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ORIGINAL RESEARCH

Therapeutic Decision-Making Under Uncertainty in the Management of Spinal Muscular Atrophy: Results From DECISIONS-SMA Study

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ABSTRACT

Introduction: There are many uncertainties about treatment selection and expectations regarding therapeutic goals and benefits in the new landscape of spinal muscular atrophy (SMA). Our aim was to assess treatment preferences and expectations of pediatric neurologists caring for patients with SMA.

Methods: DECISIONS-SMA is a non-interventional, cross-sectional pilot study that assessed pediatric neurologists with expertise in SMA from across Spain. Participants were presented with 11 simulated case scenarios of common encounters of patients with SMA type 1 and 2 to assess treatment initiation, escalation, or switches. We also asked for the expected benefit with new therapies for four simulated case scenarios. Participants completed a behavioral battery to address their tolerance to uncertainty and aversion to ambiguity. The primary outcome was therapeutic inertia (TI), defined as the number of simulated scenarios with lack of treatment initiation or escalation when warranted over the total (11) presented cases.

Results: A total of 35 participants completed the study. Participants' mean (SD) expectation for achieving an improvement by starting a new therapy for SMA type 1 (case 1, a 5-month-old) and SMA type 2 (case 6, a 1-year-old) were both 59.6% (± 21.8), but declined to 20.2% (± 12.2) for a case scenario of a 16-year-old treatment-naïve patient with long-standing SMA type 2 with severe disability. The mean (SD) TI score was 4.2 (1.7), and 3.29 (1.5) for treatment initiation. Of a total 385 individual responses, TI was observed in 147 (38.2%) of treatment choices. The multivariable analysis showed that lower aversion to ambiguity ($p = 0.019$) and lower expectation of treatment response ($p = 0.007$) were associated with higher TI after adjustment for participants' age and years of

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experience. Older age ($p = 0.019$), lower years of experience ($p = 0.035$), lower aversion to ambiguity ($p = 0.015$), and lower expectation of treatment benefits ($p = 0.006$) were associated with inertia for treatment initiation.
Conclusions: Pediatric neurologists managing patients with SMA were optimistic regarding treatment improvement in cases with early diagnosis, but had lower expectations when treatment delays and advanced patient age were present. Low aversion to ambiguity, low expectation of treatment benefits, and lower clinical experience were more likely to make suboptimal decisions, resulting in lack of treatment initiation, escalation, and TI.

Keywords: Spinal muscular atrophy; Decision making; Therapeutic inertia; Treatment preferences; Pediatric neurologists

Key Summary Points

Treatment decisions in spinal muscular atrophy (SMA) are complex because of the lack of direct comparisons between therapies and the uncertainty of long-term outcomes.

Therapeutic inertia is a common phenomenon in pediatric neurologists caring for patients with SMA.

Pediatric neurologists' aversion to ambiguity and expectation of treatment response were associated with suboptimal decisions.

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease caused by a homozygous deletion or mutation of the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13, leading to progressive muscle weakness and atrophy [1–3]. It is one of the most frequent monogenic neurodegenerative diseases with an estimated incidence ranging from 1/6000 to 1/10,000 newborns [1, 4].

In the last decade, therapeutic management of SMA has changed with the discovery and approval of antisense oligonucleotides, gene therapy, and small molecules achieving key improvements in motor and respiratory outcomes and increased life expectancy [5–7]. Current therapies are intended to slow or stop the progression of the disease by either modifying the splicing of the *SMN2* gene, replacing the *SMN1* gene, or upregulating muscle growth [5–7]. Earlier treatment after symptom onset enables a greater response than treatment after a longer disease duration according to clinical trial results [5]. The survival of treated patients with SMA has generated new clinical phenotypes and long-term outcomes are unknown [5, 8, 9]. In addition, we have no clinical trials that directly compare the efficacy and safety of different treatments [5]. In this context, treatment selection is becoming more complicated and requires considering different factors, including patient age, disease duration, comorbidities, route of administration, and patient preferences [5, 8–10].

