Review article

PRESCRIBING PROBIOTIC DRUGS IN CLINICAL PRACTICE – ARE THEY INDICATED?

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ABSTRACT

The past two decades will be remembered for the rapid advances in our understanding of the significant role that the human microbiome plays in health, illness and longevity, but it remains a vast concept, one that is largely uncharted. Its contribution to human health is brought about by a myriad microbiome-associated physiological mechanisms complemented by its genetic ability, which is around 150 times that of the human genome. Many strategies are being devised to 'engineer' or augment an unfavourable microbiome. The use of probiotic products represents one of these strategies since they can augment the gut microbiome and improve health. However, their correct, effective and safe use is clouded by many variables. Probiotic drugs are used for two main reasons: mostly to improve general health but also in some illnesses for which evidence has been generated. The use of probiotic products to maintain general health is in most instances not supported by scientific evidence. Precision in the reconstitution of an unfavourable microbiome as in disease or the maintenance of a favourable microbiome is the ultimate goal. This is not possible at the bedside because of an incomplete understanding of the human microbiome. This could lead in turn to the overuse of unregulated probiotic products which may be ineffective or even harmful, as in the case of immunocompromised individuals. The aim of this article is to offer guidance on current best practices in prescribing probiotic drugs.

Keywords: probiotic drugs, prescribing

INTRODUCTION

Human beings want to enjoy health and longevity. The 1908 Nobel Laureate for Physiology and Medicine, Elie Metchnikoff, wrote: 'The majority of diseases begin in the digestive tract when good bacteria are no more able to control bad bacteria.'[1] This concept is not new, but scientific progress has been slow, until a decade or two ago when new DNA-based technology ushered us into the midst of an unprecedented rate of microbiome-related research and discovery. It highlighted the important role that endogenous microbial communities play in health. Microbiologists spent decades identifying and curbing the microbes that cause disease. Researchers are now investing vast resources in gaining knowledge of the microbial communities that maintain the human–microbial symbiosis and health. Such microbes are now commercially sold and prescribed with the promise of improved general health and the treatment of specific diseases.

It excites, but this tsunami of new information also brings unfounded generalisation and misunderstanding. The numerous microbiome-associated variables are often too many to simplify, whereas the tipping points of disease-associated microbial profiles in individual patients are not yet well defined. It is an intriguing emerging science that is still shrouded in uncertainty, non-standardised scientific processes, conflicting results, a lack of regulatory validation and a social hype that is often fuelled by profit-driven motives.

WHAT DEFINES A PROBIOTIC?

New terminology and definitions evolved along with the development of the science related to the human microbiome. The 'microbiome' refers to the collective genetic code of microbial communities. The viable microbes that form part of microbiomes are referred to as 'microbiota'. 'Prebiotics' are substances that are non-digestible by the host and result in specific changes to the composition and/or activity of the gastrointestinal microbiota that will again affect host health. 'Postbiotics' are lifeless products of the microbiome (either itself or its metabolites) that confer health benefits on the host.

An expert working group collaboration of the Food and Agriculture Organization of the United Nations and the World Health Organization (2002) defined probiotics as 'live microorganisms which, when administered in adequate amounts, confer a health benefit on the host'.[2] A review of the definition (2014) left it largely unchanged and captures the essence of probiotics as being microbial, alive (viable) and beneficial to health if administered in adequate amounts.[3] 'Synbiotics' combine probiotics and prebiotics appropriately in one preparation whereas 'synergistic

TABLE I: MINIMAL REQUIREMENTS FOR AN EFFECTIVE PROBIOTIC DRUG[3]	
KEY PROPERTY	MINIMAL REQUIREMENT
Living microbes	The microbes must be alive in an adequate number when administered.
Identification of microbes	Strains must be identified genetically, classified according to the latest terminology and designated by numbers, letters or names.
Studies	Designated studies which are sized appropriately must be performed to designate a strain as a probiotic and using the strain(s) on the host for which the probiotics are intended.
Indication	Strains shown to confer a benefit for one condition may not have probiotic effects for another application.
Animal studies	Strains which have probiotic effects in human beings but are being used in animal studies should be clearly designated as human probiotics under experimental testing.

synbiotics' are a combination of a selected probiotic with a specifically selected prebiotic to confer a documented health benefit. It is important to note that prebiotics, postbiotics and non-viable microbes are not probiotics since they contain no viable microorganisms.

