CURE SMA

CARE SERIES BOOKLET

THIS BOOKLET EXPLAINS HOW CURRENT TREATMENTS FOR SMA WORK, WHY COMBINATION THERAPY IS BEING DISCUSSED, AND WHAT TO CONSIDER WHEN THINKING ABOUT USING MORE THAN ONE TREATMENT.

UNDERSTANDING COMBINATION THERAPY

A PLAIN-LANGUAGE GUIDE FOR PEOPLE LIVING WITH SMA, FAMILIES, AND CAREGIVERS

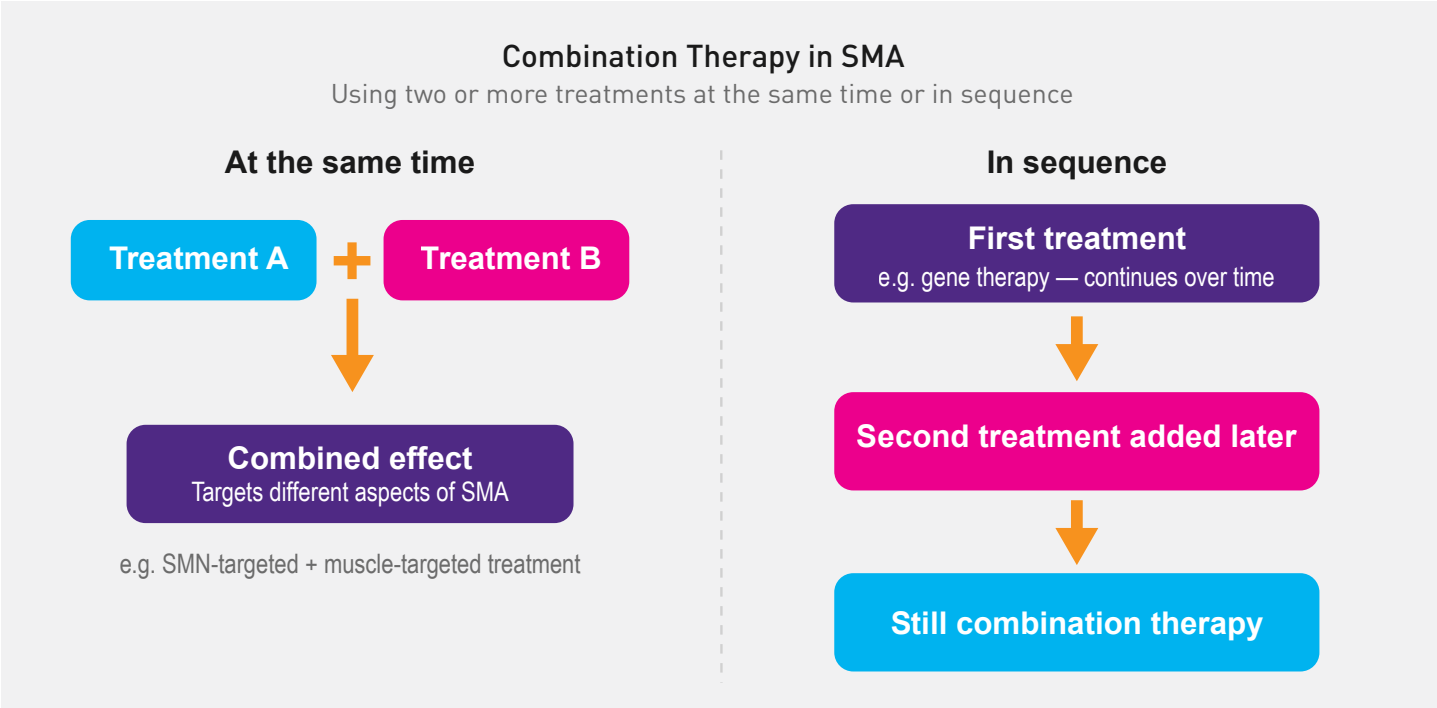
cure SMA® Make today a breakthrough.

ABOUT THIS BOOKLET

Spinal muscular atrophy (SMA) is a rare genetic disease that causes progressive muscle weakness by affecting the nerve cells that control movement. Over time, SMA can make everyday activities such as sitting, standing, walking, eating, and breathing more difficult. SMA affects approximately 1 in 15,000[1] infants born in the United States, and about 1 in every 50 Americans is a genetic carrier.

Thanks to the dedication of the SMA community and researchers, there are now several treatments for SMA.