Uncertainty is one of the most important contributing factors affecting decisions in medical care [11]. Many decisions are made with limited information from clinical trials or observational studies that may not apply to particular patients. Decisions based on erroneous assessments may result in incorrect patient and family expectations, and potentially suboptimal advice, treatment, and prognosis [11]. Despite these advances in the treatment landscape of SMA, there is limited information regarding preferences of pediatric neurologists that lead to specific therapeutic choices under uncertainty. Together, those were the concepts for design of DECISIONS-SMA study (Therapeutic Decision-Making under uncertainty in the management of SMA). DECISIONS-SMA assessed therapeutic expectations, preferences, and choices of pediatric neurologists when facing simulated case scenarios with different SMA subtypes and clinical status.

METHODS

Study Design and Participants

DECISIONS-SMA is a non-interventional, cross-sectional, web-based pilot study in collaboration with the Spanish Society of Pediatric Neurology (SENEP). The selection criteria included (i) pediatric neurologists (with or without specialization in neuromuscular disorders) and (ii) active practice either in an academic or non-academic setting. Participants were recruited by receiving an invitation by SENEP from June 3 to November 2, 2021. The study was approved by the ethics committee of Hospital Clínico San Carlos, Madrid, Spain (reference 21/313-E), and performed in accordance with the 1964 Helsinki Declaration and its later amendments. Participants provided written informed consent. Further details of the study protocol were described in a previous publication [12].

Study Objectives

The primary objective of DECISIONS-SMA was to assess preferences and expectations of pediatric neurologists regarding treatment choices for SMA. We also assessed treatment initiation and escalation when warranted by contemporary recommendations (see definitions in the next section). Participants were exposed to 11 simulated case scenarios or case vignettes (Supplementary Material; answers in bold were considered suboptimal treatment decisions). Case scenarios were designed by a research team led by GS and IM and based on the most common situations experienced by pediatric neurologists in clinical practice and after reviewing SMA clinical trials and patients' and caregivers' preferences from the literature [5, 10, 13–16].

Outcome Measures and Definitions

The primary outcome of interest was therapeutic inertia (TI), defined as the absence of treatment initiation or intensification when treatment goals are unmet [17]. As in our previous research, we created a TI score to represent the number of case scenarios where treatment initiation or escalation was warranted over the 11 presented case scenarios [18, 19]. This score may range from 0 to 11, where higher values represent a higher degree of TI. Participants with a TI score ≥ 1 (i.e., therapeutic inertia in at least one case scenario) were considered to calculate the prevalence of therapeutic inertia. An appropriate treatment switch was defined by the number of case scenarios where the initial treatment was changed given the clinical evidence provided of disease progression (i.e., a decrease in baseline scale score greater than the scale's minimal clinically important difference) over the total of five case scenarios (nos. 2, 3, 7, 8, and 9; Supplementary Material) assessing this strategy according to contemporary treatment recommendations [9, 20–24].

Given the complexity of analyzing treatment effects observed in randomized clinical trials in SMA, we also assessed participants' expectation of treatment benefit using four simulated case scenarios (e.g., a 5-month-old patient with SMA type 1, a 1-year-old patient with SMA type 2, a 16-year-old patient with advanced SMA type 2 and delayed diagnosis, and a 15-year-old stable patient with SMA type 2 diagnosed at 3 years of age; these correspond to cases 1, 6, 10, and 11, respectively—Supplementary Material). Participants were asked: "On a scale from 1% to 100%, what are your expectations of improvement in 2 years for this patient with any of the treatments currently available?" We reported participants' expectation of improvement for each case scenario and a global metric by combining all four cases.

Clinical stabilization is a success in the context of a progressive disease like SMA. However, when creating simulated case scenarios we wanted to pose the questions in a broader and more open way by including improvement. According to behavioral economics, participants made decisions on the basis of their perception of benefits (instead of clinically defined or proven motor or respiratory metrics).

