Keywords: Ulcerative colitis, Quality of life, Probiotics, Multispecies, Patient-reported outcome, Patient-centered care

Abstract

Ulcerative colitis (UC) is known to burden patients in ways that are not always clinically apparent and therefore easily overlooked in conventional treatment regimens. The medical needs of UC patients thus may be unmet, calling for novel patient-centered approaches to alleviate disease impact and improve quality of life (QoL). Probiotics are suggested as a safe and effective addition to current regimens, but the clinical evidence base appears insufficient to support efficacy verdicts. This study therefore qualitatively explored UC's impact on QoL from a patient perspective, and evaluated the potential of a multispecies probiotic for impact alleviation. Semi-structured interviews were held with 23 UC patients, who had either opted for a trial period with the multispecies probiotic Ecologic® 825 (n=14) or had not (n=9). The thematic analysis elucidates the broad nature of UC's impact, identifying 5 core impact domains and effects throughout. Furthermore, as patients' attitudes towards probiotics were predominantly positive, 57% of users reported positive impact of consumption, and the vast majority of these deemed this as (highly) relevant for improving QoL, the findings favor probiotic supplementation and warrant further clinical evaluation. In this regard, defecation frequency and stool texture seem promising outcome parameters for being most often reported.

1. Introduction

The incidence of Inflammatory Bowel Disease (IBD) has seen a rapid increase over the past decades, specifically in the populations of Western Europe and North America [1–3]. One of the most common forms of IBD is Ulcerative Colitis (UC), a chronic condition that is characterized by mucosal inflammation and ulcers on the inner lining of the human colon and rectum [4]. It is estimated that worldwide 150 out of every 100,000 people suffer from UC, although prevalence numbers appear to be positively correlated with the adoption of 'Western' dietary habits [1,5,6,7]. In the United Kingdom, for example, ten-fold higher incidence rates have been observed compared to Singapore, Korea or Japan [1,5,6,7]. Typical symptoms of UC include abdominal pain, tenesmus, (bloody) diarrhea, rectal bleeding, lack of appetite, fever and fatigue [4]. Furthermore, UC may manifest itself outside of the gastrointestinal tract, for instance in the form of episcleritis, uveitis, arthropathy or sclerosing cholangitis [8,9]. However, due to the disease’s relapsing and remitting clinical course, presented symptoms and their severity may vary significantly—both between and within patients [5]. Approximately half of patients are asymptomatic at a given point in time, whereas the other 50% suffers from mild to severe clinical symptoms [10]. In addition, an estimated 20–30% of patients develop an acute severe flare at some point during the course of their disease that requires urgent hospitalization and may present life-threatening complications [11].

Clinical management of UC is focused primarily on inducing and maintaining clinical remission [6,12]. To this end, the first line of treatment consists of aminosalicylates such as sulfasalazine or mesalazine, and in moderate to severe patients, corticosteroids are concurrently administered [6,11,13]. However, aminosalicylates are not sufficiently effective in maintaining remission rates [6,12], and repeated and long-term use of high-dose steroids is associated with
significant adverse events, such as adrenal insufficiency, osteoporosis, aseptic joint necrosis, depression or psychosis [14,15]. Furthermore, 30–40% of patients will likely not respond to steroids and require additional treatment with second-line therapies such as infliximab or cyclosporine [11]. These second-line therapies are associated with a significant risk of adverse events as well, including paresthesias, infection, nephrotoxicity, and abnormal liver functioning (Kohn, Daperno, Armuż et al., 2007; Sternthal, Murphy, George et al., 2008). Moreover, while inducing and maintaining a steroid-free clinical remission remains the standard of care [6], UC is known to burden patients in ways that are not always clinically apparent and may therefore easily be ignored [9,16]. In fact, it has been indicated that patients’ subjective experience of health and quality of life (QoL) is only poorly correlated with the physiological measures of disease impact as conventionally applied in the clinic [9,17]. A considerable body of evidence signals that conventional approaches in the clinical management of UC fail to capture the concerns, worries, inconveniences, and other less tangible impacts that are rooted in the disease [18,9]. Hence, it appears that the medical needs of UC patients are unmet, calling for novel approaches to alleviate the disease’s impact on patients’ QoL.

The intestinal microbiota may play a key role in the pathogenesis and disease mechanism of colitis [19]. Probiotic intervention has therefore been suggested as a safe and potentially effective addition to conventional treatment regimens for UC [20]. Probiotics reportedly promote (gut) health during their transient passage through the gastrointestinal tract by balancing or modulating the intestinal microbiota, improving intestinal barrier functioning, and affecting the host’s innate and adaptive immune response [20–23]. Clinical studies with probiotic intervention in UC patients have shown promising potential, demonstrating prolonged remission rates, reduced gastrointestinal complaints, and improved subjective experiences of well-being [24–26]. Despite these promising observations, however, it appears that the current evidence base remains insufficient to support clear efficacy verdicts due to the underpowered and heterogeneous nature of most clinical studies into probiotic effects [27–29]. As we have discussed before [30], this lingering uncertainty regarding therapeutic effectiveness represents a significant barrier to probiotic innovation and utilization. Considering the promising potential of probiotics for UC patients, well-designed randomized controlled trials are warranted to address this innovation barrier. Such trials should involve outcome parameters that are appropriate both in terms of their relevance to the specific wants and needs of UC patients and to the probiotic formulation at hand.

In order to guide these future trials, the current study aims to establish which types of factors shape UC patients’ subjective experience of QoL and, additionally, what parameters might be worthwhile to investigate in studies on probiotic intervention. To this end, we conducted an exploratory investigation in patients with UC, fully emphasizing the patient perspective by exploring the impacts of UC on QoL and the potential of a multispecies probiotic formulation to alleviate these impacts as perceived by patients themselves.

2. Methods

To meet the research objective, the current study took an interpretative, constructionist approach. In-depth semi-structured interviews and inductive thematic coding were used to capture and thematically analyze the subjective experiences and perceptions of UC patients, in terms of the disease’s impact on quality of life (QoL), specific probiotic effects, and the potential of probiotics in general. Not delimiting experiences and perceptions by pre-defined or measurable categories and thus allowing the inclusion of any relevant theme, the applied methodology particularly fits the highly integrated nature of the QoL concept—which makes it difficult to define and measure [31]—as well as the relationship between QoL and probiotics in IBD—which remains elusive [28].

