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Systematic Review

Guidelines for the clinical use of probiotics' and its limited value for gastrointestinal disorders

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ABSTRACT

Changes in gut microbiota composition are associated with a variety of gastrointestinal disorders, including inflammatory bowel diseases, diarrhoea and hepatic diseases. Probiotics, which are live microorganisms which can provide the host a health benefit when ingested, are widely used as a treatment to treat these gastrointestinal (GI) conditions by changing the microbiota's composition or behaviour. This analysis aimed to address show probiotics' minimal utility for GI conditions guidelines. The researcher used several papers and reviews from before. The findings of this study are a compilation of previous research, and Cochrane's systematic analysis of probiotics for GI disorders indicates that probiotics may have beneficial effects on diarrheal conditions and associated gastrointestinal symptoms. Finally, updated systematic reviews are required to reflect the entirety of existing research on probiotic treatments in the study. The results from the presented analysis would help to provide more reliable guidelines for the clinical use of probiotics' and its limited value for gastrointestinal disorders and recognize gaps in GI related probiotic research.

Keywords: Gastrointestinal, Probiotics, Medical conditions

INTRODUCTION

The World Health Organization describes probiotics as live microorganisms, which when consumed in adequate amounts confer health and benefit to the host. While most commonly eaten worldwide in the form of yogurt or other fermented dairy products, probiotics are present and distributed in many different forms including a wide range of dietary supplements and functional foods.[1] The ingestion of probiotics in their different forms is normal

and increasingly growing. Adults in the United States were found to use probiotic or prebiotic supplements, a fourfold rise since 2007.[2]

The increasingly popular use of probiotics is also reflected in sales figures that show they are one of the types of supplements that consumers most frequently buy. While overall growth in the nutritional supplement industry slowed in 2014 to 5%, probiotics rose 14.2% with revenues of nearly $ 1.4 billion.[3] A recent study found that 96% of hospitals used probiotics as part of inpatient clinical treatment, in addition to common use by consumers. The increasing use of probiotics in both hospitals and in the general public shows the rising relevance of clinical probiotic research to public health.

The AGA Institute, in its guidelines, looked at particular gastrointestinal disorders considered to have the most evidence supporting probiotic use: clostridioides diffici, inflammatory bowel disease, irritable bowel syndrome, gastroenteritis, and enterocolitis necrotizing in children. Let's look at what the evidence says in situations like these.

However, family doctors and their patients may be confused by a lack of specific instructions about when to use probiotics and the most appropriate probiotic for different gastrointestinal conditions. Probiotics play an important role in maintaining immunological equilibrium in the gastrointestinal tract through direct immune cell interaction. Probiotic efficacy can be species-, dose-, and disease specific, and clinical significance depends on the length of therapy.[4]

Over the last decade, probiotics witnessed a meteoric growth. The probiotic use is reported to have quadrupled in the United States alone. The US Food and Drug Administration do not consider probiotics to be a medicine. Consequently, the numerous admixtures, indications and distinct strains of probiotics in the branded items are essentially uncontrolled. This has prompted individuals to question what evidence supports their use. This question is aptly answered by the American Gastroenterological Association (AGA) institute in its clinical recommendations and by an accompanying technical analysis. The goal of this review is to summarize the results of previous research, which provide a solid overview of the existing evidence that we can apply in 2020 and further.[5-7]

METHODS

The findings of this study are a compilation of previous research, and Cochrane's systematic analysis of probiotics for gastrointestinal (GI) disorders indicating that probiotics may have beneficial effects on diarrheal conditions and associated gastrointestinal symptoms. Data were collected by using the keywords of the present study like probiotics, guidelines for the clinical use of probiotics', GI disorders, medical conditions associated with GI.[6]

RESULTS

Probiotics include microorganisms, most of which are bacteria similar to those naturally occurring beneficial bacteria in the human gut. Probiotics have been researched extensively in various gastrointestinal diseases.[6-7] The species most studied include *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces*. Probiotics have shown to be beneficial for acute infectious diarrhea, antibiotic associated diarrhea, *Clostridium difficile* associated diarrhea, hepatic encephalopathy, ulcerative colitis, irritable bowel syndrome, functional gastrointestinal disorders, and *Enterocolitis* necrotizing. In comparison, evidence exists that probiotics are not beneficial for acute pancreatitis and Crohn's disease. Probiotics are safe for babies, children, adults and the elderly, but caution is recommended in populations that are immunologically vulnerable. Although probiotics are widely used both by the general public and in clinical practice, evidence based inferences are currently being hindered by variability in both the probiotics used in clinical trials and in the interpretation of findings in those studies. This was the first description of the Cochrane probiotics analyses for medical conditions associated with GI. This review showed that the outcome variation appears to be related to the use of various forms of probiotics, doses, and durations of treatment in clinical trials that study probiotics. A wide range of probiotic species were tested in the trials, many of which did not specify the dose and an even greater proportion did not describe the strain. In certain cases where strain and dosage were specified different dosages were used in trials using the same probiotic strain.[8]