Prebiotics are often added to food and to some infant formulas. Postbiotics are present in a variety of foods and form part of fermented infant formulas. The commensal gut microbiota are often the source of probiotic strains, but only those strains that are specifically isolated and credibly identified for the health benefits that they confer may be labelled as probiotics.

The same applies to 'live cultures': they may contain probiotics, but not all live cultures are probiotics. The probiotic label may be added only when the microbial content is specifically defined and confirmed to confer health benefits. True probiotics are therefore identified by the genus, species, subspecies (if applicable) and an alphanumeric designation to identify the specific strain.[4]

The term 'probiotic' should be reserved for specifically identified live microbial strains that have been shown in controlled human studies to defer either a general or a specific health benefit to the recipient when administered at an effective dose.

PROBIOTIC-CONTAINING PRODUCTS

Probiotic-containing products are broadly classified (and marketed) in three categories: probiotic-containing foods, probiotic dietary supplements and probiotic drugs (biotherapeutic products).[5] The last of these in particular contain live microorganisms and are categorised as probiotic *drugs* because of their formulation and health claims for a population which is diseased or pre-diseased.[5] This is in contrast with the first two categories which are indicated for maintenance of general health.[5] On a global scale, regulatory guidelines for probiotic products are complex and not standardised, so that stakeholders and the public may have a poor understanding of the different categories and their indications, and the side-effects.[6]

For medical practitioners to be assured that their patients receive the intended prescribed probiotic, its label should specify the following:[7]

- Ingredients/allergens.
- Genus, species (subspecies) and strain of the probiotic.
- Viable count in colony-forming units (CFUs), as total count and counts for each strain should be guaranteed until the end of shelf life.
- Daily dosage, that is, the amount to be consumed daily.
- Claim or recommended use to substantiate the scientific background.
- Storage information to specify how to store the product in order to maintain the potency of the probiotic.
- Best-before date to provide information on how long the probiotic product will contain an adequate amount of probiotics to deliver any claimed benefit.
- Company name or contact information to enable consumers to contact the company for more information and to report adverse effects.[8]

A probiotic product from all three categories must be characterised, safe, be produced following quality-control measures, meet its specifications, be lawfully marketed and be adequately labelled according to the intended use with truthful messages that are supported by verifiable data.[5] Safety remains the bare minimum key factor.[5] An essential general requirement is the monitoring of adverse events and the reporting of serious ones.[5]

Other probiotic products for human consumption have also become commercially available in recent years. These include (apart from the already mentioned probiotic foods, probiotic dietary supplements and probiotic drugs) probiotic medical foods, non-oral probiotics, defined microbial consortia and probiotic infant formula.[3]

Consumers are buying these probiotic products. The monetary value of the global probiotic market was estimated at US$77.1 billion in 2022 and the projected annual market growth for the next decade exceeds the most optimistic fantasies for global economic growth at an annual rate of 8,1%.[9,10]

In practice, the following sequence of events usually unfolds following the acquisition of probiotic products by consumers:

- A consumer visiting a local pharmacy, supermarket or health shop is faced with shelves of probiotic products, each with promises of improved health but not supported by acceptable levels of evidence.
- Searches into the safety and efficacy of probiotic products usually leave consumers with a disclaimer that directs them to first seek the guidance of their medical practitioners before taking them.

TABLE II: GASTROINTESTINAL DISORDERS FOR WHICH PRESCRIPTION OF PROBIOTIC DRUGS MAY OR MAY NOT OFFER BENEFIT.

