Manipulation of the gut microbiome can also be a mediator in plasma concentrations of the ECs components.[45,51] In a germ-free mice model, there was evidence of increased CB1 receptors mRNA expression in the small bowel that resolved after fecal microbiota transplant.[52] In a clinical study, it was found that AEA and OEA were positively associated with alpha diversity, or richness of bacterial taxa, and with short-chain fatty acid–producing bacteria, such as *Bifidobacterium* and *Faecalibacterium*, and negatively associated with pathogenic bacteria (ie, *Escherichia, Shigella*).[53] It was also found that AEA and PEA correlated with reduced levels of proinflammatory cytokines (tumor necrosis factor-α and interleukin-6), mediated in part by short-chain fatty acids.[53] Another study found that exogenous PEA in vitamin D–deficient mice increased *Akkermansia muciniphila*, which has been shown to be protective in obesity and diabetes.[54] These studies allude to crosstalk between the ECs, nutrition status, and the immune system, which are mediated in part by the microbiome both in healthy and disease states.[51,55,56]

Overall these findings suggest that nutrition interventions through optimization of dietary PUFAs or though nutrition support and manipulation of the microbiome have implications in altering the ECs. However, it is unclear where nutritional intervention fits in the treatment and management for overall health and disease states.[57]

Exogenous cannabis/ECS mediators and nutrition

Despite FDA approval for appetite stimulation in patients with HIV, the overall evidence for the effects of synthetic cannabinoids on increasing appetite is modest. A systematic review of synthetic cannabinoids suggested a high risk of bias of the existing studies for the treatment of nausea/vomiting in patients receiving chemotherapy and weight gain in patients with HIV.[27] A prior study noted that the use of dronabinol did increase appetite and weight compared with placebo; however, the effect was modest (increase average weight from 0.4 up to 1.3 kg).[58] A prior randomized control trial noted that the weight gained in patients with HIV using dronabinol was mainly fat mass.[59] The use of synthetic endocannabinoids has not been shown to be effective in increasing caloric intake, weight gain, or appetite in cancer patients with cachexia in systematic reviews.[25,60,61] However, these meta-analyses pooled exogenous endocannabinoids

and synthetic endocannabinoids, so the reliability of the data is limited given high heterogeneity, and further research is needed.

CB1 blockade is an area of ongoing research for the treatment of obesity. A prior drug, Rimonabant, a potent CB1 antagonist, was pulled from the market because of significant psychiatric adverse events.[62] A prior study on diet-induced obesity in mice found decreased weight gain in chronic treatment with THC that seems to be mediated by a dose effect on the *Firmicutes* to *Bacteroidetes* ratio in stool samples, an effect not seen in lean mice.[63] Another study determined crosstalk between glucagon like peptide-1 and CB1 receptors in a preclinical mouse model that may shed light on the mechanism of treating obesity with glucagon like peptide-1 inhibitors.[64] Overall, further studies are needed to assess the role of manipulating the ECs through CB1 in the treatment of obesity.

In terms of cannabis use, there are limited studies on assessing CBD-predominant formulations for the treatment for nausea, vomiting, and cachexia.[20] Smoking cannabis was found to significantly increase weight in patients with HIV compared with placebo, but it was not as effective as dronabinol.[59] A randomized double-blind control study found no difference in amount of weight gain with placebo compared with either CBD/THC-mixed cannabis oil or a THC oil alone in patients with cancer cachexia.[65] However, in nonrandomized trials, a subjective significant increase in appetite scores (>30%) in patients with cancer cachexia was found when using cannabis.[66]

Chronic cannabis users aged 20–59 years reported a poor-quality diet as per the Healthy Eating Index 2010 scores within the NHANES 2005–2016 cohort compared with never users.[67] This same study also assessed Healthy Eating Index 2015 scores and found significantly better sodium scores, but lower reported ingestion of total vegetables and fruits.[67] An explanation may be for hedonic behaviors being influenced by cannabis use with increase high-calorie foods and percentage of calories from carbohydrates.[68] Cannabis use was associated with increased plasma levels of both ghrelin and leptin in adults with HIV, suggesting influence on appetite hormones.[69] Another explanation could be taste alterations, as a recent retrospective study of >1200 participants found that chronic cannabis smoking was associated with a decrease in bitter and salt perceptions on whole-mouth taste testing.[70] Altered taste receptors could lead to dietary changes; however, the role of edible or oral formulation of cannabis on dietary quality is unclear.

Overall, the evidence for synthetic or exogenous cannabinoids is inconsistent and limited by poor-quality studies with high risk of bias.[25] These major limitations in the evidence impedes nutrition clinicians in recommending these synthetic cannabinoid or cannabis as an appetite stimulant or to treat nausea and vomiting that may influence oral intake and nutrition status. More evidence is needed for the use of these medications for nutrition optimization.

