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ORIGINAL RESEARCH

SMA Community Priorities for Future Drug Therapies: Cross-Sectional Survey Findings Representing 410 Adults with SMA

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ABSTRACT

***Introduction*:** Despite advances in the therapeutic landscape for spinal muscular atrophy (SMA), unmet needs for those with this condition persist. This study seeks to characterize unmet needs that adults with SMA hope future therapies will address and explores associations between reported needs and health status and demographic characteristics.

***Methods*:** Close-ended questions from 2021 to 2023 Cure SMA Community Update Survey data were used to assess the importance of needs related to muscle and motor function, lung function and bulbar function, and general functioning. Data was stratified by SMA type and mobility status, and Fisher's exact tests were used to assess for statistically significant differences based on these characteristics. Variations in reported needs were further explored with regressions controlling for sex, education, maximum mobility, and drug treatment status.

***Results*:** The sample included 410 adults who answered questions on unmet needs. Most had type 2 or type 3 SMA (48% and 45%, respectively). Gaining muscle strength was the most frequently reported unmet need, and followed by improving daily functioning, achieving new motor function, and stabilizing motor function. Stratifications and regressions identified statistically significant differences in treatment needs based on health status and demographic characteristics ($p<0.05$). Most notably, people with more severe types of SMA and lower mobility were more likely to report items related to lung function and bulbar function as important.

***Conclusion*:** This research highlights treatment priorities for adults with SMA.

Keywords: Spinal muscular atrophy; Unmet needs; New treatments; Patient-focused drug development

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Key Summary Points

Why carry out this study?

Despite advances in the therapeutic landscape for spinal muscular atrophy (SMA), unmet needs for individuals with this debilitating disease persist.

This study examines priority unmet needs using cross-sectional analyses of Cure SMA Community Update Survey data from 2021 to 2023 and explores associations between reported needs and health status and demographic characteristics.

What was learned from this study?

Gaining muscle strength, improving daily functioning, achieving new motor function, stabilizing motor function, and reducing fatigue were top treatment priorities for adults with SMA.

Adults with more severe forms of SMA and lower mobility status are more likely to report items related to respiratory function and bulbar function as unmet needs.

These findings can inform drug development and evaluation in the future.

INTRODUCTION

The advent of drug treatments for the autosomal-recessive motor neuron disease spinal muscular atrophy (SMA) has drastically changed the outlook for many with this disease. Though new US Food and Drug Administration (FDA)-approved therapies are not curative, they are enabling children who may have never reached motor milestones such as crawling, sitting, standing, and walking to reach these milestones in addition to preserving motor function in older individuals [1, 2]. This progress has rendered historical type 0–4 classifications of SMA obsolete for infants and children who have been identified through newborn screening and who experienced onset in the treatment era [3].

Despite these advances, unmet treatment needs remain for many children, teens, and adults with SMA—particularly those who could or did not receive early treatment and to whom the historical type classifications still apply [4, 5]. SMA has myriad, well-documented effects on functioning and daily life, often affecting ambulation, feeding, dressing, personal hygiene, and toileting [6–8]. Symptomatic burden can vary based on SMA type, with type 1 and type 2 individuals being more likely to have breathing difficulties and choking or swallowing issues than type 3 and type 4 individuals [8]. Finally, the most frequently reported symptomatic issues are not always the most impactful: in a cross-sectional study of 359 adults, for instance, pain and breathing difficulties ranked in the bottom half by prevalence, but they were in the top half of average impact scores [8].