As more treatments become available, people living with SMA, their families, and caregivers may wonder whether using more than one treatment could help. In this booklet, this approach is called combination therapy. In SMA, combination therapy means using two or more treatments at the same time or in sequence, whether they work in similar or different ways. For example, gene therapy is given once but continues to have effects over time, so adding another treatment afterward is still considered combination therapy.



Cure SMA developed this booklet to help people living with SMA, their families, and caregivers better understand combination therapy. It explains:

- how current SMA treatments work
- why combination therapy is being explored
- what research shows so far, including potential benefits and risks
- what to know about insurance coverage and access
- what questions to bring to your SMA healthcare team

This booklet is meant to support conversations with your SMA healthcare team, not to recommend a specific treatment plan. Treatment decisions should always be made with your healthcare team.

HOW CURRENT SMA TREATMENTS WORK

SMA is caused by low levels of survival motor neuron (SMN) protein. Treatments work in two main ways, targeting different aspects of SMA.

SMN-dependent treatments **increase the amount of SMN protein in the body. They are sometimes called disease-modifying therapies (DMTs) or SMN-targeted treatments. This includes:**

- Gene therapy to replace or repair the *SMN1* gene
- Medicines that target the *SMN2* "backup" gene, encouraging the body to generate more SMN protein

SMN-independent treatments **work through other processes in the body affected by SMA, without directly increasing SMN protein levels. This includes:**

- Maintaining and restoring muscle function
- Protecting nerve cells from damage
- Improving how nerve signals are sent

Figure 1 shows where different treatments may act in the body.

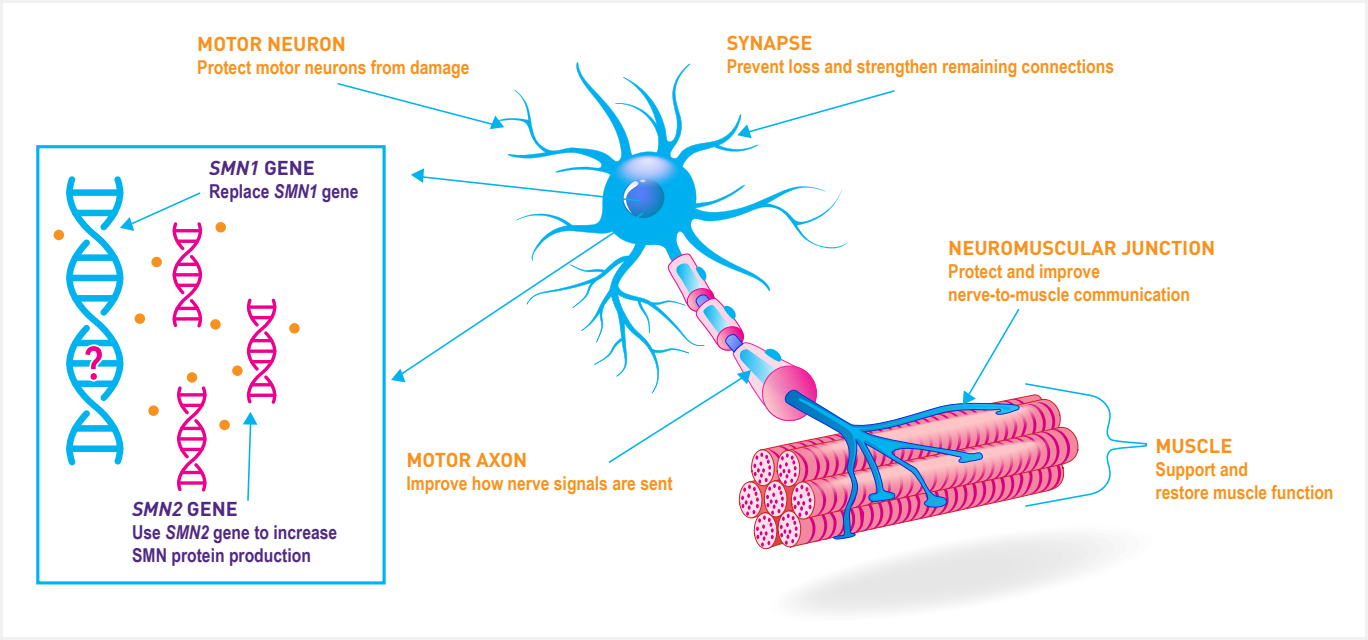


FIGURE 1: WHERE SMA TREATMENTS MAY ACT

***SMN1* gene:** The gene responsible for producing SMN protein. In SMA, this gene is missing or not working properly. ***SMN2* gene:** A "backup" gene that produces some SMN protein, but not enough on its own. **Motor neuron:** A nerve cell in the spinal cord that sends signals from the brain to the muscles. **Motor axon:** The long extension of a motor neuron that carries signals to the muscle. **Synapse:** The small gap between nerve cells where signals are passed. **Neuromuscular junction:** The point where a motor axon meets a muscle fiber and delivers the signal to move. **Muscle:** Tissue that contracts in response to nerve signals. In SMA, muscles weaken over time as nerve signals are lost.

