



Article

Physicians' Perception of Oral Nutritional Supplement Acceptance and Tolerability in Malnourished Outpatients: PerceptiONS Study

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1. Introduction

Nutrition plays a critical role in maintaining the health and wellbeing of individuals and is also an essential component of the healthcare delivery system [1]. The nutritional requirements of healthy individuals depend on several factors, including age, sex and activity [1]. An imbalance in nutritional intake leads to malnutrition [1], which arises from deficient energy and protein intake, and commonly occurs among community-dwelling individuals in developed countries [2]. Maintaining an adequate nutritional status as well as sufficient nutrient intake is key to health and quality of life (QoL) and is, thus, a prerequisite for wellbeing at older ages and a modulator of healthy aging, as defined by

the World Health Organization (WHO) [3]. Disease-related malnutrition has detrimental clinical effects, increasing mortality and morbidity and affecting the QoL, as well as having a high economic impact on the healthcare system [4].

Malnutrition is a common condition associated with a variety of pathologies. These include acute diseases such as infections, surgery and chronic conditions such as neoplasms or gastrointestinal disease.

Several conditions such as anorexia, nausea, increased catabolism and related digestive system disorders (dysphagia or malabsorption) may lead to malnutrition [5], and it is well established that malnutrition is associated with increased mortality in both acute and chronic disease [6]. Malnutrition prevalence is difficult to assess due to its different etiologies and the existence of more than one diagnostic tool [7]. The prevalence of hospital malnutrition can reach 30% according to the New Global Malnutrition Definition (GLIM) criteria and increases in the elderly [2,8]. Malnutrition is a frequent complication of a primary disease and should, thus, be adequately addressed due to the fact that the nutritional status of individuals affects their clinical outcomes [1]. Data on the prevalence of malnutrition and nutritional risk in the elderly across different healthcare settings show a wide range of malnutrition, oscillating between 8.5% in the community setting and approximately 30% in rehabilitation and subacute care conditions [9].

The elderly represent a large percentage of the population affected by malnutrition; however, other groups, such as cancer patients and patients with chronic conditions, are also at risk of becoming malnourished. Thus, malnutrition has been reported in 25–70% of cancer patients [7] and in 20% of the population with chronic diseases such as chronic obstructive pulmonary disease [10]. In this context, malnutrition is considered to be an important prognostic factor in cancer patients [11]. In this respect, cancer patients with malnutrition may suffer a negative clinical outcome, including premature death, with research reporting that around 20–30% of patients with malignancies die due to tumor-related malnutrition [11].

The diagnosis and assessment of malnutrition are still challenging and, therefore, it is often undiagnosed and untreated, despite the large population at risk and the associated burden [12]. Currently, more than 70 nutritional screening tools have been developed for use in hospitals to facilitate the evaluation of patients' nutritional status and predict poor clinical outcomes related to malnutrition [13]; however, practical and implementable clinical screening tools to support diagnosis are lacking [13].

The high-prevalence and adverse consequences of malnutrition call for the early identification of malnourished subjects and prompt and effective treatment [14]. The majority of patients with or at risk of malnutrition can be managed following different strategies, including: (1) dietary counseling as indicated in clinical guidelines, (2) increased dietary food consumption and (3) using convenient oral nutritional supplements (ONS) [14].

ONS are sterile liquids, semi-solids or powders, which provide macro and micronutrients, and are designed for oral consumption; thus, taste and format are important to improve patient adherence [4]. ONS utilization has been consistently associated with both patient-reported and clinical benefits, such as an increase in body weight (weighted mean difference 2.25 kg; 95% CI 1.7–2.7) and muscle strength, functional improvements (walking distances and activities of daily living), immune function and QoL [14]. Furthermore, several clinical trials conducted in hospital and community settings in a malnourished population receiving ONS showed a reduction in complications associated with malnutrition (RR 0.44; 95% CI 0.3–0.6), and lower mortality rates in comparison with routine care (OR 0.7; 95% CI 0.5–0.9) [14]. In addition to evidence supporting the benefits of ONS provided by clinical trials and observational studies, ONS use is also endorsed by the main scientific societies working in this ambit, such as the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), as an early approach to tackle malnutrition when enteral feeding is not contraindicated [15–17]. Moreover, ONS is also recommended in the perioperative period [18] for

cancer patients [18] and for patients with liver [19] and kidney disease [20], to mention but a few.

ONS are clinically effective in managing malnutrition if prescribed to malnourished patients or those at risk of malnutrition [15–17]. A recent systematic review indicated that ONS combined with dietary counseling in the elderly at risk of malnutrition is the most effective intervention, leading to increased dietary intake and weight [21]. These authors also explored whether the effects of intervention were influenced by study characteristics or participants' traits. Their results indicated that females as well as older and more underweight participants were more likely to respond to the intervention by increasing their energy intake [21].