We applied concepts from behavioral economics that were previously associated with suboptimal therapeutic decisions or TI [18, 19, 25]. Physicians' tolerance to uncertainty was assessed using the standardized physician's reaction to an uncertainty test [26, 27].

Participants rated their level of agreement with each question from 0 (strongly disagree) to 5 (strongly agree), and a total score was calculated [27]. Higher values indicate lower tolerance to uncertainty [18]. In the present study, a score of 12 or higher indicated low tolerance to uncertainty. Ambiguity aversion is defined as dislike for events with unknown probability over events with known probability. As in our previous studies, participants were asked to choose between a visual option represented by bars with known 50/50 probability of winning €400 (blue bar) or €0 (red bar) and an option with an unknown probability of the same outcomes in one of the following degrees of uncertainty representing a 10%, 30%, 50%, 70%, and 90% of probability of winning, illustrated by a gray area covering in the bar—Supplementary Material, concepts from behavioral economics) [18]. There was no cutoff point. The degree of aversion to ambiguity was defined as the proportion of times participants chose the 50/50 option over the ambiguous option combining all five uncertainty options.

Statistical Analysis

We used descriptive statistics to report frequency distributions of qualitative variables, measures of central tendency, and dispersion of quantitative variables using non-parametric tests, and 95% confidence intervals. Wilcoxon's sign test was used to compare participant's expectations with treatment. Factors associated with TI, treatment initiation, and intensification (switches) were analyzed using linear regression analysis with backward selection. We included the following explanatory variables: age, gender, specialization in neuromuscular disorders, years of experience as a pediatric neurologist and also seeing patients with SMA, number of patients seen per week, practice setting (academic vs. non-academic), proportion of time devoted to clinical care, co-author of a peer-reviewed publication within the last 3 years (yes/no), aversion to ambiguity, physicians' reaction to uncertainty.

We also assessed participants' expectations of improvement with treatment for different SMA scenarios (only for cases 1, 6, 10, and 11). Participants could select the expectation of improvement with treatment ranging from 0 to 100%. Results are presented as mean percentage of expected improvement (and standard deviation, SD), and illustrated by box plots. All tests were two-tailed, and p values less than 0.05 were considered significant. Unavailable data was described as missing, without any imputation/allocation. The statistical analysis will be performed using Stata Statistical Software 17.0 (StataCorp., College Station, TX, USA) and considering a significant level of 0.05.

RESULTS

Of 50 pediatric neurologists invited to participate in DECISIONS-SMA, 35 (70.0%) completed the study. The mean age (SD) was 40.6 (9.6) years and 62.9% were women. Fourteen (40.0%) were pediatric neurologists specialized in SMA. On average, participants had 11.5 (9.11) years of experience. No differences were observed in the characteristics of participants who completed the study and those who did not respond to all questionnaires. Aversion to ambiguity was observed in 20 (57.1%) participants, whereas 10 (28.6%) had low tolerance to uncertainty. Table 1 shows main the characteristics of the studied population.

Expectation of Treatment Efficacy

The mean (SD) participant expectations for achieving an improvement by starting a new therapy for SMA type 1 (case 1, a 5-month-old) and SMA type 2 (case 6, a 1-year-old) were both 59.6% (22.2 and 21.5, respectively). Conversely, the expectation for a benefit with treatment declined to 20.2% (12.2) for a case scenario representing a 16-year-old treatment-naïve patient with long-standing SMA type 2 with severe disability (case 10). There was a significant difference in treatment expectation between case 1 or case 6 vs. case 10 ($p < 0.0001$). Overall, the combination of treatment expectations for all four case scenarios was 43.9% (14.6). Figure 1 illustrates