WHY COMBINATION THERAPY IS BEING EXPLORED IN SMA

IMPORTANT UNMET NEEDS REMAIN.

As doctors and researchers learn more from SMA treatments, they are identifying where gaps remain. Even with available treatments, many people living with SMA still face challenges such as breathing problems, feeding difficulties, loss of mobility, and communication difficulties. Combination therapy may help address these.

SMA AFFECTS PEOPLE DIFFERENTLY AND AFFECTS MORE THAN ONE PART OF THE BODY.

No single treatment produces the same results for every person. How well a treatment works can depend on things like the age when symptoms started, how severe symptoms are, and when treatment began. Using treatments that work in different ways may help meet the different needs of each person living with SMA.[2]

RESEARCH IS SHOWING PROMISING RESULTS.

Recent clinical trials have reported positive findings for some combination approaches, including improvements in motor function when a muscle-targeted treatment is added to an ongoing SMN-targeted treatment. These findings have encouraged further interest in exploring combination therapy in SMA.

IMPORTANT QUESTIONS REMAIN.

At the same time, many questions remain unanswered- including whether specific combination therapies provide long-term benefits, when to add an additional treatment, and how different approaches may affect people over time.[2, 3]

WHAT RESEARCH SHOWS SO FAR

SAFETY IS CAREFULLY REVIEWED.

Before any new therapy is approved, the FDA carefully reviews clinical data. When treatments are used together, researchers and healthcare teams also need evidence about the safety of that specific combination, not just the safety of each treatment on its own. Studies and clinical trial results suggest that some combination approaches can be used safely and may increase the benefits of treatment.[2, 4]

SOME COMBINATIONS HAVE SHOWN PROMISING RESULTS.

With safety as a foundation, research is now asking whether combination therapy can improve outcomes- and early results are promising. There is now clinical trial evidence that adding a second treatment to an SMN-targeted treatment can improve motor outcomes in some people living with SMA.

- In one phase 3 clinical trial, adding a muscle-targeted treatment to an ongoing SMN-targeted treatment improved motor function when compared to adding a placebo to an ongoing SMN-targeted treatment.[5]
- In small real-world studies, adding one SMN-targeted treatment to another SMN-targeted treatment showed some improvements in motor function, with side effects reported infrequently.[6]

IMPORTANT GAPS REMAIN.

While these results are encouraging, not all combination approaches have been studied equally. Continued research is needed to understand which combinations are most helpful, when they work best, and how long added benefits last.[2, 3, 4, 7]

Researchers are continuing to look for new ways to support people living with SMA.

WHAT THIS MEANS FOR PEOPLE LIVING WITH SMA AND THEIR FAMILIES:

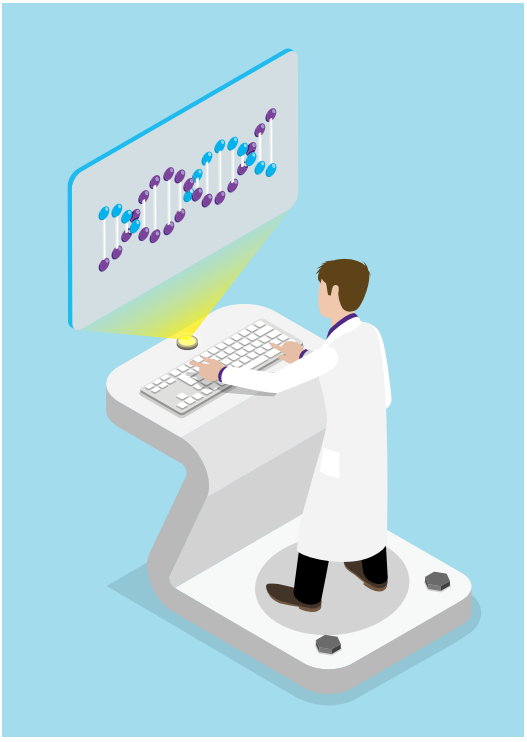
Research on combination therapy in SMA is encouraging, but it is still developing. When making treatment decisions, talk with your healthcare provider about the available evidence and safety of any treatments being considered.

