MS Society

Sativex

Treating spasticity in MS

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Experts in MS

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Executive summary

Spasticity is a disabling symptom of MS that will affect around 80% of people with MS at some point in their lives. It can progress to painfully tightened muscles in the entire body that severely affect people's mobility and their ability to care for themselves. Spasticity greatly affects people's quality of life and is also linked to high costs for the people affected, health and social care systems and society. 41% of GPs and 36% of patients with MS related spasticity are not satisfied with the effectiveness of existing treatments.

In 2019, NICE recommended Sativex as a treatment option for people with moderate to severe MS related spasticity who haven't responded well enough to other treatments. Sativex is a cannabis-based oral spray that is made up of 2.7 mg delta-9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD) per spray.

In the last two decades, Sativex has been studied in several clinical trials and large real-world studies. They have shown that Sativex is effective in reducing spasticity and related symptoms, such as spasm frequency and sleep disturbances. Clinical trials have shown that it reduces spasticity by at least 30% in around 40% of participants, while a 20% reduction was found in about 70% of people.

Research has also shown that Sativex is safe and well-tolerated. Adverse events as a result of the treatment tend to be mild and temporary. Common ones include dizziness, sleepiness and nausea. Serious adverse events are rare. Sativex also hasn't been linked to any of the serious side effects that can occur with recreational cannabis use, such as mental health or cognitive issues. The abuse potential for Sativex is low and it has not been shown to cause dependence or a withdrawal syndrome.

NICE also tested Sativex's cost-effectiveness for England by creating an economic model. They found that compared to Standard of Care treatment alone, Sativex is cost-effective, offering additional treatment benefit at £19,512/QALY.

Access to Sativex is often described as a "postcode lottery", since it's not available in many regions. It is estimated that around 4,800 people in England are eligible for a 4-week Sativex trial (and continuing treatment, if Sativex is effective for them). This means that, currently, thousands of people with MS could be missing out on a treatment that's safe, effective and could improve their quality of life greatly.

Introduction

In November 2019, the National Institute for Health and Care Excellence (NICE) published guideline NG144 on cannabis-based medicinal products. As part of this guideline, they recommended the use of Sativex, a cannabis based oral spray that combines THC and CBD, for spasticity in MS. They recommended that patients with moderate to severe spasticity who haven't responded well to other treatments should receive Sativex if their symptoms reduce by at least 20% following an initial 4-week trial.

Although the NICE guideline was published in late 2019 and Sativex has been licensed for nearly a decade (36), Sativex still isn't available for all eligible patients who want to try it. It's not available in all regions of England and access is often described as a "postcode lottery". According to the Clinical Commissioning Groups' (CCG) formulary websites, less than half of all CCGs in England have Sativex on their formulary. And in the ones that do, patients often still struggle to access it. In many regions, only specialists can prescribe Sativex, which creates many hurdles and means that patients rarely get the chance to try it.

NICE estimate that around 24,200 adults in England have MS related spasticity that is moderate or severe. And that 4,800 of those struggle with spasticity that is not being treated effectively by current treatments (1). But these numbers are based on the assumption that 90,500 people in England have MS. Public Health England have since calculated a higher prevalence of MS in England - 105,000 people (37) - so NICE's estimates probably underestimate the number of people that could benefit now. Thousands of people with MS are likely missing out on a treatment that could potentially improve their lives greatly.

Based on the research and evidence that is currently available, we are confident that Sativex is safe and effective and can improve the lives of people with MS related spasticity. In this evidence pack we have compiled key research findings on the use of Sativex for spasticity in people with MS.

What is spasticity in MS?

Spasticity is a common and disabling symptom of MS. It can progress to painfully tightened muscles in the entire body severely affect people's mobility and their ability to care for themselves. Spasticity greatly affects people's quality of life and is also linked to high costs for the people affected, our health and social care systems and wider society.

41% of GPs and 36% of patients with MS related spasticity are not satisfied with existing treatments. For people with moderate to severe spasticity that hasn't responded well to treatments, the options are very limited. Some treatments for moderate to severe spasticity are very invasive and Sativex could offer an additional, less invasive option.