2.1. Interview participants

The study was conducted in patient volunteers between 18–70 who had been clinically diagnosed with UC (> 1 year), had mild to moderate symptoms, did not suffer from comorbidity, and did not use probiotics. To optimize the likelihood of capturing all relevant themes, the number of interview participants was based on recommendations provided in the methodological literature on qualitative data saturation [32–34]. A lower prevalence threshold of 20% was applied for themes to be considered relevant. Accepting a 90% probability of capturing the least prevalent theme (i.e., power), and assuming an 80% chance of patients actually expressing a theme upon its occurrence, a minimum number of 14 participants proved to be required. Patients were recruited via online communication channels of the Dutch patient association for IBD, ‘Crohn & Colitis Ulcerosa Vereniging Nederland’ (CCUVN), in October 2016.

2.2. Probiotic formulation

At recruitment by CCUVN, interview participants were given the opportunity to opt for a sample kit of the multispecies probiotic Ecologic® W25 (Winclove Probiotics B.V., The Netherlands, available on the Dutch market as Winbiotic® PRO•IB), containing nine bacterial strains (Bifidobacterium bifidum W23; Bifidobacterium lactis W51; Bifidobacterium lactis W52; Lactobacillus acidophilus W22; Lactobacillus casei W56; Lactobacillus paracasei W20; Lactobacillus plantarum W62; Lactobacillus salivarius W24; Lactobacillus lactis W19) with a total cell count of 2.5 × 10^9 colony forming units (cfu) per gram. Sample kits contained 84 sachets, each containing a daily dosage of 3 g of the probiotic formulation (7.5 × 10^9 cfu per day in total) in powder form, to be ingested orally after dissolving in water, milk, or yoghurt.

2.3. Interview design

A single in-depth interview was conducted with each participant at least 6 weeks after the distribution of all sample kits by CCUVN, allowing for a sufficient period of daily consumption of the probiotic formulation—when opted for. All interviews were conducted by the same researcher, either face-to-face in the participant’s home setting or via telephone, taking into account the participant’s preference. A semi-structured interview guide (see Appendix for a translated example) was used to optimize (intra-rater) consistency. This guide was broadly structured according to the QoL impact domains as suggested by Devlen et al. [35] for IBD in general. Hence it provided a sensitizing conceptual basis for the exploration of patient experiences and perceptions in the context of UC, while enabling the emergence of any altered or novel themes and domains present in the studied population [36].

2.4. Primary study parameters

Subjective experiences and perceptions of UC patients regarding the impact of UC on QoL, probiotic effects on QoL, and probiotics in general were the primary outcome parameters in the present study.

2.5. Data-processing and analysis

All interviews were audiotaped and transcribed semi-verbatim (i.e., adhering to sentences and phrasing while editing grammatically incoherent content for purposes of clarity and readability) by the same researcher. Transcripts were coded and constructed into thematic categories in an iterative and comparative manner [37]. The resulting thematic framework was reviewed by two independent researchers and concurrently finalized.
3. Results

3.1. Interview participants

A total of 23 UC patients were included in the present study, 14 of which reported to have opted for and used the multispecies probiotic formulation Ecologix® 825 during the period prior to the interview (‘users’) and 9 of which reported to have not (‘non-users’). Characteristics of the interview participants are included in Table 1.

3.2. Impact of ulcerative colitis on patients’ quality of life

Patients were asked about the broad impact of UC on their quality of life (QoL). Five distinct core impact domains were identified upon thematic analysis of the interview data, i.e., ‘Physical’, ‘Psychological’, ‘Social Relationships’, ‘Lifestyle’, and ‘Daily Activities’. As visualized in the resulting conceptual model (Fig. 1), UC’s broad impact on QoL was shown to be highly integrated, with effects in a certain domain affecting other domains in turn (e.g., the physical effect of being fatigued causing the social-relationship effect of being unable to attend to the needs of a spouse, in turn causing the psychological effect of being worried about the relationship with a spouse). Furthermore, while treatment may obviously have a beneficial impact on patient QoL by alleviating UC’s direct effects in the five core domains, treatment-related effects take an inevitable share in the burden of living with the disease as well. Visualized by the mediating ring in Fig. 1, treatment-related and thereby indirect effects of UC were shown to affect all five QoL impact domains. The mean number of reported themes was significantly larger for female participants than for male participants (31.6 vs. 22.6; t(21) = −12, p < 0.05). Below, the most prevalent themes are discussed for each of the identified domains, as well as for treatment-related impact. An overview of all patient-reported impact themes and their absolute and relative reporting frequencies is provided in the appendix (Table A1).

3.2.1. Physical

Impact in the Physical domain relates to effects of UC perceived through the bodily senses as opposed to the mind. All 23 patients reported effects in the Physical domain, negatively impacting their QoL. The most commonly reported physical themes were being fatigued and therefore needing more rest (by 65% of total patient participants), bowel hypersensitivity to certain foods or drinks (61%), and an increased stool frequency or duration (43%).

3.2.2. Psychological

Impact in the Psychological domain relates to effects of UC perceived through the mind as opposed to the bodily senses. Again, all 23 patients reported to perceive psychological impact of UC, most often expressed as being worried or anxious about a variety of disease-related risks or imminent effects (by 91% of total patient participants), such as incontinence, developing cancer, disease progression, the need for a stoma, or having a flare. Furthermore, 70% of patient participants reported feelings of loss of control—primarily caused by the often inexplicable links between symptoms and causes and the unpredictable course of the disease—to negatively impact their QoL. In addition, patients frequently communicated the notion of being unable to meet their former (healthy) standards of living and expectations for life (43%), affecting their psychological QoL. Other frequently mentioned themes in the Psychological domain were a difficulty with identifying the properties of interactions with other individuals. Of the interviewed patients, 78% reported effects in this domain to negatively impact their QoL.

3.2.3. Social Relationships

Impact in the Social Relationships domain relates to effects of UC on the properties of interactions with other individuals. Of the interviewed patients, 78% reported effects in this domain to negatively impact their social QoL. Patients often reported being burdened by a lack of understanding of their health condition, resulting from unfamiliarity with UC and the invisible nature of the disease (52%). Other high-prevalent impact themes within this domain were restricted participation in social events and the associated social separation (43%), the need to explain the disease to others (26%), and being unable to attend to the needs of a spouse, family or friends (22%).