WHY DOES RESEARCH ON COMBINATION THERAPY TAKE TIME?

Studying two treatments together is more complex than studying one treatment alone. It can involve more testing, more regulatory review, and sometimes coordination between different research teams. This takes time, but it helps make sure any new treatment approach is safe and supported by evidence.

BALANCING BENEFITS, RISKS, AND DAILY-LIFE CONSIDERATIONS

Deciding whether combination therapy is right for you involves weighing the possible benefits against the possible risks, costs, and daily-life considerations.



SOME IMPORTANT THINGS TO CONSIDER INCLUDE:

Possible benefits. Combination therapy may be most helpful when using more than one treatment could address different aspects of SMA or lead to better results than one treatment alone.

Possible risks. Combination therapies may increase the risk of side effects or interactions between treatments. In some cases, adding a second treatment may offer little or no additional benefit. When treatments have been studied together in clinical trials and reviewed by the FDA, families and healthcare providers have stronger evidence to weigh the risks when making treatment decisions.

How the treatments work. Treatments work in different ways. Understanding how they may work together to address different aspects of SMA is important when considering combination therapy.

When treatment begins. Starting treatments at different stages of disease may raise different questions about expected benefits, treatment goals, and risks.

Daily life considerations. Combination therapy may add costs, appointments, monitoring, travel, or other demands. A treatment approach can make medical sense and still not fit a person's or family's daily life at a particular time. These considerations should be discussed with your SMA healthcare team.

The goal with any combination treatment is meaningful benefit that fits the needs of each person living with SMA and their family.

UNDERSTANDING INSURANCE COVERAGE AND ACCESS

Access to combination therapy involves more than science and safety. Insurance coverage, reimbursement, and out-of-pocket costs may all affect whether a treatment approach is possible.

When reviewing a request for combination therapy, insurance companies often look at:

- Evidence from clinical trials
- Whether the drug has been approved by the FDA for use in combination with another approved treatment
- Information collected after a treatment is in use, sometimes called real-world data
- Whether there is evidence that using treatments together adds benefit and can be done safely

Coverage decisions may also vary from one plan to another, and the same studies may be interpreted differently by different plans. Review your plan carefully to understand what services, treatments, and equipment are covered.

In practice, access to combination therapy may depend on:

- Referrals
- Prior authorization
- A letter of medical necessity from the healthcare team

Some plans may deny coverage if they decide a treatment is not medically necessary, or if their policies do not allow more than one treatment to be used at the same time. Even when treatment is covered, out-of-pocket costs and network limits may still affect access.

HELPFUL RESOURCE

For more information about prior authorization, letters of medical necessity, denials, appeals, and out-of-pocket costs, families can refer to the Cure SMA Care Series booklet: *A Health Insurance Roadmap for People Living with Spinal Muscular Atrophy (SMA) and Their Caregivers*.[8]

IF COVERAGE IS DENIED

A denial does not always mean the process is over. Families can work with their healthcare team to understand the reason for the denial and discuss possible next steps.

QUESTIONS ABOUT COMBINATION THERAPY

Families and people living with SMA may still have questions after reading about the science, safety, insurance, and daily-life issues in this booklet. The questions below are meant as a starting point for conversation with your SMA healthcare team. They are not medical advice.

WHY ARE FAMILIES ASKING ABOUT COMBINATION THERAPY?

Because SMA affects more than one part of the body, some people wonder whether treatments that work in different ways could help when used together or at different stages. This question has become more common as more treatment options have become available and unmet needs remain. (See page 4)

WHAT DOES "COMBINATION THERAPY" MEAN IN THIS BOOKLET?

In this booklet, combination therapy means using two or more treatments together or at different stages, even if one of them was given once but continues to have effects on the body over time. (See page 2)

DOES COMBINATION THERAPY ALWAYS MEAN BETTER RESULTS?

No. More treatment does not automatically mean more benefit. In some situations, adding a second treatment may offer little added benefit or may increase side effects or other demands compared with using one treatment alone. (See page 6)

WHY MIGHT ONE PERSON'S SITUATION BE DIFFERENT FROM ANOTHER'S?

SMA does not affect every person in the same way. Age, how far SMA has progressed, severity of symptoms, when treatment begins, current function, and other health considerations can all affect how a treatment works for each person. (See page 4)

DOES HOW A TREATMENT WORKS MATTER?