Exogenous cannabis-induced conditions/ adverse events

Adverse events of long-term cannabis use includes conditions such as cannabis use disorder, cannabis-induced psychotic disorder, cannabis-induced anxiety disorder, cannabis-induced sleep disorder, and cannabis hyperemesis syndrome (CHS).[71,72] Cannabis use disorder is characterized by problematic pattern of cannabis use leading to distress or impairment in daily activities associated with significant cravings and inability to cut down on cannabis.[71] In a recent study of reported cannabis users in a US cannabis recreational legalized state, the prevalence of cannabis use disorder was 21.3%, with a higher prevalence of severe cannabis use disorder among recreational users (7.5% compared with 1.3% in medical users).[73]

CHS is a subset of cyclical vomiting syndrome.[74] Classified by distinct medically refractory vomiting in the setting of long-term cannabis use, people who experience CHS have distinct relief by hot showers or baths.[75] CHS is typically seen in daily users and can occur at any point of time after initiation, with a lag period up to 16 years. It is unclear which subset of cannabis users will develop CHS or what type of cannabis is more associated with CHS.[75] Symptoms can be severe, leading to dehydration, electrolyte disturbances, and hospitalization.[74] There are limited studies on the impact of CHS on overall nutrition status and need for nutrition support. There has been an increase in hospitalization for CHS in the United States, even in nonlegalized states.[35] The mainstay treatment includes intravenous fluid support, antiemetics, and withdraw of cannabis products. The duration in timing of abstinence from cannabis is dependent on number of episodes and amount of use, but consensus is minimum 4 weeks.[76] It may be difficult to convince users to stop cannabis use as a recent survey demonstrated that cannabis users reported higher efficacy of cannabis compared with other antiemetics.[77]

FUTURE DIRECTIONS

Current literature has made tremendous gains in clarifying the heterogenous role of the ECs in metabolism; however, gaps remain on the differences in sex and certain disease states. It is difficult to determine specific

profiles in individuals, and with the need for precision medicine, it is important to understand a specific individual's ECs tone and how dietary and/or exercise interventions can affect it. Currently, the role for measuring metabolites and the ECs levels in disease monitoring and treatment is unclear. Exercise is a known mediator of the ECs[53,78,79] and combination of exercise and nutrition support may help alter disease processes. As previously discussed, the role of manipulating the microbiome-ECs axis, in terms of metabolism and behaviors, is also being developed further.[55]

In terms of exogenous cannabinoids, there has been a consistent increase in the number of clinical trials on cannabinoids or cannabis-based medications since 2013, with majority sponsored by industry and focusing on use of cannabinoids on chronic pain, metabolism, and neurodevelopmental disorders.[80] There has also been an increase in the number of patents of drugs and other applications, such as agriculture, for the *Cannabis* plant.[81] Others are also assessing the use of other ECs compounds, mainly PEA for its anti-inflammatory properties in treating gastrointestinal inflammation and promotion of health.[6] In terms of nutrition support, the role of ECs in the setting of parenteral nutrition is unclear, especially in terms of ω-3–enriched enteral and parenteral nutrition. Finally, there have been studies assessing the value of hemp use as a nutritionally beneficial additive in the food industry,[82] although long-term effects of hemp products on the ECs have yet to be determined. Overall, these advances highlight the growing field of better clarifying the ECs and use of exogenous cannabis on disease treatment and health.

CONCLUSIONS

This review provides a brief introduction to the ECs and the role of exogenous cannabinoids in nutrition status and metabolism. Manipulation of the ECs through exercise, microbiome, and dietary intake of ω-3 or ω-6 PUFAs may lead to treatment of nutrition-related diseases. The use of exogenous cannabinoids may not have robust influence on nutrition status and have adverse effects. Nutrition clinicians should be aware of the effects of cannabis on nutrition health, such as gastrointestinal symptoms that may influence dietary intake, quality of diet, and altered metabolism.

Many patients who use cannabis may not necessarily volunteer use to healthcare professionals. Therefore, it is important to approach the subject in a nonjudgmental way and clarify the amount and route used of cannabis products. Assessing for cannabis use is an important aspect of the nutrition assessment/care plan because of potential influences of cannabis on nutrition status.

With the increasing legalization of cannabis and marketed CBD-containing products, awareness of the ECs and use of cannabis/hemp products should be a vital aspect of the nutrition assessment. However more prospective studies are needed to better clarify the role of endogenous cannabinoids on nutrition to help develop guidelines for clinical care.

AUTHOR CONTRIBUTIONS

K. Condo and T. DeFlorville and L. Russell equally contributed to the conception and design of the review; L. Russell conducted the literature search, and all authors contributed to the interpretation of the literature; L. Russell drafted the article. All authors critically revised the article, agree to be fully accountable for ensuring the integrity and accuracy of the work, and for reading and approving the final article.

CONFLICT OF INTEREST STATEMENT

L. Russell received an honorarium from Takeda and Baxter and holds an investigator grant from Napo Therapeutics unrelated to this manuscript. The remaining authors declare no conflict of interest.

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