Spasticity is a very common and disabling symptom of MS that has a big impact on people's quality of life (2). Previous research estimates that around 80% of people with MS will be affected by spasticity at some point in their life (3).

Spasticity symptoms can range from mild to severe. On the mild end, people can experience a feeling of stiffness in a limb which causes mild problems with walking, for example. But on the severe end, people can suffer from tightened muscles in their whole body. This can impair their ability to move independently and to care for themselves without help. It can also lead to other complications, including muscle shortening, pain and permanent muscle deformities (4, 5).

MS spasticity impairs people's daily lives greatly and the level of impairment is directly connected to the severity of the spasticity (2, 6, 7). That's why it's important to treat and manage it early and as best as possible.

The cost of spasticity

On top of the big impact spasticity has on a person's quality of life, it's also very costly for patients, our health and social care systems and wider society. It's difficult to estimate exact costs associated with spasticity because spasticity management is individual and multi-faceted. Also, few estimates take into account the affect that MS spasticity has on people's ability to work and on the lives of unpaid carers, which could also add considerable cost.

One study from 2015 (8) asked 221 health care specialists to estimate the resource use for different severity levels of spasticity in MS. From that information, the annual cost of spasticity management was calculated. It's split into five 'disease states', which are based on spasticity numerical rating scale (NRS) scores and represent different levels of severity. The NRS categorises spasticity severity from 0 (no symptoms and disability) to 10 (worst possible disability). The costs are broken down in Figure 1 and Table 1.

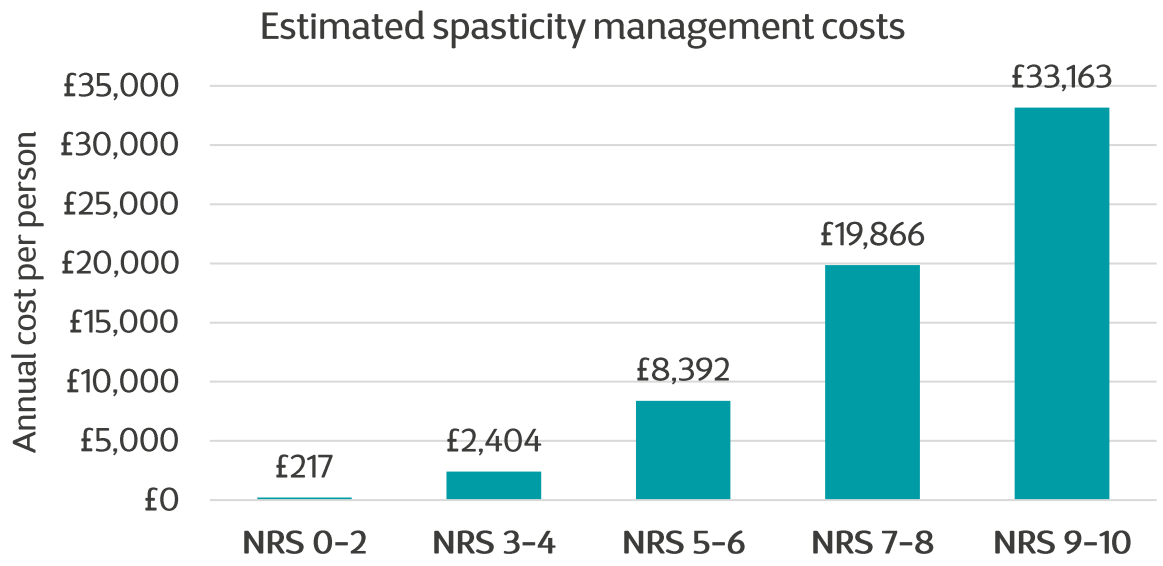

Figure 1: Estimated annual spasticity management costs by NRS scores, adapted from (8)

Table 1: Estimated spasticity costs per year per person, adapted from (8)

	NRS 0-2	NRS 3-4	NRS 5-6	NRS 7-8	NRS 9-10
Community-based visits	£41	£57	£116	£440	£869
Outpatient clinic visits	£144	£616	£1,528	£2,073	£2,652
A&E visits	£4	£10	£28	£37	£59
Hospital admissions	£7	£44	£147	£467	£885
Home care visits	£1	£1,628	£6,465	£16,605	£28,398
Equipment cost	£19	£48	£108	£245	£301

As shown above, the cost of spasticity management rises with the severity of the symptoms. This is another reason why we need to treat it early and manage it well, to delay or prevent its progression.