Table 1 Main characteristics of participants in DECISIONS-SMA

Characteristics	*N* = 35
Age, years, mean (SD)	40.6 (9.6)
Age ≥ 40 years old, *n* (%)	16 (45.7)
Sex, female, *n* (%)	22 (62.9)
Years of experience as pediatric neurologists, mean (SD)	11.5 (9.1)
Years of experience managing SMA, mean (SD)	8.9 (7.9)
Patients with SMA managed per week, mean (SD)	1.5 (2.2)
Specialist in neuromuscular diseases, *n* (%)	14 (40.0)
Practice setting, specialized SMA clinic, *n* (%)	12 (34.3)
Participation in clinical trials, *n* (%)	11 (31.4)
Authorship of scientific manuscripts in peer-reviewed journals/congresses, *n* (%)	16 (45.7)
Behavioral characteristics	
Physician's tolerance to uncertainty score, mean (SD)	9.7 (4.6)
Participants with low tolerance to uncertainty, *n* (%)	10 (28.6)
Aversion to ambiguity score, mean (SD)	3.0 (1.3)
Participants with ambiguity aversion, *n* (%)	20 (57.1)

SMA spinal muscular atrophy, *SD* standard deviation

differences in treatment expectations of pediatric neurologists by case scenario.

Therapeutic Inertia and Associated Factors

Overall, each participant had to make a therapeutic choice for each of the 11 simulated case scenarios, accounting for a total of 385 individual responses. TI was observed in 147 (38.2%) of individual responses. The mean (SD) TI score was 4.2 (1.7), whereas the TI scores for not initiating treatment and not escalating treatment (switches) when there was evidence of disease progression were 3.29 (1.5) and 3.71 (1.13), respectively. There was no difference in the TI score between participants with vs. without specialization in neuromuscular disorders [mean TI scores 4.14 (1.56) vs. 4.23 (1.61); $p = 0.86$)].

The multivariable analysis showed that lower aversion to ambiguity ($p = 0.019$) and lower expectation of treatment response ($p = 0.007$) were associated with higher TI scores after adjustment for participants' age and years of experience. Similar results were observed for treatment switches (Table 2). Older age ($p = 0.019$), lower years of experience ($p = 0.035$), lower aversion to ambiguity ($p = 0.015$), and lower expectation of treatment benefits ($p = 0.006$) were associated with inertia in treatment initiation (Table 2). Physicians' tolerance to uncertainty, specialization in neuromuscular disorders, and number of patients managed per week were not associated with treatment initiation, escalation, or TI. Observed vs. predicted scores for TI, treatment initiation, and treatment escalation derived from multivariable linear regression models are shown in Fig. 2. This figure illustrates how models predict participants' treatment choices compared to the observed ones. Note the higher slopes in panels a and c compared to panel b, reflecting higher TI overall and for treatment intensification.

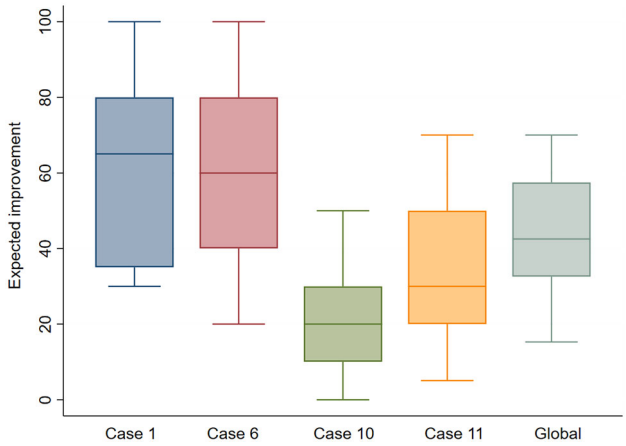

Fig. 1 Expectations of treatment efficacy by case scenario. Case 1, a 5-month-old patient with SMA type 1; Case 6, a 1-year-old patient with SMA type 2; Case 10, a 16-year-old patient with advanced SMA type 2 and delayed diagnosis; Case 11, a 15-year-old stable patient with SMA type 2 diagnosed when age 3, Global combination of treatment expectations for all case scenarios. This figure illustrates participants' expectations of improvement with treatment for different SMA scenarios. Participants could select the expectation of improvement from 0 to 100%. Responses are presented as box plots displaying the minimum, first quartile, median, third quartile, and maximum values. The box represents the first quartile to the third quartile with a horizontal line representing the median. On average, the overall median expectation for improvement with treatment was 42.5% [IQR 32.5–57.5%] with a minimum of 15.3–70%