This analysis showed that positives of diarrhea related conditions were usually found. All four Cochrane reviews that obtained a "A" conclusion suggesting strong evidence of probiotic gain centered on the conditions associated with diarrhea. This possibly reflects the fact that these reports, released between 2010 and 2015, provide the most up to date and full image of evidence currently available. This review also reported a number of clinical trials in recent years that centered on probiotics.[8] This is significant because most of the 'C' reviews were published prior to 2011, and if they had more recent data, they would have made better conclusions (either 'A' or 'B'). The other three categories of GI disorders, Crohn's disease, colitis, and liver conditions, included Cochrane reviews which received a "C" conclusion suggesting that there was insufficient evidence available to assess the benefits from probiotics. Crohn's disease and colitis are two disorders associated with changes in the microbiota where primary treatment strategies concentrate on symptom alleviation, disease inactivation, and avoidance of relapses. There is also growing evidence to indicate a connection between changes in gut microbial composition and chronic liver disease. More specifically, probiotics

are used as a complementary solution to treating the dysbiosis associated with these conditions. Searches for newer probiotic trials for these conditions should be performed so that the Cochrane reviews can be revised if applicable, and the probiotic review results can represent the current basis of the results. It should be a priority to update those older reviews and to provide timely evidence.

The difficulty of probiotic impact on GI disorders is partially due to the fact that probiotics are incorporated into several different items, including foods, dietary supplements and functional foods. In addition, the word "probiotics" is also used as a catch-all term for probiotics, prebiotics (non-digestible food ingredients that can promote gut bacteria growth), and symbiotics (a mixture of probiotics and prebiotics). The types of probiotics used to include the strains, dosages, and duration of action have been highly variable, complicating conclusions drawn from probiotics research. It is extremely important to remember that the health benefits attributed to probiotics differ significantly by strain, the number of trials describing the strains used in the Cochrane reviews varied considerably. It is critically important that clinical trials define the strains of the species in the probiotic and do not include the species alone, given the widely varying stress-promoting health effects. Therefore, when these data are available, systematic reviews and meta-analyses can provide information on the strains of the probiotic organisms.[9]

In addition, most reports and included trials did not answer the question of product storage or the consistency of probiotics used in the trials. Most studies have also failed to establish the viability or microbiological identity of the probiotic species in the commodity that is possibly affecting subsequent outcomes. We found one analysis discussing the efficacy of the probiotics used in the trials, but this aspect was not discussed consistently via evaluations, likely because it was not discussed in the individual trials.[10]

In order to further complicate the interpretation of the results, there are more than 1000 different species and more than 3 million unique genes discovered within the microbiome. Additionally, microbiome diversity varies significantly between healthy individuals; however, the marked difference is more commonly observed among infants and appears to decrease. More specifically, novel bacterial populations such as *Bifidobacterial* and butyrate producing colon bacteria or *Akkermansia muciniphila* are currently being investigated for possible protective benefits due to regular interactions in adults with healthy microbiota, which may potentially be used as a treatment strategy to restore intestinal b. If the research pool around the microbiome grows, it will continue to investigate the role of these complex systems and probiotics within the human gut.[11]

In addition to the above mentioned concerns about the variability of the probiotics being tested, considerable heterogeneity was found among the Cochrane reviews with respect to the findings evaluated in the trials. For example, Goldenberg and colleagues stated that the definition of diarrhoea by primary investigators differed between studies; 9 different definitions of diarrhoea were used among the 23 clinical trials included in this Cochrane review. The use of consistent meanings for outcomes is critical because if the outcomes are somewhat different or described in distinctly different ways, they might not be suitable to include in a meta-analysis. Ideally, trials based on the same health condition and intervention should measure and collect the same clinically relevant results in a similar manner to allow pooling, meta-analysis and comparison between trials. Core outcome sets can be useful because they ensure that trials obtain the same findings in similar ways, which enhances the availability of the most interesting and applicable meta-analysis information.[12] One initiative focused on this work is the core outcome measures in effectiveness trials (COMET) which recommends providing a minimum set of outcomes to be assessed and reported on a specific condition in clinical trials.[13-14]