INDICATION	ESPGHAN RECOMMENDATION (QUALITY OF EVIDENCE)	AGA RECOMMENDATION (QUALITY OF EVIDENCE)
Treatment of acute infective diarrhoea	Conditional weak (low)	None (moderate)
Prevention of antibiotic-associated diarrhoea	Conditional to strong (moderate)	Conditional for specific probiotics (low)
Treatment of *Clostridioides difficile*-associated diarrhoea		Only in context of a clinical trial (knowledge gap)
Treatment of Crohn's disease	None	None (knowledge gap)
Treatment of ulcerative colitis	None	None (knowledge gap)
Treatment of pouchitis	None	Conditional for specific 8-strain probiotic drug (very low)
Treatment of irritable bowel syndrome	None	Only in the context of a clinical trial (knowledge gap)
Prevention of necrotising enterocolitis in premature infants <37 w	Conditional (low)	Conditional for specific probiotic drugs (moderate/high)
Treatment of infant colic	Conditional weak for breastfed infants (moderate)	
Prevention of infant colic	None	
Eradication of *Helicobacter pylori*	Conditional weak (very low)	
Reduction of pain intensity in functional abdominal pain disorders	Conditional weak (moderate)	
Treatment of functional constipation	Weak (moderate)	
Management of coeliac disease, small intestinal bacterial overgrowth & pancreatitis	No evidence	

(Summarised from the 2023 Position Paper of the ESPGHAN Special Interest Group on Microbiota and Modifications and the 2020 American Gastroenterology Association (AGA) Clinical Practice Guidelines)

Green background = adults and children; Yellow background = children only

And what do medical practitioners really know about probiotic products and their effect on the human microbiome, since microbiome science and probiotics do not form part of regular curricula? Medical practitioners themselves are also to blame for inflicting significant harm on the human microbiome. Common medical practices such as non-indicated caesarean deliveries resulting in failed exclusive breastfeeding and infant-formula supplementation, inappropriate antibiotic prescriptions and proton pump inhibitor overuse can lead to dysbiosis and downstream health consequences.[11] Ill-informed medical practitioners may then turn to probiotic products and even probiotic drugs to improve their patients' health and redeem the undesired side-effects of potentially harmful medical interventions. In most cases these products have not been subjected to scientific scrutiny in the form of randomised controlled trials and prescription is induced by medical representatives.

The aim of this article is to offer guidance on current best practices in prescribing probiotic drugs. The current evidence is mainly limited to the prevention and treatment of illness of the gastrointestinal tract (GIT).

PRESCRIBING PROBIOTIC DRUGS

Many microbiome 'engineering' strategies are under investigation for various medical indications for which probiotic drugs are used. Probiotic drugs are made to resemble pharmacological preparations and are on offer at pharmacies as 'medication'.

Certain health effects such as 'improved gut health' can be ascribed to probiotics in general. Probiotic examples for which non-strain-specific claims may be made include certain *Bifidobacterium* and *Lactobacillus* species when they are delivered at 1 × 10^9 colony-forming units (CFUs) per intake.[3]

But it is different when probiotic drugs are prescribed to be of benefit for specific medical conditions. The probiotic label is often abused and the prescriber must therefore guard against generalisation. Some probiotics may not benefit all health outcomes and the merit of probiotic drugs must be evaluated for their specific indications. The prescriber must be informed of the evidence supporting the benefit that it is being prescribed for. The onus is therefore on the prescriber to select a probiotic drug that contains specific live microbial strains which will effect a specific desired health benefit when administered in adequate doses; it must also have the minimum requirements to be effective (see Table I).[3]

Probiotic drugs are classified into three drug classes: (1) yeast probiotics, (2) bacterial probiotics and (3) bacterial spore probiotics. These drug classes differ in their properties, advantages and disadvantages. The prescriber should consider

properties such as viability in the gastro-intestinal environment (where gastric and bile acid may inhibit efficacy), susceptibility to and risk of acquiring resistance to co-prescribed antibiotics, ability to hinder pathogen adhesion, and possible alteration to the pre-existing gastro-intestinal microbiome.[12]