Good adherence to ONS is important to achieve both clinical efficacy and cost-effectiveness [4]. The literature suggests adherence is variable, possibly due to differences in study design [4]. Adherence to ONS is usually hampered by individual flavor perception, which may limit oral intake [4]. Therefore, to improve adherence to ONS, recent efforts have aimed to develop novel ONS with flavors, texture and compositions according to patients' preferences [22]. ONS tolerability is another barrier to adherence since the development of gastrointestinal symptoms may lead to their discontinuation [23]. A recent systematic review found the adherence to enteral nutrition of hospitalized patients to be >80%, but this dropped to 50% in non-hospitalized patients [23]. ONS adherence may also depend on the amount, type and duration of supplementation [23]. Low adherence is not limited to ONS, and patients' adherence can be challenging even for persons with home enteral nutrition, where up to 10% of users fail to reach 80% of the prescribed total dose [24].

ONS provide a nutritional support option that is widely used and recommended in various clinical situations associated with disease-related malnutrition. This study aims to explore physicians' perception of patients' adherence, acceptance/satisfaction and benefits in malnourished outpatients receiving ONS in the Spanish public healthcare system.

2. Materials and Methods

PerceptiONS is a descriptive, cross-sectional observational study based on an ad hoc electronic survey designed to explore physicians' perception of malnourished outpatients' adherence, acceptance/satisfaction, tolerance and benefits of receiving ONS.

The study was led by a steering committee, composed of five Spanish endocrinological experts in malnutrition management. All the members of the steering committee were working in a hospital within the Spanish public healthcare system. They were selected based on their extensive experience in malnutrition management (supported by their participation in studies and/or publications in this field) and their willingness to participate in the study.

2.1. Study Participants

The electronic survey addressed physicians working in Spain's public healthcare system with experience in managing malnourished adult patients. Physicians were selected and invited to participate by the sponsor. Study participants were selected based on their expertise in malnutrition management and their readiness to participate in the study. Moreover, to provide a holistic view of the management of malnutrition in real-world clinical practice in Spain, healthcare professionals from different specialties (digestive, endocrinology and nutrition, geriatrics, hematology, internal medicine, medical oncology, radiation oncology and others) and healthcare areas were invited to participate.

Once the members of the PerceptiONS group had agreed to participate, they were provided with a personal access password by email and the link to the electronic questionnaire posted on a specific website developed for the project. The electronic survey included an electronic informed consent form, which participants had to read and accept before accessing the questionnaire; otherwise, they would not be able to participate in the project. The questionnaire was launched and made available between 1 January 2022 and 31 July 2022.

2.2. Electronic Survey

The steering committee developed the content and design of the electronic survey based on a literature review dealing with studies on the management of malnutrition with ONS in patients with a variety of pathologies.

The electronic survey explored each physician's perception of the experience of five malnourished outpatients that received ONS in their medical practices. The survey questions were grouped into two sections. The first one gathered information regarding the sociodemographic (age, sex and autonomous region) and professional characteristics (specialty and years of experience) of physicians. The second one included three blocks of questions to collect each physician's perception of the patient's experience with ONS. The first block contained two questions about the physician's perception of patient adherence to ONS. The second block comprised five questions about the physician's perception of patient acceptance or satisfaction. The third included two questions about the physician's perception of the patient's clinical improvement after taking the ONS. One of the questions included in this last block was an ad hoc question specific to each ONS. Finally, the basic characteristics of the patient such as age, sex, underlying pathology and time in treatment with the ONS were collected to characterize the sample. In order to obtain a full picture of the management of the malnourished patient in real-world clinical practice, a question was included to determine which pathology justified treatment with ONS (for all patients' pathologies, see Table S1).

The electronic survey included closed-ended questions (multiple choice) and 4-point Likert-type scale questions (not at all, a little, quite a lot, a lot) (for the full survey, see Table S2 in Supplementary Materials).

Each physician reported their perception of the experience of patients over 18 years of age with a diagnosis of malnutrition; non-palliative situation (>6 months life expectancy); without previous experience of ONS (3 months prior) or home parenteral nutrition; without a high degree of dependency or severe cognitive impairment. Patients started to receive one of the three different ONS at the physician's discretion: (i) hypercaloric, high-protein peptide-based ONS rich in medium-chain triglycerides (MCT) without fiber; (ii) hypercaloric, high-protein ONS enriched with HMB and fructooligosaccharides (FOS) or (iii) hypercaloric, high-protein diabetes-specific ONS with high mono-unsaturated fatty acids (MUFA), for a minimum of 30 days.

2.3. Statistical Analysis

A descriptive analysis using statistical software for data science (STATA V.14.2) was conducted. The mean and standard deviation (SD) were calculated for continuous variables, and frequency (n) and percent (%) were calculated for categorical variables.

The minimum sample size was estimated by using the formula of the population proportion estimation. The criterion of maximum variability was applied, with a 95% confidence interval and a 5% margin of error. A minimum sample size of 385 physicians' perspectives on patients was required.

Different subgroup analyses were carried out. The first one was according to the ONS prescribed by the physicians, the second one was performed based on the age of the patients (≤ 65 and > 65 years) and the last one according to the underlying pathology (pathologies were grouped into two categories: oncological or non-oncological pathologies).