Today, the SMA drug pipeline includes several late-stage programs that have attained full enrollment [9]. Ongoing trials are evaluating approaches to optimize dosing and delivery of approved SMN-enhancing drugs. Industry researchers are also exploring the efficacy of myostatin inhibitors as an SMN-independent therapeutic approach that may be used in combination with disease-modifying therapies. Additionally, significant work has been done to develop outcome measures that are relevant to the SMA population and sensitive to changes considered meaningful by people with SMA. For example, the Spinal Muscular Atrophy Independence Scale Upper Limb Module (SMAIS-ULM) has recently been developed as an outcome measure for persons with SMA who are 12 years of age or older, and an observer-reported measure for caregivers of children with SMA who are older than 2 years of age specifically capturing the level of assistance required to perform daily activities, as maintaining independence has been a common important aspect of quality of life for individuals affected by SMA [10]. Additionally, the modified spinal muscular atrophy functional rating scale (SMAFRS) was developed to evaluate 10 activities of daily living in adults with SMA [11].

With these continued advances in SMA treatment and evaluation, there is ample reason to examine SMA community views on unmet

treatment needs [5, 9]. Cure SMA, a US patient advocacy organization that supports individuals affected by SMA and funds and directs research for SMA, undertook the research presented herein to understand outstanding needs that adults with SMA hope will be addressed by future drug treatments. Leveraging responses to Cure SMA's annual Community Update Survey (CUS) from 2021 to 2023, this manuscript presents priority unmet needs and explores associations between reported needs and health and demographic attributes. To our knowledge, this is the largest study to quantify these unmet needs in adults with SMA to date.

METHODS

The CUS is an annual survey that captures self- and caregiver-reported demographic information as well as information on disease status from individuals in the Cure SMA membership database who opt in to the survey [12]. The survey has evolved since it was initiated in 2017 to include questions on mobility status, surgeries, and hospitalizations as well as scales and indices that address functional status and health-related quality of life information. From 2019 to 2023, the CUS included a question on unmet needs for adults that asked "What are your most significant current unmet needs that you hope new therapies would address?" Respondents were presented with several items for which they respond "Yes," "Don't know," or "No" to indicate whether each answer option is an unmet need of theirs. Items were developed by Cure SMA staff members and families affected by SMA and modified annually as needed based upon community feedback. Institutional review board (IRB) approval was obtained by WCG IRB (IRB ID: 20173058). This study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All subjects provided informed consent to participate in this study.

CUS data presented in this paper is limited to 2021–2023 data to ensure that the treatment landscape was the same in each year. (Each of these surveys was fielded after nusinersen, onasemnogene abeparvovec-xioi, and risdiplam had been approved by the FDA.) To maximize our sample size while ensuring that each individual was only represented once in our dataset, we used the most recent survey responses from people who had answered the unmet needs question. We limited our dataset to people with types 1–4 who were in the USA, were over 18 years, and had completed the survey for themselves. Data cleaning and analyses were conducted using StataIC 16.

The following demographic and health status variables were used to characterize the sample: age, sex assigned at birth, race, education, family income, English as primary language, SMA type, current mobility level (non-sitter, sit or stand, walk), history of surgery due to SMA, and history of treatment with drugs indicated for SMA. As a result of limitations of treatment data in the CUS datasets, treatment history was limited to whether someone had been treated with a drug indicated for SMA. Reported unmet needs were tabulated for all survey respondents across all survey years and stratified based upon SMA type and current maximum mobility. For each year of survey data, Fisher's exact tests were used to test whether reported unmet needs (structured as a binary variable with no or don't know versus yes) differed based upon SMA type and mobility status. Finally, logistic regressions were also used to explore relationships between unmet needs and current maximum mobility controlling for sex, education, maximum mobility, and drug treatment status. Mobility was selected over SMA type because the two can be closely related and mobility better reflects current functional status.