GUIDELINE-BASED INDICATIONS FOR PRESCRIBING PRPOBIOTIC DRUGS

The efficacy of a probiotic drug relies on a specific clinical indication and the correct choice of a specific probiotic strain at the strain's effective dose. Prescribers face many obstacles in choosing the correct product for the desired indication. The evidence is often of low quality backed by inconclusive meta-analyses due to the heterogeneity of trial designs. Products also often fail label claims.[13] Other problems such as die-off during storage, contamination and a lack of oversight by regulatory authorities raise scepticism even further and haunt the possible benefits offered by probiotic drugs. Healthcare providers are under the whip to offer sound advice and effective prescriptions, while probiotic drugs are generally not cheap. This leaves the prescriber in a difficult position, but several treatment guidelines now endorse or reject specific probiotic drugs for specific indications.

Probiotic drugs are central to the GIT. We focus here on GIT-based indications and tabulate the recommendations and quality of evidence as outlined in the 2023 guidance from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the 2020 guidance of the American Gastroenterology Association (AGA)(see Table II).[14,15]

No probiotic drug was found to be strongly recommended, supported by high-quality evidence as a possible therapeutic agent in the 13 GIT-related conditions listed in Table II. The highest (but conditional) recommendation is for the prevention of antibiotic-associated diarrhoea and it is based on evidence of low to moderate quality. Some probiotics may offer a potential benefit in reducing the severity and duration of acute infectious diarrhoea in children, but the quality of the evidence is also low. It is tempting to suggest probiotic prophylaxis in patients who are at risk of developing *C difficile* diarrhoea: there is moderate certainty that probiotics may be of benefit, but this indication also serves as a warning of potential probiotic side-effects.[16] Patients who are at risk of *C difficile* diarrhoea are often critically ill or immune-compromised and more prone to probiotic side-effects.

PROBIOTICS TO AID IMMUNE DEVELOPMENT AND PREVENT ALLERGY

Probiotics are often touted as a solution to immune regulation and deficit. A healthy GIT microbiome is key to immune tolerance and the development of adaptive immunity, but prescribing specific probiotic strains to treat or prevent specific forms of immune deficit has not been validated. The World Allergy Organization (WAO) supports a probable net benefit in allergy prevention from the use of probiotics to prevent eczema. The WAO suggests using probiotics in a pregnant woman at high risk of having an allergic child; in women breastfeeding infants at high risk of developing allergy; and in infants at high risk of developing allergy. These recommendations are again conditional and supported by very low-quality evidence.[17]

SAFETY OF PROBIOTIC PRODUCTS

Probiotic strains are usually isolated from the human gut microbiome or fermented food. Their pathogenic potential is therefore considered as low in healthy immune-intact individuals. But probiotics are living microbes and are unsafe in patients with compromised immune systems, patients with underlying disease and young patients under one year of age. Only probiotics with proven safety and efficacy should be prescribed to these at-risk patients and in accordance with best-practice guidelines and evidence-based reccomendations.[18,19]

CONCLUSION

Probiotic drugs must contain designated live probiotic strains in sufficient numbers to confer a health benefit that has been validated in at least two randomised controlled trials. The evidence related to the designated strains and outlined in published guidelines should be used to guide clinical decision-making and prescription. Various factors have rightfully left medical practitioners sceptical about the clinical application of probiotics, yet they are still prescribed liberally, seemingly without regard for their potential side-effects. Advances in our knowledge of the human microbiome should eventually facilitate its reconstitution in a personalised fashion to ensure precision and not in the current haphazard manner which is aggravated by the lack of regulatory control. Until such time as that is a reality, it remains prudent *not* to prescribe probiotic drugs in a manner which is non-indicated and non-evidence-based.

It follows that medical practitioners should have an *up-to-date* working knowledge of probiotic products as obtained from the medical literature. The prescription of probiotic drugs should then be in line with evidence-based indications and must be sourced from reliable manufacturers.

CONFLICT OF INTEREST

A van Niekerk is a speaker at Sanofi & Nutricia CME events. No further conflicts to declare.

This article has been peer-reviewed.

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