3. Results

A total of 595 physicians were invited to participate in the study, of whom 573 completed the electronic survey and reported their perspectives of 2872 patients. However, due to incomplete survey data or to patients not receiving one of the three study ONS, 349 patients' experiences were excluded from the statistical analysis. Thus, the final analysis included data reported by 548 physicians on how they perceived the experience of a total of 2516 patients.

Most of the physicians participating were men (63.69%) with a mean age of 39.29 years (SD: 8.59) and a mean experience in the management of malnutrition of 10.36 years (SD: 8.25). Most of the Spanish regions were represented (Andalusia, 27.01%; Madrid, 23.18%; Valencian Community, 12.96%; Castile la Mancha, 6.75%; Castile and Léon, 6.39%, among others). Table 1 summarizes the sociodemographic and clinical characteristics of the physicians participating.

Table 1. Physicians' sociodemographic and clinical characteristics (n = 548).

Characteristics	% or Mean (SD)
Age, years, mean (SD)	39.39 (8.59)
Male, %	63.69
Experience, years, mean (SD)	10.36 (8.25)
Medical Specialty, %	
Digestive	7.30
Endocrinology and Nutrition	37.41
Geriatrics	14.23
Hematology	0.91
Internal Medicine	16.97
Medical Oncology	5.66
Radiation Oncology	10.77
Other *	6.75

* Other (>2%): General and digestive surgery and family and community medicine.

Physicians reported their perception of the experience of 2516 malnourished outpatients (53.58% men; 37.68% older than 75 years) who received the ONS for an average of 85.58 (SD: 24.65) days. Regarding the underlying pathology for which the ONS was prescribed by physicians, the most frequent one was digestive tumor (18.20%), followed by convalescent pluri-pathological patients (17.13%), oncology patients undergoing active chemotherapy or radiotherapy treatment (14.79%) and head and neck tumor/ear–nose–throat (ENT) surgery/maxillofacial (11.72%). Regarding the number of pathologies, 80.6% had one underlying pathology, 14.70% had two and 4.7% had \geq three pathologies (for all patients' sociodemographic characteristics, see Table S1).

When asked about the most frequent tool employed to evaluate patient malnutrition, the physicians most commonly named GLIM (30.88%), followed by Malnutrition Universal Screening Tool (MUST) (22.69%) and Mini Nutritional Assessment (MNA) (20.23%). A similar pattern of nutritional assessment tool use was observed among endocrinologists and nutritionists (N = 205/548) (48.70% GLIM, 25.18% MUST and 12.17% Subjective Global Assessment, SGA). However, a different pattern was revealed when analyzing the rest of the specialties (N = 343/548) (digestive, geriatrics, hematology, internal medicine, medical oncology, radiation oncology and others). Thus, we found that the most frequently used tool in these specialties was the NMA (28.23%), followed by MUST (21.16%) and GLIM (19.87%). Figure 1 shows the tools employed to evaluate patient malnutrition as well as the differences between endocrinologists and nutritionists versus the rest of the specialties.

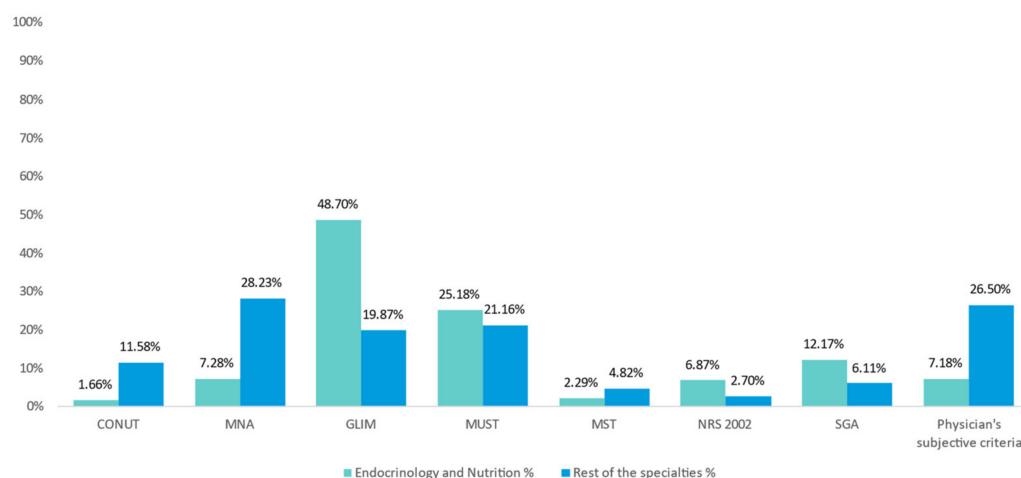


Figure 1. The tool employed to evaluate patient malnutrition by endocrinologists and nutritionists vs. the rest of the specialists (digestive, geriatrics, hematology, internal medicine, medical oncology, radiation oncology and others).