DISCUSSION

Recent discoveries targeting different disease mechanisms have altered the treatment landscape and management of SMA [5, 6]. Despite these advances, we have limited information on how pediatric neurologists make treatment selection [10, 15]. Diagnosis and follow-up of patients with SMA in Spain can be carried out in all hospital-based neuromuscular units in the country. However, the administration of SMA agents is centralized in referral units.

DECISIONS-SMA specifically assessed participants' therapeutic expectations and preferences, as well as their choices regarding treatment initiation, intensification (e.g., switches), and TI. We found a high prevalence of TI among all participants in at least one simulated case scenario, affecting nearly 4 out of 10 (38.2%) therapeutic decisions. On average, pediatric neurologists had a modest (43%) overall expectation for improvement, which was significantly higher for SMA with a recent diagnosis compared to those with a longer disease course (59% vs. 20.5%). Lower aversion to ambiguity and lower expectation of treatment response were the two factors associated with higher TI after adjustment. Similar results were observed for treatment switches, whereas older age, lower years of experience as pediatric neurologist, lower aversion to ambiguity, and lower expectation with treatment were associated with inertia in treatment initiation.

The therapeutic landscape of SMA has become more complex with the approval of new therapies unveiling physicians' inherent uncertainties when starting a new agent [5, 10, 24]. Most studies have been evaluating therapeutic decision-making in SMA from the perspective of patients and their caregivers and family members [13–16, 28–31]. Briefly, these studies highlighted the importance of maintaining functional status and the need to develop sensitive scales able to detect small changes in a patient-centered spectrum of dimensions beyond motor function. McGraw et al. conducted a qualitative study among patients, parents, and clinicians in the USA to understand what they considered as a meaningful change in SMA type 2 and 3 [15].

Table 2 Outcome measures: therapeutic inertia, lack of treatment initiation, and lack of treatment escalation

Variables	TI score			TI score for treatment initiation			TI score for treatment escalation		
	β	95% CI	*p* value	*β*	95% CI	*p* value	*β*	95% CI	*p* value
Age ≥ 40 years	1.53	− 0.51, 3.11	0.057	1.78	0.31, 3.25	0.019	0.71	− 0.43, 1.84	0.21
Years of experience	− 0.077	− 0.16, 0.008	0.073	− 0.085	− 0.16, − 0.007	0.035	− 0.043	− 0.10, 0.017	0.15
Ambiguity score	− 0.44	− 0.83, − 0.049	0.029	− 0.46	− 0.82, − 0.098	0.015	− 0.35	− 0.62, − 0.065	0.018
Overall expectation with treatments	− 0.049	− 0.084, − 0.013	0.009	− 0.048	− 0.081, − 0.015	0.006	− 0.036	− 0.06, − 0.011	0.007

Derived from linear regression analysis adjusted for all presented variables. Age was dichotomized by the median split because there was collinearity between age and years of experience (variance inflation factor < 3)

Note the consistency of results showing that lower aversion to ambiguity and lower expectation of treatment response were associated with higher TI score, TI in treatment initiation and TI for treatment escalation after adjustment for participants' age and years of experience

CI confidence interval, *β* beta coefficient, *TI* therapeutic inertia

Clinicians cited the importance of small motor improvements, usually undetected by the scales used in clinical trials and clinical practice, but which have an impact on activities of daily living and autonomy of patients and families. However, the perspective of the treating clinician has been little studied, especially in their behavioral aspects that could influence decision-making. The relationship between TI and aversion to ambiguity is intriguing. Participants who were more prone to choose options with unknown probability were more likely to select treatment options that were not based on recommended guidelines (higher TI scores). This finding may reflect that those participants may feel more comfortable in dealing with ambiguity resulting in making choices outside best practice recommendations. Previous studies showed that the preference for ambiguity was attributed to overconfidence, which could be a potential explanation for our findings [32, 33].