3.2.4. Lifestyle

Impact in the Lifestyle domain relates to effects of UC on the patient’s habits and behavior patterns. Of the interviewed patients, 70% mentioned lifestyle-related themes that hampered their QoL, all of which reporting some kind of behavioral or habitual change. The most prevalent of these were the restricted consumption of certain foods or drinks (52%) and the development of precautionary habits against sudden disease symptoms (17%). Furthermore, several patients (17%) reported a lack of spontaneity or excitement as a result of these modified behaviors to negatively affect their lifestyle-related QoL.
3.2.5. Daily Activities

Impact in the Daily Activities domain relates to effects of UC on the characteristics of the patient’s ‘daily doings’, including work, school, parenting, household, and leisure-related activities. All 23 patients reported that UC negatively affected their QoL via impact in the Daily Activities domain, with 52% of patients indicating the need to quit a job or cut down on working and 48% mentioning hospitalization as a burdensome effect. Other frequently reported themes were the need to schedule the day according to the impact of UC (43% of patients)—often exemplified by the need to plan for several moments of rest to battle disease-related fatigue—and the disease being present in all activities in some way or another, thus dominating daily life (39%). Furthermore, patients often reported the notions of having to balance and prioritize their daily activities, having to quit or cut down on sports activities, and suffering from impaired professional or academic performance as a result of UC (each 30%). Identified daily-activity effects were grouped into three thematic categories, i.e., ‘schedule and planning’, ‘travel and leisure’, and ‘occupational’. 

3.2.6. Treatment-related impact

Treatment-related impact relates to effects that are rooted in the interventions that are taken in response to the patient’s health condition. Treatment-related impact may therefore manifest itself in all of the five previously covered QoL impact domains, either indirectly by mediating UC’s impact in these domains or through direct effects (e.g., physical side-effects of medication). All interviewed patients reported alleviated UC impact as a result of treatment, whereas 91% of patients reported treatment-related impact to hamper QoL. Treatment-related impact themes were reported for all of the five domains, with the most prevalent theme being physical side-effects of medication (by 83% of patient participants) in the Physical domain. Other frequently reported themes were a difficulty in finding effective treatment (30%) hampering QoL via the Daily Activities domain, and being worried or anxious about a variety of treatment-related factors (26%), such as the long-term impact of drug regimens or combining medication with pregnancy, affecting QoL through the Psychological impact domain.

3.3. Probiotics for improving patients’ quality of life

Patients were asked about any recent experiences with the consumption of probiotics. Of the 23 interview participants, 14 reported to have opted for and consumed the probiotic formulation Ecologic® 825 during the period prior to the interview (‘users’). These participants were interviewed on the perceived impact of the formulation on their QoL.

3.3.1. Consumption characteristics

The 14 users had consumed the probiotic formulation for a mean total of 56 days at the moment of interviewing (Table 2). Ten reported to have consumed the formulation on a daily basis accordant to the general instructions for use, while three reported near-daily consumption (i.e., 5–6 days per week). One user reported to have consumed the formulation on a more occasional basis, being concerned about overstressing the intestine. Furthermore, one user reported to cease consumption of the probiotic formulation just prior to monitoring visits in the hospital, clarifying to be concerned that its potentially beneficial intestinal effects could persuade the practitioner to temper regular treatment, in turn increasing the chance of disease relapse. A summary of consumption characteristics is provided in Table 2.

3.3.2. Effects

Nine users (64%) reported effects following consumption of the probiotic formulation, of which eight users reported positive effects (57%; ‘responders’) and one user reported a neutral effect (7%), i.e., an effect that was noticeable yet neither positively nor negatively correlated to QoL. The remaining five users (36%) indicated to have experienced no effect at all. No negative effects were associated with the consumption of the probiotic formulation. Female users significantly more often reported effects (t(12) = 2.34, p < 0.05) and significantly more often reported positive effects (t(12) = 3.48, p < 0.01) than male users. Patient-reported effects were sorted according to the previously identified QoL impact domains (see 3.2) and are discussed over the paragraphs below. The Physical domain appeared to be most positively affected by probiotic consumption, with 57% of users (100% of responders) reporting positive impact in this domain. Additionally, two users (14% of users; 25% of responders) reported positive impact of probiotic consumption in the Psychological domain. Effects are visualized in Fig. 2, and a complete list of patient-reported themes regarding probiotic effects is provided in Table 3.

3.3.2.1. Physical

Nine users (64%) reported to have perceived physical impact of consumption. Effects relating to bowel habits were most prevalent, with 57% of users reporting themes within this category. In this respect, users most often stated to have experienced a decrease in stool frequency and an enhanced stool texture (29% of users; 50% of responders). Furthermore, three users reported other bowel-related effects, such as a decrease in abdominal pain and rumbling and the feeling of having more intestinal ‘resilience’ (14% of users; 25% of responders), for instance reflected in a quicker recovery from unpleasant intestinal sensations. Additional, less prevalent physical effect themes are included in Table 3.

3.3.2.2. Psychological

Two users (14%) reported to have perceived psychological effects, with one user mentioning a good and healthy feeling as a consequence of consumption (7% of users; 13% of responders), and another indicating happiness as a result of experiencing positive physical effects (idem).

3.3.2.3. Social Relationships, Lifestyle, and Daily Activities

No specific effects were reported for the Social Relationships, Lifestyle, and Daily Activities impact domains as defined in 3.2.3–3.2.5.

3.3.3. Effect relevance

Of the eight users reporting positive effects, four (29% of users; 50% of responders) indicated deeming these effects to be highly relevant in terms of improving their QoL, while three (21% of users; 38% of responders) reported the experienced effects to be moderately relevant in this respect. Of the latter three, one responder explained perceiving the effect of having stools with enhanced texture as a sign of increased intestinal health, rather than it directly improving QoL. Another explained the effect of a decreased stool frequency to be only moderately relevant, as stool frequency did only limitedly impact this user’s QoL. The third reported experiencing a relatively low impact of the disease on QoL during the period of using the probiotic, leaving only room for moderately relevant effects. Non-relevance was reported by two of the users experiencing effects (14% of users; 13% of responders), one of which had only experienced an altered stool scent and the other clarifying that the effect of enhanced stool texture, while positive, disappeared too rapidly to bear relevance. In conclusion, 50% of users or
88% of responders reported a relevant impact of consuming the probiotic formulation.

3.3.4. Attitudes towards probiotic consumption

Patients, both users and non-users, were additionally interviewed on their attitudes towards probiotic consumption. All 23 interview participants expressed a positive general attitude towards probiotics, frequently reported by users as a curiosity towards the potential beneficial effects on their QoL (by 64% of users, 0% of non-users; 39% of total) and by both users and non-users as a belief in the underlying theoretical rationale (21% of users; 44% of non-users; 30% of total). Furthermore, 44% of non-users and 7% of users (22% of total) reported to be positive yet cautious, awaiting convincing evidence of beneficial effects. With respect to the consumption of probiotics specifically in the context of managing UC, frequently reported themes by both users and non-users were perceiving no harm in trying probiotics (50% of users; 33% of non-users; 43% of total) and not having any major expectations in terms of effects (21% of users; 33% of non-users; 26% of total). Additionally, while several participants expressed to have no specific effect expectations (29% of users; 11% of non-users; 22% of total), 22% of total participants perceived probiotics as particularly relevant for symptom alleviation during periods of gut disbalance or flares, expecting mild alleviation of disease symptoms in general and therefore to feel slightly better overall. Furthermore, participants often stated to expect a difficulty in linking the use of a probiotic to any perceived effects (29% of users; 33% of non-users; 30% of total). With regard to probiotic products, especially non-users reported to perceive good products as often too expensive (7% of users; 44% of non-users; 22% of total), as well as having little belief in the quality and efficacy of cheaper probiotic alternatives (7% of users; 33% of non-users; 17% of total). A complete list of identified themes regarding attitudes towards probiotic consumption is included in the appendix (Table A2).