RESULTS

Sample Characteristics

Demographic characteristics of survey respondents ($N = 410$) are presented in Table 1. Relative to Cure SMA's estimates for the USA-based SMA population, this sample was more heavily female, overrepresented people who identified as white, had a similar income distribution but

Table 1 Characteristics of Cure Spinal Muscular Atrophy (SMA) Community Update Survey participants who responded to questions about unmet needs, 2021–2023 ($N = 410$)

Demographic characteristics	Number	Percent	SMA-related characteristics	Number	Percent
Age (mean (sd))	40.2 (15.3)		SMA type		
Sex			Type 1	17	4.2
Men	130	31.7	Type 2	195	47.6
Women	279	68.1	Type 3	184	44.9
Unknown	1	0.2	Type 4	14	3.4
Race			Current maximum motor function		
White	357	87.1	Non-sitter	112	27.3
Black or African American	10	2.4	Sit or stand	141	34.4
American Indian or Alaskan Native	1	0.2	Walk	57	13.9
Asian	15	3.7	Unknown[a]	100	24.4
Native Hawaiian or Other Pacific Island	1	0.2	Past surgery or surgeries due to SMA		
Other	18	4.4	Yes	241	58.8
Unknown	8	2.0	No	165	40.2
Ethnicity			Unknown	4	1.0
Hispanic or Latinx	46	11.2	Treatment with drugs for SMA		
Education			Yes	345	84.2
HS or less	66	16.1	No	58	14.2
Some college or associates	107	26.1	Unknown	7	1.7
Bachelors or greater	237	57.8			
Family income			Survey year	*n*	%
Under $20,000	82	20.0	2021	91	22.2
$21,000–40,000	49	12.0	2022	93	22.7
$41,000–70,000	63	15.4	2023	226	55.1
$71,000–100,000	52	12.7			
$101,000 and above	82	20.0			
Unknown	82	20.0			
English as primary language					
Yes	378	92.2			
No	31	7.6			
Unknown	1	0.2			

HS high school, *SD* standard deviation

[a]A skipping error in the survey prevented collection of mobility status for many participants in 2021

with more people whose income was unknown and fewer people whose income exceeded $100,000, and had a higher proportion of people treated with an SMA drug [13].

Reported Unmet Needs

Gaining muscle strength was the most frequently reported unmet need across all respondents (Table 2), followed by improving daily functioning, achieving new motor function, stabilizing motor function, and reducing fatigue. Improving respiratory function and improving swallowing were reported as needs by about half of survey respondents while improving communication was identified by one-third.

Stratification by SMA Type and Maximum Mobility

When responses were stratified according to SMA type (Table 2), items related to respiratory function and bulbar function—improving respiratory function, improving swallowing, and improving communication through speech and/or technology—emerged as more likely to be important to those with type 1 than those with type 3 as well as to those with type 2 than those with type 3 SMA ($p < 0.05$). Improving communication was also more likely to be important for people with type 1 than people with type 2 SMA ($p < 0.05$). Similar trends were seen when the data was stratified by mobility status (Table 3), with respiratory function and bulbar function items being more likely to be reported as unmet needs for those with lower levels of mobility than those with higher levels of mobility ($p < 0.05$). There were no significant differences across types or mobility status for the motor function items or items related to general functioning.

Logistic Regressions

Logistic regressions revealed several statistically significant associations ($p < 0.05$) between unmet needs and maximum mobility, controlling for sex, education, and treatment status (see Supplementary Material for output). Improving respiratory function was less likely to be important with higher levels of mobility (odds ratio (OR) 0.31 for sit or stand versus non-sitters and OR 0.04 for walkers versus non-sitters), improving swallowing was also less likely to be important with higher levels of mobility (OR 0.28 for sit or stand versus non-sitters and OR 0.05 for walkers versus non-sitters), and improving communication was less likely to be important to people who could walk compared with non-sitters (OR 0.15).

The logistic regressions also revealed that improving respiratory function was more likely to be important to women than men (OR 2.53); improving communication was less likely to be important to people with a bachelor's degree or greater than people with high school education or less (OR 0.46); muscle strength and new motor function were both more likely to be important to people who had received a drug treatment compared to those who had not (ORs 6.18 and 3.35, respectively); and reducing fatigue was more likely to be important to people with a bachelor's degree or greater than people with high school education or less (OR 2.58) and people who had received an SMA drug treatment (OR 2.68).