Age, baseline functional status, SMA type, and the number of copies of *SMN2* are the most important factors predicting response to disease-modifying therapies [6, 34–36]. There is convincing evidence that early initiation of treatment, ideally in the presymptomatic stage of the disease, is associated with markedly better clinical outcomes compared to delayed treatment initiation [5]. A recent consensus panel including family members of patients with SMA also supports these recommendations [37]. Our study findings are clearly aligned with both consensus statements as reflected by the results on treatment expectations for different SMA scenarios. Furthermore, families of patients with SMA also highlighted the risk that decisions be influenced by subjective and individual preferences of pediatric neurologists rather than being primarily based on evidence [37]. This is a well-known concept in the medical literature [38, 39]. We opted to have a better understanding of participants' preferences with treatment versus no treatment and the treatment modality in order to avoid any bias related to a specific agent. By providing pediatric neurologists' preferences and treatment choices, our study explicitly illustrates some real concerns raised in the family member-based consensus statement [37]. For example, TI was

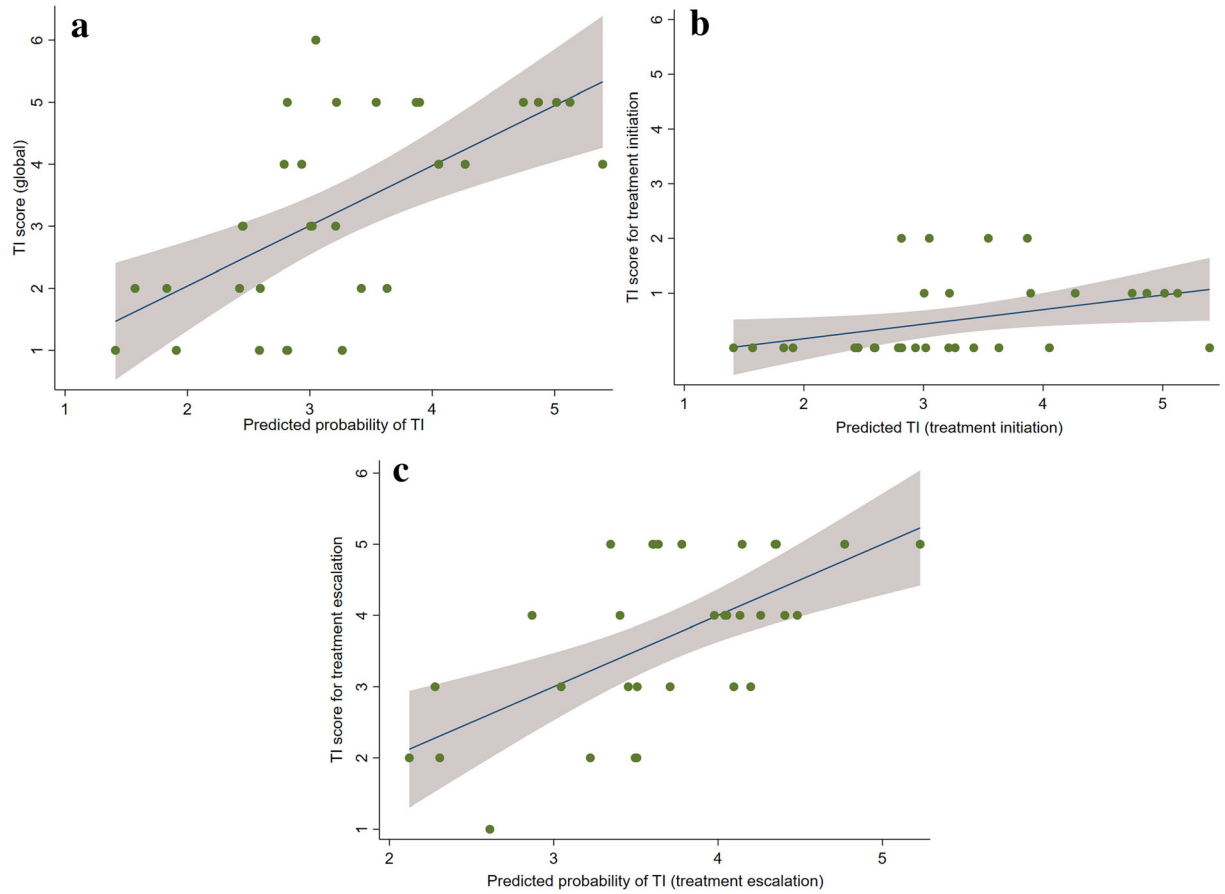

Fig. 2 Observed vs. predicted probability of TI (**a**), treatment initiation (**b**), and treatment escalation (**c**). This figure illustrates how models predict participants' treatment choices compared to the observed ones. Note the higher slopes in **a** and **c** compared to **b**, reflecting higher TI overall and for treatment intensification

observed in nearly all participants affecting on average over one-third of therapeutic decisions.

Our study has some limitations that deserve mention. First, our sample size is relatively small, which may affect outcome estimates, as well as the association of specific variables with the outcomes of interest (type II error due to low power to detect differences). In addition, observations could be clustered per neurologist and possibly also per simulated case. However, it was not possible to perform a mixed-effects model analysis of all original observations with a random intercept per neurologist because of the small sample size. Second, although other multicenter studies showed that TI is a global phenomenon, our results should be seen as a pilot study and are not necessarily generalizable to therapeutic decisions in SMA in other countries. Third, we have not covered the whole case-mix of SMA to avoid overwhelming participants with additional layers of uncertainty. Instead, therapeutic decisions were assessed