4. Conclusion and discussion

Here we have investigated the unmet needs of patients with ulcerative colitis (UC) from a patient perspective, by exploring the subjective impact of the disease on quality of life (QoL). The findings elucidate the omnipresent and highly integrated nature of UC’s broad impact on patients’ QoL, establishing effect themes throughout five interconnected core impact domains. In the Physical domain, bowel hypersensitivity to certain foods or drinks, increased stool frequency or duration, and fatigue were the most reported effects. Disease-related worries and anxieties, for instance about incontinence or developing cancer, and feelings of loss of control, for instance due to the unpredictable course and uncertain causes of UC symptoms, prevailed in the Psychological domain. Regarding Daily Activities, patients most often reported their QoL to be hampered by hospitalization, the need to quit or change jobs, and by being forced to schedule their daily life according to the disease’s symptoms. A lack of understanding of UC among others, together with restricted participation in social events were the most prevalent impact themes in the context of Social Relationships, and the modification of habits (e.g. restricting consumption of certain foods or drinks) was most often reported in the Lifestyle domain. Treatment-related effects were reported throughout the five impact domains, with physical side-effects of medication being the predominant theme.

Although no conclusions on causal efficacy can be drawn due to the
nature of the design, the findings favor the hypothesis of probiotic inter-
vention representing a safe and potentially effective addition to con-
tventional approaches for alleviating this impact and addressing the
unmet patient needs: Ninety-one percent of patients reported a burden
of their treatment, patients’ attitudes towards applying probiotics in
the management of their disease were predominantly positive, and over
half of UC patients who had consumed the multispecies probiotic for-
mulation Ecologic® 825 on a regular basis (‘users’) reported beneficial
effects (‘responders’). Probiotic effects on bowel habits were most
prominent, with half of responders experiencing a decreased stool fre-
quency as well as enhanced stool texture. Moreover, the vast majority
(88%) of responders deemed the observed effects to be relevant or even
highly relevant in terms of improving their QoL, whereas none of the
users reported negative effects of consumption. Though it should be
realized that the current study’s explorative design and limited number
of patients justifies only preliminary statements, these findings are
promising and warrant further clinical evaluation along the chosen
avenue. By clarifying effect themes throughout five interconnected core

Table 3
Half of total patient participants report probiotic consumption to improve their quality of life. Patient-reported themes regarding probiotic effects, and absolute and relative reporting frequencies.

| Reported themes | n | % | %b | %c | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|-----------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No effects reported | 5 | 36% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Effects reported | 9 | 64% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Neutral | 8 | 57% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Positive (responders*) | 1 | 7% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Negative | 0 | 0% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Relevance of effects reported | 4 | 29% | 50% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Reported effects moderately relevant for QoL | 3 | 21% | 38% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Reported effects not relevant for QoL | 2 | 14% | 13% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Specifications of effects reported | 9 | 64% | 100% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Bowel habits | 8 | 57% | 89% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● Lower stool frequency | 4 | 29% | 50% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● Enhanced stool texture | 4 | 29% | 50% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● More regular bowel movement | 1 | 7% | 13% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● Decreased urge | 1 | 7% | 13% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● Better bowel emptying | 1 | 7% | 13% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● Altered stool scent | 1 | 7% | 0% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Bowel-related (other) | 3 | 21% | 38% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● Less abdominal pain and rumbling | 2 | 14% | 25% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● Stronger / more-resilient / faster-recovering bowel | 2 | 14% | 25% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● Bowel less susceptible to stress | 1 | 7% | 13% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical (other) | 3 | 21% | 38% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● Feeling physically better overall | 1 | 7% | 13% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● More energetic / active | 1 | 7% | 13% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● Enhanced sleep | 1 | 7% | 13% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● Enhanced feeling of satiety | 1 | 7% | 13% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● Less itching | 1 | 7% | 13% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Fewer pimples | 1 | 7% | 13% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● Better lab results during monitoring check | 1 | 7% | 13% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Psychological | 2 | 14% | 25% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● Feeling good and healthy | 1 | 7% | 13% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ● Happy as a result of the positive effects | 1 | 7% | 13% | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

*a Absolute number of users mentioning the theme.
*b Percentage of total users (n = 14) mentioning the theme.
*c Percentage of responders (n = 8) mentioning the theme. Responders are defined as users who reported positive effects.

Table 4
Suggestions for future research based on limitations of the current study.

| Features of the current study limiting the ability to identify probiotic effects: | Suggestions for future research into probiotic efficacy: |
|--------------------------------|--------------------------------------------------|
| Inductive, qualitative design aimed at exploring patient perceptions, introducing the risk of positive bias. | Robust, randomized placebo-controlled design. |
| Patient-reported difficulty in confidently linking perceived effects to specific causes, complicating reports. | Intervention period that is adequate for substantiating hypothesized second-order effects. |
| Changes in external factors that were reported by patients to influence their UC symptoms (e.g. fatigue, stress, treatment regimen, dietary habits or supplements) during the period of probiotic consumption. | Apply event logs (e.g. daily diary apps) to establish a chronological chain of reports and shorten recall periods. |
| Several users reported a relatively low impact of UC symptoms during the period of probiotic consumption, leaving little to improve. | Assess these patient-specific factors beforehand, minimize the likelihood of and monitor for changes in their presence during intervention. |

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tervention representing a safe and potentially effective addition to con-
tventional approaches for alleviating this impact and addressing the
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(88%) of responders deemed the observed effects to be relevant or even
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avenue. By clarifying effect themes throughout five interconnected core

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impact domains, identifying patient-relevant probiotic effects, and gaining insight into patient attitudes and consumption experiences, the current study can guide the design of such clinical follow-up research.