DISCUSSION

This research illuminates important unmet needs that the SMA community would like future therapies to address. The most frequently identified priorities for adults with SMA in our sample were gaining muscle strength, improving daily functioning, achieving new motor function, reducing fatigue, and stabilizing motor function. Improving respiratory functioning, improving swallowing, and improving communication through speech and technology were also priorities for many, with clear relationships emerging between the importance of these latter items and disease state as reflected by SMA type and mobility.

Our findings that the importance of certain priorities varies based on SMA type and mobility

Table 2 Reported unmet needs with stratification by spinal muscular atrophy (SMA) type

Muscle strength and motor function items					Respiratory function and bulbar function items					Items related to general functioning				
Need	SMA type	Total responses	% reporting as need	*p* value[a]	Need	SMA type	Total responses	% reporting as need	*p* value[a]	Need	SMA type	Total responses	% reporting as need	*p* value[a]
Gaining muscle strength	All	408	97.3		Improving respiratory function	All	394	61.2		Improving daily functioning 2021 and 2022 only	All	180	90.6	
	1	17	94.1	0.536		1	16	81.3	< 0.001		1	8	87.5	0.649
	2	194	97.9			2	193	82.4			2	83	92.8	
	3	183	96.7			3	174	35.6			3	85	88.2	
	4	14	100.0			4	11	63.6			4	4	100.0	
Achieving new motor function	All	403	89.3		Improving swallowing	All	395	51.1		Reducing fatigue	All	400	84.0	
	1	17	76.5	0.206		1	17	82.4	< 0.001		1	16	81.3	0.297
	2	193	90.7			2	191	69.6			2	190	81.6	
	3	181	89.5			3	176	27.8			3	181	85.6	
	4	12	83.3			4	11	54.6			4	13	100.0	
Stabilize motor function	All	403	88.6		Improving communication through speech and/or technology	All	390	31.3						
	1	15	86.7	0.197		1	17	70.6	< 0.001					
	2	192	89.6			2	189	43.4						
	3	182	89.0			3	173	14.5						
	4	14	71.4			4	11	27.3						

Survey respondents were asked whether each item in the "Need" columns was a significant current unmet need that they hoped new therapies would address. Fisher's exact tests were used to test for statistically significant differences based on SMA type

[a]All pairwise tests comparing responses for types 1 and 3 and types 2 and 3 were significant at the $p < 0.05$ level, as was the test comparing type 1 and 2 responses for the item about improving communication. None of the pairwise tests comparing type 4 responses to other types were significant

Table 3 Reported unmet needs with stratification by current motor function

Muscle strength and motor function items					Respiratory function and bulbar function items					Items related to general functioning				
Unmet need	**Motor function**	**Total responses**	**% reporting as need**	***p* value[a]**	**Unmet need**	**Motor function**	**Total responses**	**% reporting as need**	***p* value[a]**	**Unmet need**	**Motor function**	**Total responses**	**% reporting as need**	***p* value[a]**
Gaining muscle strength	All	308	97.4		Improving respiratory function	All	296	60.8		Improving daily functioning	All	95	91.6	
	Non-sitter	111	96.4	0.81		Non-sitter	107	82.2	< 0.001		Non-sitter	31	93.6	0.78
	Sit or stand	141	97.9			Sit or stand	138	59.4			Sit or stand	48	91.7	
	Walk	56	98.2			Walk	51	19.6			Walk	16	87.5	
Achieving new motor function	All	306	89.5		Improving swallowing	All	297	51.2		Reducing fatigue	All	303	85.5	
	Non-sitter	111	89.2	0.41		Non-sitter	107	75.7	< 0.001		Non-sitter	109	83.5	0.71
	Sit or stand	141	91.5			Sit or stand	139	46.0			Sit or stand	141	85.8	
	Walk	54	85.2			Walk	51	13.7			Walk	53	88.7	
Stabilize motor function	All	305	89.5		Improving communication through speech and/or technology	All	294	29.6						
	Non-sitter	108	88.9	0.97		Non-sitter	104	43.3	< 0.001					
	Sit or stand	141	90.1			Sit or stand	139	26.6						
	Walk	56	89.3			Walk	51	9.8						