Yes. Treatments often work in different ways- some target the nerves, some target the muscles, and some do both. Using treatments that work in different ways may help address different aspects of SMA. That is one reason combination therapy is being studied. (See page 3)

WHAT SAFETY QUESTIONS COME UP WITH COMBINATION THERAPY?

When treatments are used together, side effects may change, new side effects may appear, or treatments may interact with each other. Importantly, the safety of a specific combination needs to be studied and not just the safety of each treatment alone. (See page 5)

HOW DO DOCTORS AND RESEARCHERS STUDY WHETHER COMBINATION THERAPY IS WORKING?

Clinical trials are the most rigorous way to study whether a specific combination is safe and effective. In this controlled setting, researchers can compare a combination approach with an existing treatment. After a clinical trial, the FDA reviews the trial data for safety and effectiveness before a treatment is approved. Real-world data, information gathered after treatments are in use, can also offer useful information about how combination therapy works outside of a clinical trial. (See page 5)

DOES TIMING MATTER?

Yes. Earlier treatment may offer the greatest chance for benefit in some situations. Starting treatment at a later stage may raise different questions about treatment goals, expected benefits, and risks. (See page 6)

WHAT DO WE STILL NOT KNOW ABOUT COMBINATION THERAPY?

There is still a lot to learn. Published results have been encouraging in some situations, but questions remain about long-term safety, how long any added benefit may last, who may benefit most, and the best timing and sequencing of treatment. (See pages 4 and 5)

WILL INSURANCE ALWAYS COVER COMBINATION THERAPY?

It depends. Coverage decisions may differ from one plan to another. Plans may require prior authorization, referrals, or a letter of medical necessity. (See page 7)

WHAT IF INSURANCE SAYS NO?

A denial does not always mean the process is over. You can work with your healthcare team to review the denial, gather supporting documents, and pursue an appeal. Nearly three-quarters of appealed SMA treatment denials wereultimately approved.[8] (See page 7)

COULD COMBINATION THERAPY AFFECT DAILY LIFE, EVEN IF IT IS MEDICALLY APPROPRIATE?

Yes. Treatment schedules, how treatments are given, travel, time away from school or work, and added safety monitoring may all affect daily life for people living with SMA and their families. (See page 6)

WHAT GOALS ARE WORTH DISCUSSING WITH YOUR SMA HEALTHCARE TEAM?

It may help to think about what you hope treatment will do. Goals may differ from person to person and may include preserving function, improving strength, supporting breathing or feeding, maintaining mobility, or addressing symptoms that remain. Sharing those goals with your SMA healthcare team can help them tailor treatment decisions to what matters most to you and your family.

QUESTIONS TO ASK YOUR SMA HEALTHCARE TEAM

- What is the goal of adding another treatment?
- What evidence exists for this approach in SMA?
- How would we know whether it is helping?
- What risks, burdens, or tradeoffs should we consider?

CONCLUSION

Cure SMA is committed to supporting research into new treatment approaches, whether they are used on their own or as part of combination therapy. This booklet was created to help people living with SMA, their families, and caregivers better understand combination therapy, an area of growing interest as new treatments become available and important unmet needs remain.

There is growing evidence that some combination approaches can be effective in SMA, and many people living with SMA and their families have questions about how combination therapy could help. At the same time, researchers continue to investigate safety, effectiveness, long-term benefits, and the best timing and sequencing of treatments.

Cure SMA hopes this booklet supports helpful conversations with your SMA healthcare team. As always, treatment decisions should be made with your healthcare providers based on what is best for you and your family.

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CURE SMA

Cure SMA is a non-profit organization and the largest worldwide network of families, clinicians, and research scientists working together to advance SMA research, support affected individuals/caregivers, and educate the public and professional communities about SMA.

Cure SMA is a resource for unbiased support. We are here to help all individuals living with SMA and their loved ones, and do not advocate any specific choices or decisions. Individuals and caregivers make different choices regarding what is best for their situation, consistent with their personal beliefs. Parents and other important family members should be able to discuss their feelings about these topics, and to ask questions of their SMA care team. Such decisions should not be made lightly, and all options should be considered and weighed carefully. All choices related to SMA are highly personal and should reflect personal values, as well as what is best for each individual and their caregivers.

Cure SMA is here to support you. To continue learning, please see additional Care Series booklets, including:

- Health Insurance Roadmap
- Nutrition Basics
- Understanding SMA

For the full library of Care Series booklets, visit www.curesma.org/care-series-booklets

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