4.1. Study and findings in context

It is increasingly recognized that the subjective perceptions of patients represent valuable outcomes for clinical research and practice, for patients harbor experiential knowledge that may offer unique insights into the effects of a disease and its treatment [38–40]. Hence, revealing these insights represents an important step towards achieving optimal patient-centered health care in any area of disease [41]. This holds particularly true however for the clinical management of UC, as our findings confirm that the burden of living with UC is comprehensive and includes intangible impact themes that may not always be apparent to the caregiver. Though there are several instruments available to these caregivers for assessing the health condition of UC patients (e.g., the Mayo Score [42], Ulcerative Colitis Disease Activity Index [43], IBD Disability Index [44], or Simple Clinical Colitis Activity Index [45]), many of these are limited to physical disease activity and symptomatology and therefore seemingly fail to account for the full burden of living with the disease [9,16,17,46,47]. This contributes to a gap in perception of health and QoL between patients and caregivers, plausibly impeding the ability of the latter to provide optimal, patient-centered care [48,49].

Several authors have called for the development of novel instruments that take a more comprehensive perspective on UC’s impact on the patient and consequently may address this gap [44,46,47]. Yet, the number of qualitative studies investigating beliefs, behaviors and needs from a UC patient perspective has remained limited [9,48]. While there are instruments in the context of inflammatory bowel disease (IBD) that expand on the conventional measures of disease by incorporating patient-reported outcomes (e.g. the IBD Quality of Life Index [50], IBD-Control Questionnaire [51], Manitoba IBD Index [52], Rating Form of IBD Patient Concerns [53], or IBD Numeric Rating Scale [54]), these generally do not differentiate between UC and Crohn’s disease [55]. Since there may be significant differences between the two disease indications, for instance in terms of disease behavior and natural history [56], hospitalization and emergency care use [16], and patient concerns [53], identical impact profiles should not be assumed. Moreover, it has been suggested that current patient-reported outcome measures (or PROMs) lack coverage with respect to patient-relevant and therefore vital impact constructs [35,46]. Having qualitatively explored impact on QoL from the perspective of UC patients, and thus having established a profile of patient-relevant UC impact themes, the current study may contribute to the development of a measuring instrument that is UC-specific and appreciative of previously underexposed impact constructs.

In this respect, our UC impact profile features notable departures from the current set of PROMs for IBD. First, it adds to several existing PROMs by providing an additional level of detail. For instance, compared to the IBD Quality of Life Index—a widely applied PROM that summarizes the patient’s physical, social and emotional health for the two preceding weeks—our profile includes additional patient-reports regarding UC’s impact on social functioning and regarding disease-specific worries, anxieties and their underlying reasons. Compared to the IBD-Control Questionnaire—a rapid, generic PROM that focuses on disease control within four core domains, being physical, social, emotional, and treatment functioning—our overview includes a dozen bowel-related UC symptoms, rather than aggregating bowel symptoms into a single impact item. Others such as the Manitoba IBD Index and IBD Numeric Rating Scale omit symptom-level information overall.

Whereas the routine application of PROMs in day-to-day disease management is likely to benefit from simplicity and ease-of-use [51], a comprehensive perspective on disease impact as provided here can reveal relevant targets for treatment intervention. To illustrate, in terms of treatment decision-making one can imagine the significance of knowing whether a patient suffers from worries as a consequence of drug side-effects or from worries about having a flare. Moreover, since the fit between existing PROMs and UC patient experiences is suggested to be imperfect [35,46], establishing additional levels of detail seems a necessary step that ought to precede construct prioritization and reduction. However, although the number of interview participants was based on recommendations for qualitative data saturation, we do not claim that the provided inventory of patient-reports is exhaustive. Future research should therefore complement and validate the identified UC impact constructs.

A second noteworthy departure from existing PROMs is the integrated conceptualization of five core impact domains and a distinction between UC’s direct impact and treatment-related (and as such ‘indirect’) impact on these domains. To our knowledge, this conceptualization represents one of the first attempts to consolidate the full burden of UC into a single framework. A holistic perspective on the burden of disease is important for not neglecting any patient-relevant constructs [35,46]. For IBD, Devlen et al. [35] similarly introduced a conceptual model of impact that is credited for its integrality and comprehensiveness. However, while Devlen et al. [35] visualize impact from treatment as a defined element in the consolidated picture of disease burden and this should be noted as an addition to the literature, it does so by portraying it amidst other impact domains. This might confuse the distinction between causes and effects and underexposes the possibility of treatment-related effects across the full range of impact domains. Supported by the patient-reports in the current study, we argue that treatment-related effects can occur in any impact domain, and that treatment should thus be visualized as an intermediary causal element between the disease and the impact domains—mediating the direct impact of the former on the latter, while also directly impacting the latter.

It has been indicated that current approaches in the clinical management of UC are limited for failing to address the full range of UC patient needs [9]. Moreover, many treatment options are associated with negative side effects [14,15], and indeed, 91% of patients in the current study reported a burden of treatment-related effects. Probiotics have been suggested as a promising approach to target these unmet medical needs [20]. Yet, the current evidence base remains insufficient to support clear efficacy verdicts due to the heterogeneous and underpowered nature of clinical studies along this line [27]. As concluded by a recent comprehensive review [57] past clinical trials with probiotics in UC have emphasized induction and prolongation of clinical remission as trial endpoints. These studies have yielded mixed results [23,58]: while some suggest efficacy for probiotics such as non-pathogenic *Escherichia coli*, *Saccharomyces boulardii*, *Lactobacillus reuteri*, or VSL#3, others have been less favorable. Furthermore, as discussed before, these parameters do not necessarily reflect the well-being of UC patients [9,17]. By allowing patients to freely express their experiences, the current study has induced impact constructs that appear to respond well to habitual consumption of the multispecies probiotic Ecologic® 825 and, moreover, simultaneously appear to be relevant in terms of improving QoL from the patient perspective. Positive effects were reported by 57% of users (‘responders’) and concerned primarily physical, bowel-related themes. A decrease in stool frequency and an enhanced stool texture were most often communicated, with 50% of responders
mentioning these effects. Considering that these two effects were regarded as highly relevant in terms of improving QoL by the majority (66%) of their reporters, these represent promising end-points for subsequent clinical trials.

4.2. Limitations and considerations for future research

Based on a consideration of the design, course and outcomes of the present study, this paper concludes with suggestions to optimize follow-up research.