by simulated case scenarios as representative of the most common situations faced by pediatric neurologists in routine clinical practice. Fourth, although optimal therapeutic choices for case scenarios were based on the recommended guidelines, some participants may have selected options prioritizing the principle of safety over treatment efficacy (primum non nocere) in a context of uncertainty and little comparative drug evidence. Finally, we cannot rule out the possibility of residual confounders given the limitations in the adjustment as a result of the

small sample size. Despite these limitations, our study provides additional perspective and answers regarding the existing gaps for the management of patients with SMA. The application of concepts from behavioral economics under uncertainty revealed some unconscious biases (e.g., status quo) that lead to lack of treatment initiation, escalation (treatment switches), and overall TI. We expect that lessons learned from our results would allow the development of educational interventions and health policy strategies that ultimately improve the well-being and outcomes of patients with SMA and their families. Further research would be desirable to confirm the study findings and explore their generalizability to other countries with different backgrounds and healthcare systems.

CONCLUSIONS

DECISIONS-SMA provides new insights regarding treatment decisions by pediatric neurologists in the management of SMA. Pediatric neurologists had expectations of improvement with new therapies for simulated cases with early diagnosis of SMA type 1 and 2 at a young age. Their expectation of improvement markedly decreased for scenarios with a delayed diagnosis at an older age. Participants with low aversion to ambiguity, low expectation of treatment benefits, and lower clinical experience were more likely to make suboptimal decisions, resulting in lack of treatment initiation, escalation, and TI. Our results may contribute to the growing evidence of the relevance of value-based shared decision-making for the current management of SMA.

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Compliance with Ethics Guidelines The study was approved by the ethics committee of Hospital Clínico San Carlos, Madrid, Spain (reference 21/313-E), and performed in accordance with the 1964 Helsinki Declaration and its later amendments. Participants provided written informed consent.

Data Availability Qualified researchers may request access to individual patient-level data through the corresponding author. The datasets generated during the analysis of the study are available from the corresponding author on reasonable request.

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