3.1. Physicians' Perception of Patient Adherence to ONS

Survey results regarding the physicians' perception of patient adherence to ONS indicated that 57.11% of patients adhered to over 75% of the prescribed ONS. Smell (43.72%) was the ONS characteristic that most impacted adherence, followed by flavor (37.12%) and texture (53.93%) (Figure 2A). Moreover, physicians considered that the organoleptic properties of ONS exerted the most positive impact on adherence (Figure 2B).

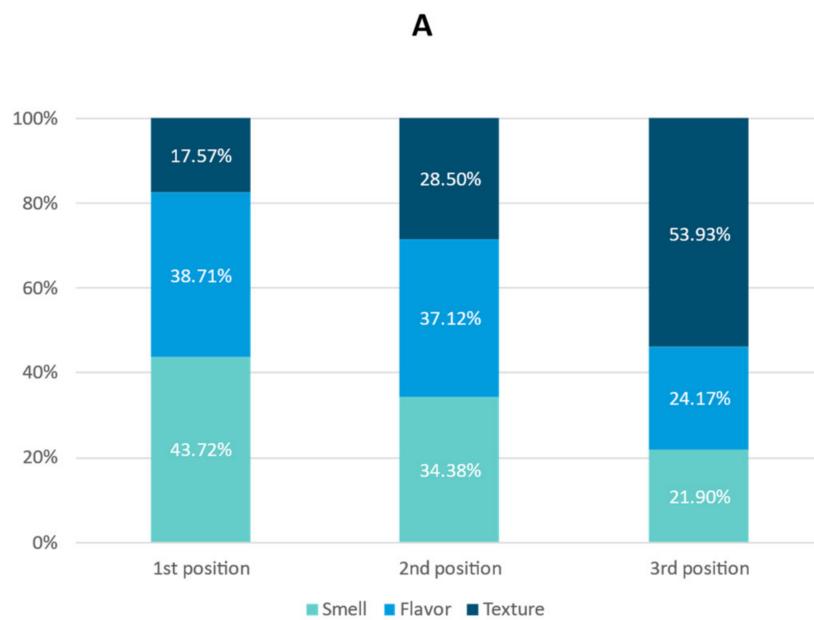


Figure 2. Cont.

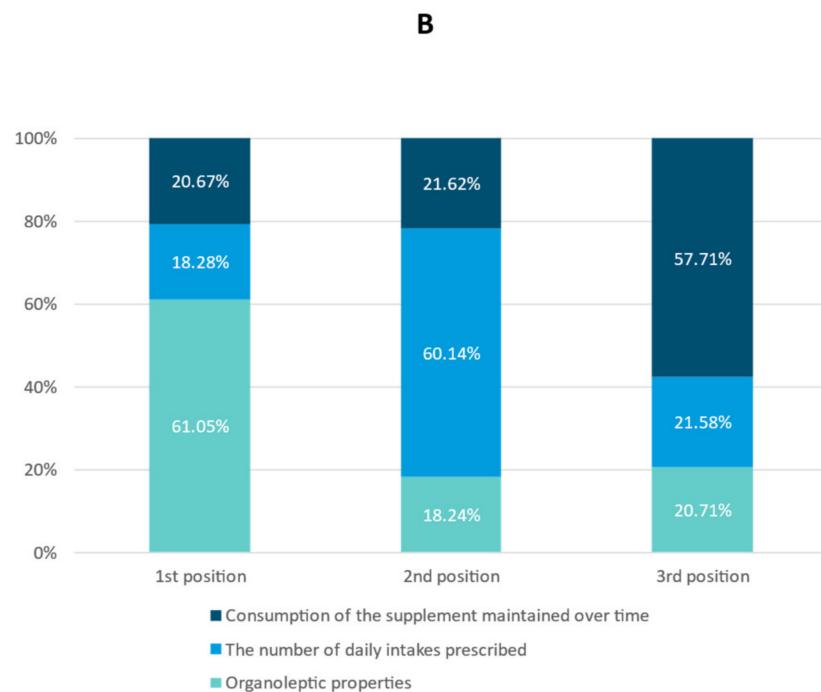


Figure 2. (A) Which of these organoleptic properties: smell, flavor or texture, has the most influence on adherence to the nutritional supplement? (B) Which of these options: organoleptic properties, the number of daily intakes prescribed or the consumption of the supplement maintained over time, has influenced ONS adherence most positively?

3.2. Physicians' Perception of Patient Acceptance/Satisfaction with ONS

Most physicians reported that, from their point of view, patient satisfaction with the ONS prescribed was 'quite a lot' or 'a lot', detailed as follows: overall satisfaction (90.10%) (Figure 3A); benefit of ONS (88.51%) (Figure 3B) and satisfaction with organoleptic properties of the ONS (smell 81.16%, taste 88.16%, texture 84.86%) (Figure 3C).