First of all, while the current study’s inductive qualitative design fits the aim of exploring a broad range of patient perceptions, the lack of a control group may have contributed to a positive bias in reported probiotic effects. Additionally, while no effects were reported for three of the five identified impact domains, the highly integrated nature of UC’s impact on patients’ QoL (see 3.2) does indicate the plausibility of beneficial probiotic impact in these areas. For instance, one could anticipate a decreased stool frequency (Physical domain) to have an impact on a patient’s daily schedule (Daily Activities domain), when within this patient both the target symptom (i.e., increased stool frequency) and the probiotic effect (i.e., a decrease) are manifested at sufficient strength. Along the same line, while this too remains purely hypothetical, a stronger, more resilient bowel is intuitively linked to perceiving more liberty in consuming foods or drinks, plausibly alleviating the most frequently reported impact theme in the Lifestyle domain, i.e., restricted consumption of certain foods or drinks. Therefore, and needless to say, subsequent research aimed at investigating probiotic efficacy demands a robust, randomized placebo-controlled design. The finding that females significantly more often reported effects than males is noteworthy in this respect, and should be taken into account when comparing results between clinical trial arms. Furthermore, trial designs should include inclusion criteria that ensure the presence of targeted symptoms, as well as an intervention period that is adequately long for substantiating second-order effects. Moreover, it is recommended that such trials consider the stool frequency and stool texture of participants as one of their primary outcome parameters, as they were shown to be positively impacted by probiotic supplementation and may improve patient QoL in the Physical domain. In this regard, a continuous outcome superiority trial with probiotic supplementation versus placebo is arguably best suited to measure the differences between groups on these outcome parameters, contrasting our preliminary binary assessment.

Second, as with the impact of UC (see 3.2.2)—and in agreement with the earlier identified patient expectations regarding probiotic effects (see 3.3.4)—several users expressed a general difficulty in confidently linking perceived effects to probiotic consumption, complicating interpretation of their reports. The use of event logs to establish a chronological chain of reports (e.g. regarding effects, diet, medication, daily activities) and to shorten recall periods could address this complication.

Third, users provided insight into factors that they perceived as potentially confounding their observation of probiotic effects. Of the eight users reporting positive effects, one mentioned increased pressure at work as a factor that might have prevented the experience of a beneficial, alleviating effect on the significant impact of fatigue on this user’s QoL. Furthermore, two of these eight users reported to perceive a relatively low disease impact during the period of using the probiotic as potentially hindering the detection of more (beneficial) effects. One of these eight users reported the occasional use of a probiotic dairy drink (Yakult) as well as canabidiol oil as potentially affecting observations. Of the other users reporting no or a more neutral effect, three users similarly mentioned to perceive a relatively low disease impact as a factor that could have prevented the detection of probiotic effects. Two expressed other possible clarifications for their lack of perceived effects, being a relatively unhealthy eating habit during the period of use and the prior use of probiotic products. A complete list of confounder-related patient-reports is included in the appendix (Table A3). Taking these potentially confounding factors into account in the design of follow-up research could therefore improve the observation of patient-reported effects. Risks of confounding could for instance be reduced by qualitatively assessing the often highly patient-specific factors that are likely to influence disease symptomatology on patient intake, and subsequently minimizing the likelihood of- and monitoring for changes in their presence during the period of probiotic consumption. Suggestions for future research are summarized in Table 4.

Ethics statement

IB is employed by Winclow Probiotics B.V. as Manager Research Partnerships. EC is an independent consultant to several parties on probiotics, none of which are in direct conflict with the subject matter of this paper. All research procedures were performed in accordance with the Helsinki Declaration of 1975, as revised in 2008.

Conflict of interest statement

Ms. Isolde Besseling-van der Vaart, MSc is employed by Winclow Probiotics B.V. as Manager Research Partnerships. Professor Eric Claassen is an independent consultant to several parties on probiotics, none of which are in direct conflict with the subject matter of this paper. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Appendix A

Table A1

| Ultracerevol colitis hampers patients’ quality of life through five interconnected impact domains, via direct effects and indirect (treatment-related) effects. All patient-reported impact themes and their absolute and relative reporting frequencies are shown. |
|---|---|---|
| Reported themes | n<sup>a</sup> | %<sup>b</sup> |
| **Physical** | | |
| Bowel habits | | |
| ● Increased stool frequency or duration | 18 | 78% |
| ● Increased (sudden) urge, stool incontinence | 10 | 43% |
| ● Bloody / slimy stool | 9 | 39% |
| | 7 | 30% |

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Table A1 (continued)

| Reported themes | n | %b |
|-----------------|---|----|
| Diarrhea        | 7 | 30%|
| Irregular stool textures | 1 | 4% |
| **Bowel-related (other)** | | |
| Bowel hypersensitivity to certain foods / drinks | 14 | 61% |
| Abdominal discomfort, cramps, rumbling, bloating, flatulence | 9 | 39% |
| Abdominal pain | 8 | 35%|
| Increased bowel sensitivity to stress | 7 | 30%|
| Irritable bowel | 3 | 13%|
| Less resistant to antibiotic treatment | 1 | 4%|
| Sore anus | 1 | 4%|
| **Bowel (other)** | 22 | 96%|
| Fatigued, increased need for rest | 15 | 65%|
| Feeling weak, low energy levels | 8 | 35%|
| Malaise, feverish | 6 | 26%|
| Aching, joint / muscle aches | 5 | 22%|
| Impaired cognitive functioning, mentally fatigued | 4 | 17%|
| Nausea, vomiting | 3 | 13%|
| Weight loss | 3 | 13%|
| Headaches | 2 | 9%|
| Need for short meal intervals | 2 | 9%|
| Physical drug or supplement dependence | 2 | 9%|
| Pimples, pustules | 2 | 9%|
| Poor physical condition | 1 | 4%|
| Ceasing to menstruate | 1 | 4%|
| Allergic, hay feverish | 1 | 4%|
| Irritable bowel to light | 1 | 4%|
| Reduced vision | 1 | 4%|
| Puffy eyes | 1 | 4%|
| **Physical (other)** | 23 | 100%|
| Worry / anxiety | 21 | 91%|
| About incontinence | 6 | 26%|
| About developing cancer | 5 | 22%|
| About disease progression | 4 | 17%|
| About need for stoma / ostomy, impact of having a stoma | 4 | 17%|
| About having a flare | 4 | 17%|
| About treatment ceasing to be effective | 3 | 13%|
| About inability to cope / make a living | 3 | 13%|
| About inability to satisfy ambitions / achieve goals | 3 | 13%|
| About having to leave familiar environment / travel | 3 | 13%|
| About inability to raise kids | 2 | 9%|
| About health risk for fetus | 2 | 9%|
| About being stigmatized, seen differently | 2 | 9%|
| About being a burden to others | 2 | 9%|
| About lack of future treatment options | 2 | 9%|
| About death / shortened lifespan | 1 | 4%|
| About developing comorbidities | 1 | 4%|
| About becoming stressed | 1 | 4%|
| About menopausal impact on disease course | 1 | 4%|
| About impact on relationship with spouse | 1 | 4%|
| About becoming dependent on others | 1 | 4%|
| About physical impact of the disease | 1 | 4%|
| **Emotional (other)** | 12 | 52%|
| Feelings of loss of control / power / independence | 16 | 70%|
| Uncertainty about / inexplicability of causes and effects | 12 | 52%|
| Fluctuating, irregular nature / unpredictability of disease course | 11 | 48%|
| Having to adhere to rules set by the disease | 1 | 4%|
| Feeling dependent on understanding of others | 1 | 4%|
| Helplessness, powerlessness, discouragement | 5 | 22%|
| Embarrassment | 8 | 35%|
| Feeling embarrassed | 3 | 13%|
| About incontinence | 3 | 13%|
| About pimples, pustules | 1 | 4%|
| About frequency / duration of stool | 1 | 4%|
| Feeling dirty | 1 | 4%|
| **Embarrassment** | 8 | 35%|
| Feeling embarrassed | 3 | 13%|
| About incontinence | 3 | 13%|
| About pimples, pustules | 1 | 4%|
| About frequency / duration of stool | 1 | 4%|
| Feeling dirty | 1 | 4%|
| Emotional (other) | 12 | 52%|
| Depressive / down | 4 | 17%|
| Frustrated / sad about lack of understanding / willingness of others to understand | 3 | 13%|
| Irritable | 3 | 13%|
| Sense of unfairness / injustice | 3 | 13%|
| Feeling of letting others down | 3 | 13%|
| Feeling left out / let down by others | 2 | 9%|