In Cochrane reviews, subgroup analyzes are often performed as a means of answering specific questions regarding certain patient or intervention characteristics that may explain some of the variability within the meta-analysis and expose discrepancies in intervention effects across subgroup variables. It is necessary for reviews to pre specify subgroup analyzes in order to prevent the results of the study from affecting the variables are being examined and thus may lead to misleading results. Approximately half of the reviews specified at least one subgroup analysis in the methods section in our overview of Cochrane systematic reviews; although in many instances insufficient data existed to perform the proposed subgroup analysis. Five of the fourteen Cochrane reviews aimed to analyze the form of probiotic used, including dose, organisms, or strain, and due to inadequate data were unable to do so. In order to translate these findings to clinical practice, clinical trials need to disclose this important information about the probiotics under review, especially given the wide variety of probiotics and dosages used in the randomized clinical trials. In addition, none of the studies mentioning subgroup research intended to analyze age gaps. This is an field which needs to be discussed in future studies given the age-related changes in the microbiome.[15]

This Cochrane-focused review of the impact of probiotics in GI disorders has several strengths. Cochrane reviews are known globally as the golden standard of evidence-based healthcare information. A dedication to accountability and mitigating bias by conducting robust peer review processes and eliminating conflicts of interest further reinforce the approach used by Cochrane. The partnership with Cochrane also maintains consistency by updating the reviews as new information arises. Strength

in Cochrane reviews is that the adverse effects are listed as a predetermined outcome. However, the Cochrane reviews did not discuss adverse effects by a significant proportion of the individual RCTs included. There was often no clear record of adverse events within the individual studies, so that data on adverse events could not be collected for review. This is important when considering probiotic safety, and adverse events should be included as a key measure of outcome in potential probiotic clinical trials.[16]

DISCUSSION

When we talk about probiotics, first we should describe what they are. The United States Food and Agriculture Organization and the World Health Organization describe probiotics as live micro-organisms that confer health benefits on the host when consumed in an adequate amount. That's the backbone of what those agents are meant to be doing. The guidelines concluded that there was not enough evidence to justify the use of probiotics outside of a clinical trial in patients with *C difficile* infections. There was, however, a conditional recommendation based on poor quality evidence that certain types of probiotics could be recommended in patients at risk for *C difficile*, including *Saccharomyces boulardii*, a number of admixtures with *Lactobacillus* and *Bifidobacterium*, and some species of *Streptococcus salivarius*.[17]

The guidelines are consistent with a 2017 Cochrane review that indicated the benefits of probiotics were guided by patients at high risk for *C difficile* rather than those at medium, indeterminate or average risk. There is evidence that probiotics in patients at higher risk of infection, such as those with indwelling lines, in the intensive care unit, or in immunocompromised states, should theoretically be avoided. Hence the use of probiotics as a method to prevent *C difficile* in patients that are not at high risk should be treated with some skepticism.[18]

CONCLUSION

The findings of this analysis of Cochrane 's systematic probiotic studies for GI disorders indicate that probiotics may have beneficial effects on diarrheal conditions and associated gastrointestinal symptoms. Although encouraging, more studies are needed to draw definitive inferences about the effectiveness of probiotics for colitis, Crohn's disease, and liver disorders. Among the factors that lead to the inconclusive evidence for these disorders is the variation in the results measured by clinical trials, the inconsistent nature of the documentation in the scientific literature on key aspects of the probiotics being tested, and the even greater variability in the composition and efficacy of the probiotics used in the studies. Future clinical trials of probiotics, systematic studies, and meta-analyses should also identify essential and sometimes unreported information including the organisms, strain, dosage, and manufacturing processes and storage conditions of the probiotics used in the study. Furthermore, future research will preferably also provide key outcome measures that are obtained in a standardized manner to allow a more reliable evaluation of probiotic efficacy. Future systematic studies should examine these aspects of the application of the probiotic, as well as whether patient characteristics (e.g. age, food consumption, antibiotic use, etc.) and length of treatment are linked to treatment impact. Finally, updated systematic reviews are required to reflect the entirety of existing research on probiotic treatments in the study.

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