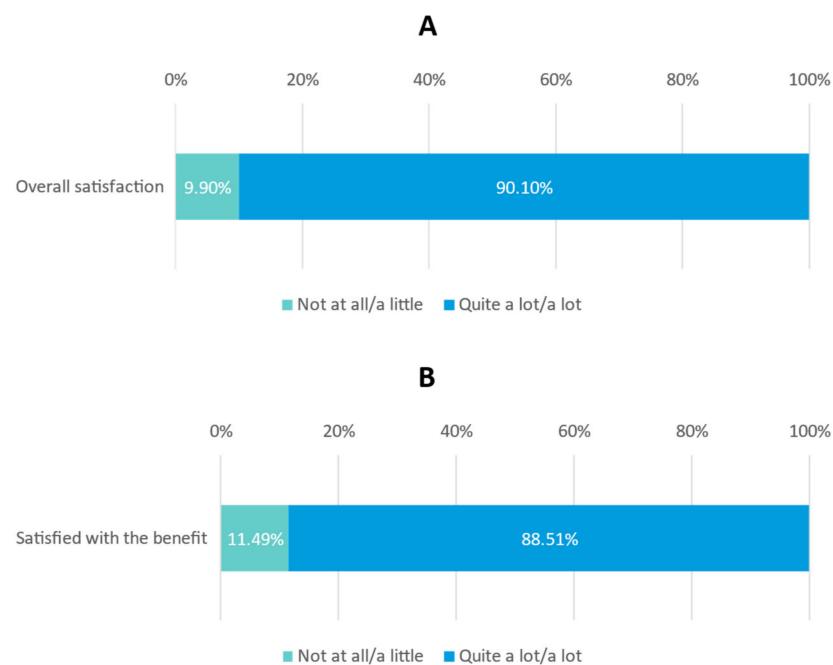


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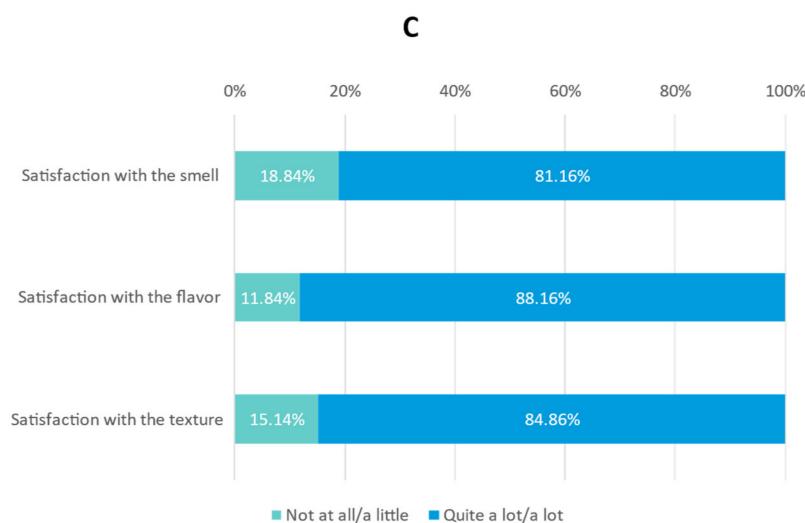


Figure 3. (A) Overall patient satisfaction with the ONS received; (B) Level of satisfaction with the benefit of the ONS; (C) Patient satisfaction with the organoleptic properties.

Moreover, most participants considered that the organoleptic properties influenced patient satisfaction ‘quite a lot’ or ‘a lot’ (90.42%) (Figure 4A) and that patients accepted the ONS in their daily diet ‘quite a lot’ or ‘a lot’ (88.63%) (Figure 4B).

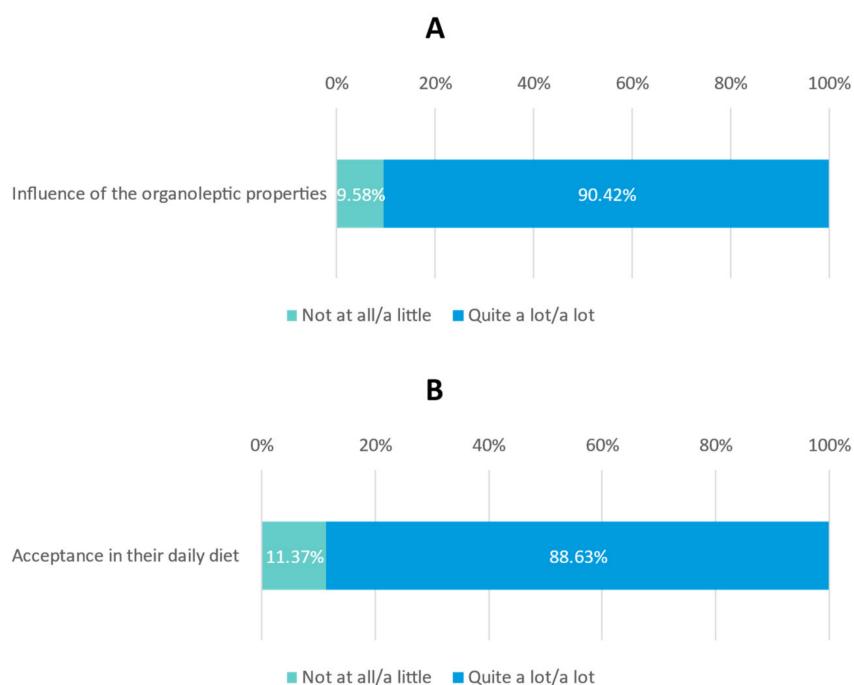


Figure 4. (A) Influence of organoleptic properties on patient satisfaction; (B) Degree of acceptance of the patient’s ONS in their daily diet.