(continued on next page)
| Reported themes | n  | %  |
|-----------------|----|----|
| **Self-concept** |    |    |
| ● Inability to meet former standards / expectations, having to lower standards / expectations | 10 | 43% |
| ● Difficulty with identifying as chronically ill | 6 | 26% |
| ● Inability to satisfy ambitions / achieve goals | 5 | 22% |
| ● Difficulty accepting disease | 4 | 17% |
| ● Inability to be who you want to be | 4 | 17% |
| ● Change in body image, lack of trust in body | 3 | 13% |
| ● Impaired self-confidence / trust in self-perception | 3 | 13% |
| ● Feeling let down by own body | 2 | 9% |
| ● Feeling useless | 1 | 4% |
| **Psychological (other)** |    |    |
| ● Omnipresence of the disease, continuity of its effects | 6 | 26% |
| ● Having to stop, while the world moves on | 3 | 13% |
| ● Reluctant to use medication | 1 | 4% |
| ● Distrust in ability / willingness of others to understand | 1 | 4% |
| ● Feeling pressured to explain disease and behavior | 1 | 4% |
| ● Feeling pressured to compensate for professional / social absence | 1 | 4% |
| **Social Relationships** |    |    |
| ● Lack of understanding due to unfamiliarity with / invisibility of the disease | 12 | 52% |
| ● Among spouse / family / friends | 3 | 13% |
| ● Among care practitioners / health and safety officers | 3 | 13% |
| ● Lack of willingness to understand among others | 1 | 4% |
| ● Being stigmatized, treated differently | 1 | 4% |
| **Communication** |    |    |
| ● Having to explain disease to others | 6 | 26% |
| ● Having to be cautious in communicating / unable to be transparent about being chronically ill | 3 | 13% |
| ● Receiving unsolicited lifestyle advice | 2 | 9% |
| **Social relationships (other)** |    |    |
| ● Restricted participation in social events, separation | 10 | 43% |
| ● Unable to attend to needs of spouse / family / friends | 5 | 22% |
| ● Altered network / types of friends | 3 | 13% |
| ● Alienation from spouse / family / friends | 2 | 9% |
| ● Being a burden to spouse / family / friends | 2 | 9% |
| ● Conflict with spouse / family / friends | 2 | 9% |
| ● Break-up / divorce | 2 | 9% |
| ● Becoming more self-centered in social relationships | 1 | 4% |
| ● Difficulty dating / finding a partner | 1 | 4% |
| **Lifestyle** |    |    |
| ● Modify habits / behaviors | 16 | 70% |
| ● Restricted consumption of certain foods or drinks | 12 | 52% |
| ● Developing precautionary habits (against sudden urge / incontinence, flares) | 4 | 17% |
| ● Maintain healthier, more health-conscious lifestyle | 3 | 13% |
| ● Lack of spontaneity / excitement / outgoingness | 4 | 17% |
| **Daily Activities** |    |    |
| ● Having to quit / cut down on sports activities | 7 | 30% |
| ● Inability to travel, homebound | 4 | 17% |
| ● Having to take into account the disease when travelling | 1 | 4% |
| **Occupational** |    |    |
| ● Having to quit / cut down on working, change jobs | 12 | 52% |
| ● Impaired professional / academic performance | 7 | 30% |
| ● Difficulty finding a job | 4 | 17% |
| ● Being turned down professionally due to chronic disease | 3 | 13% |
| ● Having to hide symptoms from colleagues | 2 | 9% |

(continued on next page)
| Reported themes | n  | %  |
|-----------------|----|----|
| **Reported themes** |    |    |
| **Treatment-related (indirect)** | 23 | 100% |
| UC impact alleviation | 23 | 100% |
| **Physical** | 21 | 91% |
| Physical side-effects of medication | 19 | 83% |
| More susceptible to colds / flu | 4 | 17% |
| Puffiness / weight gain | 4 | 17% |
| Alcohol intolerance | 3 | 13% |
| Oversensitive to sunlight | 3 | 13% |
| Eczema / itching / rash / dry skin | 3 | 13% |
| Hair loss | 2 | 9% |
| Acne | 2 | 9% |
| Muscle aches / acidification | 2 | 9% |
| Osteoporosis / arthrosis | 2 | 9% |
| Skin spots, bad skin | 2 | 9% |
| Weight loss | 2 | 9% |
| Hot flashes | 2 | 9% |
| Palpitations | 2 | 9% |
| Fatigue | 1 | 4% |
| Impaired sleep | 1 | 4% |
| Tinitis | 1 | 4% |
| Joint pain | 1 | 4% |
| Vascular disease | 1 | 4% |
| Nausea | 1 | 4% |
| Chest aches | 1 | 4% |
| Pinch eating | 1 | 4% |
| Shakiness / wobbliness | 1 | 4% |
| Headaches | 1 | 4% |
| Decrease in white blood cells | 1 | 4% |
| Colonoscopy: abdominal discomfort / pain | 4 | 17% |
| Colonoscopy: prep discomfort, nausea, malaise | 3 | 13% |
| Klysma use: discomfort, inconvenience | 2 | 9% |
| Post-infusion fatigue / malaise | 2 | 9% |
| Anaphylactic shock from infusion therapy | 1 | 4% |
| Drug habituation, decreased drug efficacy | 1 | 4% |
| **Psychological** | 13 | 57% |
| Worry / anxiety | 6 | 26% |
| About inability to combine medication with pregnancy, inability to raise kids | 3 | 13% |
| About side-effects / long-term effects of medication | 3 | 13% |
| About progression of side-effects | 1 | 4% |
| About receiving bad test results | 1 | 4% |
| About developing cancer when reducing medication | 1 | 4% |
| Psychological side effects of medication | 3 | 13% |
| Mood swings | 3 | 13% |
| Restlessness | 1 | 4% |
| Difficulty with the idea of being dependent on drugs | 3 | 13% |
| Feeling that medication harms as well / of poisoning the body | 3 | 13% |
| Feeling / reminded of being ill by medication / hospital visits | 2 | 9% |
| Colonoscopy: feeling vulnerable / embarrassed / anxious / stressed | 2 | 9% |
| Klysma use: feeling embarrassed near others | 1 | 4% |
| **Social Relationships** | 2 | 9% |
| Impact of side-effects downplayed by practitioner / found to be subordinate to treatment benefits | 1 | 4% |
| Hospital visits: require to be open about having the disease to colleagues | 1 | 4% |
| Hospital visits: give off impression of illness to colleagues | 1 | 4% |
| **Lifestyle** | 4 | 17% |
| Restricted alcohol consumption | 3 | 13% |
| Restricted sunbathing | 3 | 13% |
| Maintain healthier / more health-conscious lifestyle as a consequence of treatment adherence | 1 | 4% |
| **Daily Activities** | 7 | 30% |
| Difficulty finding effective treatment | 7 | 30% |
| Having to take into account medication at all times | 3 | 13% |
| Having to schedule daily life according to medication | 2 | 9% |
| Financial burden of care | 2 | 9% |
| Having to take into account medication when travelling | 2 | 9% |
| Administrative burden of care | 1 | 4% |
| Hospital visits: having to take days off, logistical burden | 1 | 4% |
| Constant need for monitoring check-ups | 1 | 4% |