Survey respondents were asked whether each item in the "Need" columns was a significant current unmet need that they hoped new therapies would address. Fisher's exact tests were used to test for statistically significant differences based on motor function. The total number of responses is smaller than in Table 2 because a skipping error in the survey prevented collection of mobility status for many participants in 2021

[a]All pairwise tests for each of the bulbar function items were also significant at the $p < 0.05$ level

status are consistent with other research exploring the prevalence and impact of certain issues associated with SMA. In particular, our findings that those with more severe disease and symptoms were more likely to report respiratory functioning, improving swallowing, and improving communication as unmet needs accord with Mongiovi et al.'s findings that the same groups of individuals are more likely to experience and report higher impacts of breathing difficulties and choking or swallowing issues [8].

The greatest strengths of this study lie in its novelty and sample size. We are not aware of any other research that presents views on treatment priorities from as large of a sample of adults with SMA, while also looking at how functional status interrelates with treatment priorities. However, there are several limitations to this work. First, all data are self-reported. Second, neither the term "unmet needs" nor the items that were included as answer options were defined in detail. It is possible that respondents may have interpreted these terms differently or have been thinking about different facets of their disease when answering the unmet needs survey question. Sampling bias is also an issue. As noted, there are important differences between the characteristics of this sample and the USA-based SMA community, creating concerns about generalizability. We sought to address these in part with subgroup analyses that account for SMA type and mobility status and regressions that include the latter, but future analyses leveraging weighting as well as expanded efforts to recruit underrepresented subgroups are warranted. Finally, most survey respondents had received treatment with drugs indicated for SMA and we do not know as much about the views of untreated individuals. Because of limitations to our dataset and the level of detail available regarding drug treatments, we could not examine differences in views based on *SMN2* copy number, specific type(s) of treatment received, timing of treatment initiation, duration of treatment, or response to treatment.

CONCLUSIONS

This work explored unmet therapeutic needs in the context of the evolving SMA treatment landscape and choices that people with SMA have made about their treatments, demonstrating that even with the great strides made in SMA treatment in recent years, further advances are required. The views reflected in this survey data are those of a highly engaged and highly treated population. Nevertheless, all but one of the possible treatment priorities included in the CUS between 2021 and 2023 were reported as unmet needs by at least half of respondents in our sample, with many items being selected by the vast majority.

As both SMN-enhancing and non-SMN enhancing approaches move through the pipeline, these findings suggest the need for tailored approaches to assessing treatment outcomes that take patient priorities into account, as well as payer coverage for additional treatments. This research is important in the broader patient-focused drug development context and can inform future directions for SMA treatment and management. This work also expands the foundation for additional research on improvements in health-related quality of life, including how outcomes and health-related quality of life vary based on SMN copy number and disease status at time of treatment.

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Author Contributions. Ilse S. Peterson: Conceptualization (lead); data curation (supporting); formal analysis (lead); methodology (lead); writing—original draft preparation (lead); and writing—review and editing (lead). Ramaa Chitale: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); methodology (supporting); writing—original draft preparation

(supporting); and writing—review and editing (supporting). Mary A. Curry: Conceptualization (supporting); supervision (lead); writing—review and editing (supporting). Lisa T. Belter: Conceptualization (supporting); data curation (lead); formal analysis (supporting); methodology (supporting); writing—review and editing (supporting).

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Ilse S. Peterson, Ramaa Chitale, Mary A. Curry, and Lisa T. Belter have nothing to disclose.

Ethical Approval. Institutional review board (IRB) approval was obtained by WCG IRB (IRB ID: 20173058). This study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All subjects provided informed consent to participate in this study.

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