3.3. Physicians’ Perception of Patients’ Clinical Improvement after Taking the ONS

From the physicians’ perception, ONS contributed ‘quite a lot’ or ‘a lot’ to improving the patients’ general condition (87.04%), the patients’ QoL (81.96%) and the patients’ vitality/energy (81.28%) (Figure 5) (for all patients’ clinical improvement, see Table S3).

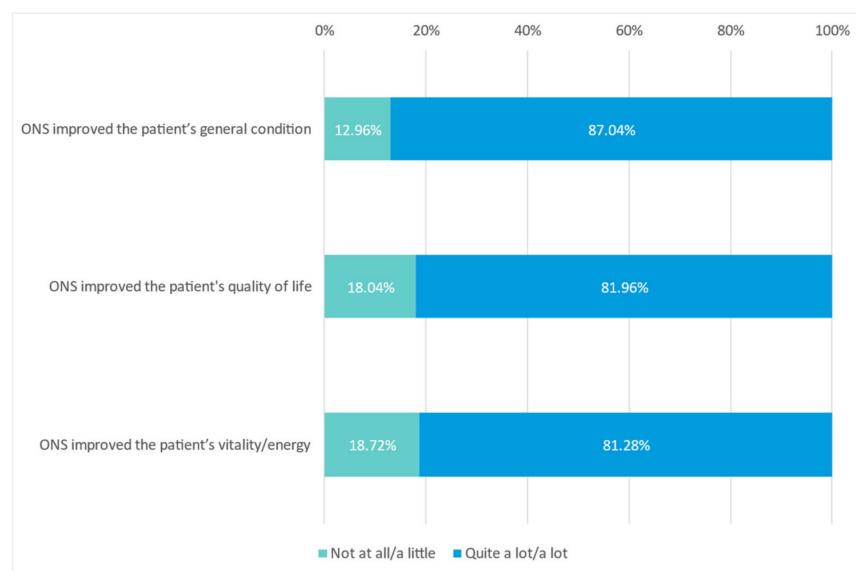


Figure 5. Improvement in the patients' general condition, vitality/energy and QoL by ONS.

A specific question on each ONS was included in the survey. Results for this specific question are shown in Figure 6. Thus, 71.47% of physicians considered that the hypercaloric, high-protein peptide-based ONS rich in MCTs without fiber improved patients' gastrointestinal discomfort 'quite a lot' or 'a lot' (71.47%). In addition, physicians considered that for those patients who presented diarrhea (80.25%), nausea (61.13%), vomiting (46.69%), abdominal pain (77.90%) or bloating (78.21%), ONS improved these symptoms 'quite a lot' or 'a lot': diarrhea (73.63%), nausea (58.46%), vomiting (54.89%), abdominal pain (66.40%) and bloating (70.74%) (Figure 6).

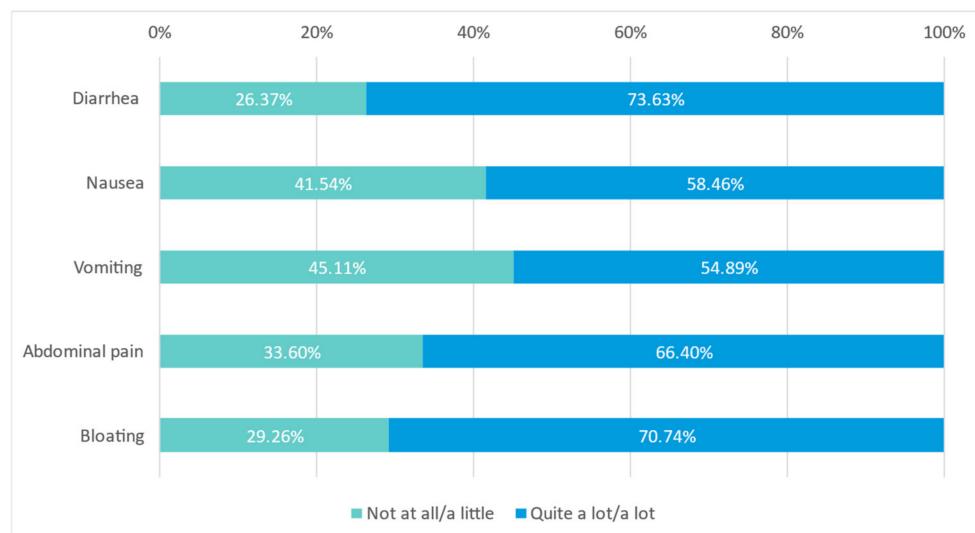


Figure 6. Improvement in the patients' symptoms (diarrhea, nausea, vomiting, abdominal pain, bloating) by ONS (N = 638 physicians).