*a Absolute number of patients mentioning the theme.

b Percentage of total patients (n = 23) mentioning the theme.
Table A2
Patients generally report a positive attitude towards probiotics and their potential role in managing their health state. All patient-reported themes regarding attitudes towards probiotics, and their absolute and relative reporting frequencies are shown.

| Reported themes | All (n=25) | Users (n=27) | Non-users (n=2) |
|-----------------|-----------|-------------|-----------------|
| **General attitude towards probiotics** | | | |
| Curious | 9 (39%) | 9 (64%) | 0 (0%) |
| Belief in theoretical rationale | 7 (30%) | 3 (21%) | 4 (44%) |
| Cautiously positive (still needs convincing, awaits evidence) | 5 (22%) | 1 (7%) | 4 (44%) |
| Confidently positive | 3 (13%) | 2 (14%) | 1 (11%) |
| Hopeful | 1 (4%) | 1 (7%) | 0 (0%) |
| **Probiotics in managing UC** | | | |
| No harm in trying, why not | 10 (43%) | 7 (50%) | 3 (33%) |
| No major expectations | 6 (26%) | 3 (21%) | 3 (33%) |
| Different than a drug | 3 (13%) | 1 (7%) | 2 (22%) |
| Expectant towards the long-term future regarding the relevance of probiotics in managing UC | 3 (13%) | 1 (7%) | 2 (22%) |
| **Expected effects** | | | |
| No specific effect expectations | 5 (22%) | 4 (29%) | 1 (11%) |
| Symptom alleviation / support during gut disbalance, flares | 5 (22%) | 4 (29%) | 1 (11%) |
| Attenuated symptoms, feeling slightly better overall | 5 (22%) | 2 (14%) | 3 (33%) |
| Healthy feeling | 3 (13%) | 0 (0%) | 3 (33%) |
| Enhanced stool texture | 3 (13%) | 2 (14%) | 1 (11%) |
| Becoming less dependent on drugs / conventional treatment | 3 (13%) | 1 (7%) | 2 (22%) |
| Less abdominal discomfort | 2 (9%) | 1 (7%) | 1 (11%) |
| Less flares | 2 (9%) | 0 (0%) | 2 (22%) |
| Effects expected to differ between patients | 2 (9%) | 2 (14%) | 0 (0%) |
| Not the one solution | 2 (9%) | 1 (7%) | 1 (11%) |
| Being less preoccupied with having the disease | 1 (4%) | 1 (7%) | 0 (0%) |
| Increased gut resilience | 1 (4%) | 0 (0%) | 1 (11%) |
| Increased energy level | 1 (4%) | 0 (0%) | 1 (11%) |
| Immune system support | 1 (4%) | 1 (7%) | 0 (0%) |
| Less diarrhea | 1 (4%) | 1 (7%) | 0 (0%) |
| **Effect valuation** | | | |
| Difficulty linking probiotic consumption to effects | 7 (30%) | 4 (29%) | 3 (33%) |
| Drugs expected to undo any potential beneficial effects | 2 (9%) | 1 (7%) | 1 (11%) |
| Hard to be sure about efficacy | 2 (9%) | 2 (14%) | 0 (0%) |
| Effects could be largely imperceptible | 1 (4%) | 1 (7%) | 0 (0%) |
| **Probiotic products** | | | |
| Good probiotic products often too expensive | 5 (22%) | 1 (7%) | 4 (44%) |
| Little belief in cheaper probiotic products | 4 (17%) | 1 (7%) | 3 (33%) |
| Complex probiotic formulations are better than simpler cheaper products | 3 (13%) | 1 (7%) | 2 (22%) |
| Product characteristics are subordinate to efficacy | 3 (13%) | 2 (14%) | 1 (11%) |
| Ease of use is an important factor in product choice | 2 (9%) | 0 (0%) | 2 (22%) |
| Type of carrier matrix is an important factor in product choice | 1 (4%) | 0 (0%) | 1 (11%) |
| Difficulty comparing products, due to indirect, delayed nature of effects | 1 (4%) | 1 (7%) | 0 (0%) |

Note: Patients may report multiple themes within a specific category, making the total number of reported themes exceed the total number of participants.
Table A3
Confounder-related reports. Users reported several factors that they perceived as potentially confounding their observation of probiotic effects.

| Reported themes | n | % | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|-----------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No potentially confounding factors | 5 | 36% | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Relatively low disease impact | 5 | 36% | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Mere occasional use of the study probiotic | 1 | 7% | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Fatigue due to pressure at work | 1 | 7% | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Unhealthy diet during period of use | 1 | 7% | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Prior use of probiotics products | 1 | 7% | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Increased medication | 1 | 7% | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Taken more rest | 1 | 7% | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Decreased milk consumption | 1 | 7% | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Increased stress due to illness of relative | 1 | 7% | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Occasional use of probiotic dairy drink (Yakult) and canabidiol oil | 1 | 7% | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

a Absolute number of users mentioning the theme.

b Percentage of total users (n = 14) mentioning the theme.

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