Most physicians (82.16%) agreed that the hypercaloric, high-protein ONS enriched with HMB and FOS improved the patients' physical condition 'quite a lot' or 'a lot' (Figure 7).

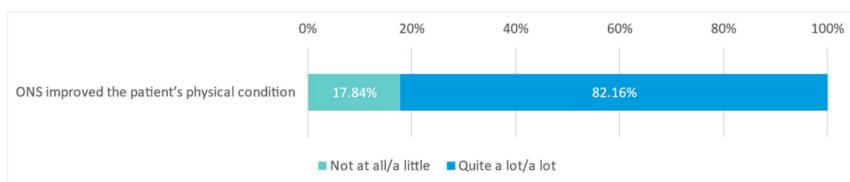


Figure 7. Improvement in the patients' physical condition by ONS (N = 863 physicians).

Finally, 75.57% of participants indicated that the diabetes-specific hypercaloric, high-protein ONS with high MUFA contributed to better glycemic control 'quite a lot' or 'a lot' (Figure 8).

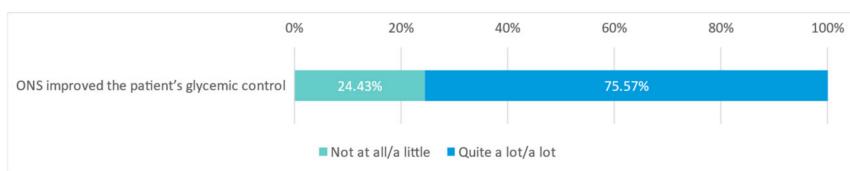


Figure 8. Improvement in the patients' glycemic control by ONS (N = 749 physicians).

3.4. Physician Satisfaction

After their experience prescribing ONS, almost all the physicians stated they would prescribe the same ONS again, in 96.4% of the cases.

3.5. Subgroups Analyses

No differences were observed according to the type of ONS [(i) hypercaloric, high-protein peptide-based ONS rich in MCT without fiber; (ii) hypercaloric, high-protein ONS enriched with HMB and FOS and (iii) hypercaloric, high-protein diabetes-specific ONS with high MUFA].

The subgroup analysis according to patients' age (≤ 65 and > 65 years) assessed differences regarding the following questions: how much has the ONS contributed to (i) improving the patient's autonomy/functionality, (ii) achieving weight gain in the patient and (iii) the patient's degree of adherence to the prescribed treatment? Results showed no differences between groups.

The last subgroup analysis carried out based on patients' underlying pathology (oncology or non-oncology patients) evaluated the responses to the following questions: (i) how much has the ONS contributed to influencing the patient's daily intake, (ii) the patient's satisfaction with the taste of the ONS, (iii) the patient's degree of acceptance of ONS in their daily diet and (iv) the degree of adherence to the prescribed treatment? Results did not detect any differences (for all subgroup analysis results, see Table S4).

4. Discussion

PerceptiONS is a study describing the perception of physicians with experience in the management of ONS in malnourished patients (mean 10.36 years; SD: 8.25) in Spain. This electronic survey provided representative data on the physicians' opinions.

Nearly 38% of participants were specialists in endocrinology and nutrition (37.41%), who routinely used validated screening methods (GLIM, MUST or MNA, a total of 73.81%) to detect patients who would benefit from an ONS-based intervention. Only 7.2% of endocrinologists and nutritionists did not employ some screening tools. This contrasts with rest of specialists, who did not use a validated screening malnutrition tool in 26.5% of cases. Barriers to the use of appropriate screening methods may be the lack of resources (time, staff, etc.), lack of training or the lack of care pathways to guide action after screening; however, this was not evaluated [25].

Participants reported their perceptions regarding the experience of 2516 patients receiving ONS for almost three months (90% for a duration of 60–120 days). Most patients

suffered from digestive neoplasms or a multi-pathological condition, thus broadly representing real-world clinical practice. In addition, 63.47% of patients were over 66 years old, with the main part of the sample >75 years (37.68%). A subset of elderly patients probably provides more evidence for using ONS in fragile subjects, in that older age implies greater risk of fragility.

Our data showed that the participating physicians perceived that most patients (57.11%) adhered correctly to ONS usage, consuming at least 75% of the prescribed dose. According to the physicians, smell and flavor were the two main factors conditioning adherence. Organoleptic characteristics were the main features favoring adherence, in the physicians' opinion. Adherence to ONS reported in our study based on the physicians' perception was higher than previously described rates. In a systematic review and meta-analysis performed in 2019 by Gea-Cabrera et al. [23], high adherence was only found in hospitalized patients, where it reached 80%, whereas adherence rates in outpatients tended to be around 50%. This variance could be explained by methodological and study population differences between the two studies, as the aforementioned meta-analysis included studies in which the main pathologies considered were represented less frequently in our study, such as type 2 diabetes, Chron's disease and obesity, and an exclusively geriatric population. Additionally, such variance could relate to improvements in the organoleptic characteristics due to new developments, which may have contributed to enhancing adherence rates.

In general, our results suggest that physicians considered that patients were satisfied (90.10%) with the ONS, deeming that organoleptic properties influenced patient satisfaction 'quite a lot' or 'a lot' (90.40%). A high satisfaction rate with ONS was expected, given that previous studies based on less convenient enteral feeding strategies reported they had been well tolerated by patients. A prospective study including 149 patients (80% male) with gastrointestinal neoplasms (76% adenocarcinomas) treated via jejunostomy reported a 96% compliance rate and a mean satisfaction score $>70 \pm 11/100$ (QLQ-C30 questionnaire) [26].

Physicians' appreciation of the effect exerted by ONS on clinical improvement was remarkably positive on all the parameters studied, including patients' general condition, QoL and vitality. The results of our study show the positive effects of ONS on improving patients' functional status, thereby dispelling the existing doubts on whether clinical trial findings translate to real-world clinical practice settings [27]. Regarding gastrointestinal symptoms management, physicians considered that the peptide-based ONS contributed to reducing diarrhea, abdominal pain and bloating. A recent observational study performed in 19 medical sites in Spain reported similar results in 90 malnourished adult patients with gastrointestinal malabsorption symptoms [28]. It showed that peptide-based ONS reduced symptoms and improved patients' nutritional status [28]. The ONS enriched with HMB and FOS were perceived as effective for recovering the patient's physical condition. Similarly, the diabetes-specific ONS were deemed suitable for achieving glycemic control.

Tolerability is a challenge to maintaining enteral nutrition feeding. Thus, in an observational, multicenter study conducted in Spain involving a total of 148 patients and 114 physicians, tolerability was paramount for patients receiving home enteral nutrition (HEN). Significantly, younger patients had stronger preferences for tolerability, whereas elderly patients (≥ 75 years) were more concerned about the ease of handling. By comparison, physicians assigned a greater relative importance to tolerability, nutrition and calories compared to patients ($p = 0.002$) [29]. An observational, prospective, multicenter study ($n = 90$) conducted in Spain evaluated nutritional status and compliance with a high-protein peptide-based ONS in a malnourished population with gastrointestinal intolerance over a 12-week period [30]. Gastrointestinal tolerance was good (75.0% of patients did not have abdominal pain or pain improved), with a decrease in the number of episodes of diarrhea, abdominal distension, nausea and vomiting. Stool consistency also improved during treatment. The adherence rates were in line with the tolerance rate (75.5%) [29].

Consistent with the high adherence rates, good clinical benefits and tolerability perceived, almost all physicians (96.40%) stated they would use the same ONS in similar

patient profiles in the future. Our results provide evidence in favor of prescribing ONS to malnourished patients, supporting their use as a strategy to combat malnutrition.

One of the main strengths of the PercepiONS study lies in its large study sample. Our results describe the perception of 548 physicians regarding the experience of 2516 malnourished outpatients receiving ONS in the Spanish public healthcare system. In addition, our results show that there are no differences in the use of the different nutritional supplements according to either the patient's age or underlying pathology. This suggests that our results could be extrapolated to other patients. However, this study has some limitations, some of which are inherent to the study design. Firstly, all the parameters studied were assessed from each physician's subjective perception, which may potentially have led physicians to misinterpret their patients' experiences. Although the physician's perception may not fully reflect the patient's perception, the information provided will be useful to better understand and optimize patient management in this context.

Secondly, the study is based on an ad hoc questionnaire, making it more difficult to compare these results with similar investigations. Thirdly, the study was carried out in Spain; therefore, our findings may not be extrapolated to other settings. Finally, it would also have been desirable to perform diagnostic tests to quantify certain clinical features. For instance, ultrasound or bioimpedanciometry could be used to measure muscular mass, and this information could be compared with the improvements perceived by the physicians in the patient's condition and strength. Further studies exploring the patients' perception of the issues addressed in this project would be of great interest.

5. Conclusions

To our knowledge, PercepiONS is the first study exploring physicians' perceptions of malnourished outpatients prescribed ONS regarding adherence, acceptance/satisfaction, tolerability, and benefits. From the physicians' perspective, most patients adhered correctly to the ONS prescribed. Smell and flavor were deemed the main factors conditioning ONS adherence. In addition, physicians perceived that ONS were well tolerated, mainly due to their organoleptic characteristics, and considered that they improved patients' general condition, energy and QoL.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/nu15051219/s1>; Table S1: Patients' sociodemographic characteristics; Table S2: Complete questionnaire; Table S3: Physicians' perspective on patient's clinical improvement after taking the ONS; Table S4: Subgroup analyses.

Author Contributions: Conceptualization, P.B.P.-M., C.D.-d.-M., J.M.G.-B., M.R.-F. and C.S.-V.; methodology, A.C.-B. and L.L.-T.; formal analysis, A.C.-B. and L.L.-T.; data acquisition: PercepiONS Group; writing—original draft preparation, P.B.P.-M., C.D.-d.-M., J.M.G.-B., M.R.-F., C.S.-V., A.C.-B. and L.L.-T. All authors have read and agreed to the published version of the manuscript.

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Appendix A

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