Why do we need more spasticity treatments?

There are already a number of different drugs for spasticity. However, about one third of people continue to have problems after receiving first line drugs and need a combination of medicines to treat their spasticity (9).

A study showed that 41% of GPs of patients with MS spasticity and 36% of patients with MS spasticity aren't satisfied with the effectiveness of the spasticity drugs available (2). Besides, some of the treatments that are commonly prescribed (such as benzodiazepines) cause side effects that many can't tolerate, including memory problems, depression and withdrawal syndrome if suddenly stopped (10).

People who don't respond well to those treatments or can't tolerate the side effects have limited options. At that stage, people often have to consider treatments that are very invasive, such as having a baclofen pump surgically implanted. This procedure requires a trial that includes a lumbar puncture and the implantation is carried out under general anaesthesia, which means it's not an option for everyone.

There is a real need for additional treatments that could help people whose spasticity has not responded well to existing treatments and those who can't tolerate the side effects. Sativex is much less invasive than some existing treatments and could offer an additional treatment option.

"My legs are constantly stiff and I often can't sleep because of the pain. I sometimes really struggle as I want to get up because it hurts, but I also don't want to get up because it hurts so much. I can't do anything to reduce the pain.

I know that Sativex is available and is changing people's lives. It is so hard to hear that other people are getting it (I am really pleased for them) as it is something I know could help me but I can't even try it."

– Anne, 40, living with relapsing-remitting MS

"I've tried every medication to help, but they've either not worked, or given me bad side effects. When I used Baclofen to treat the muscle spasms it made me vomit.

It is so frustrating that there is a treatment available and approved by NICE that I know can help and completely change my life, but I can't get it. I've been asking for Sativex for ten years. My MS team says things are moving, but they never have. I am still in pain, can't sleep and can't function but still can't get Sativex which I know would help.

If only the people who make the decisions about prescribing Sativex could wake up each morning, not having slept much and feeling how my wife and I feel. They wouldn't find it so easy to say no then."

– Chris, 52, living with relapsing-remitting MS (married to Anne)

"I am so used to the constant spasms and pain I can't imagine what it would be like without them. But I want to get that feeling if it is possible. My quality of life would be significantly improved, I might get a full night's sleep and not be constantly thinking about pain. I could do anything...

Sativex may not work for me, but I want the opportunity to try."

– Paul, 50, living with secondary progressive MS

Is Sativex effective?

The last two decades of research have shown that Sativex is an effective treatment for spasticity in MS and that it has the potential to improve people's lives greatly. The benefits of Sativex have been shown in clinical trials as well as in the real-world. Using Sativex, around 70% of people achieve at least 20% reduction in spasticity and around 36% to 40% achieve a reduction of 30% or higher. Sativex also improves spasticity related symptoms, like sleep quality or pain and improves people's ability to carry out daily living tasks. These effects stay over time and people don't develop a tolerance to Sativex.

Clinical Trials

Several randomised clinical trials (RCTs) have provided evidence for the efficacy of Sativex. Most trials classed participants as responders if they achieved a reduction of at least 30% in their spasticity numerical rating scale (NRS) scores. In the RCTs, between 36% and 40% of participants were classed as responders (11, 12). This percentage was significantly higher than for the placebo. Some participants (17.5% in one trial (11)) experienced even greater reductions of 50% or more.

But even a reduction of around 20% (shown in 70.5% of people in previous studies (13, 14) could offer many people with MS relief from spasticity and improve their quality of life (15). It's easy to dismiss seemingly small changes in spasticity that Sativex could cause. But for the people affected by spasticity even a reduction of 20% could have a big impact and improve their quality of life.

The mean (average) changes in NRS ranged from 1.18 to 1.3 in single phase trials (11, 12). The changes were bigger in trials with an enriched design, meaning that only participants who respond to the treatment in an initial treatment phase are included in the full trial. In these trials, the mean changes in NRS ranged from 3.01 to 3.5 (16, 13).

One study found no statistically significant change between the Sativex and placebo groups using the NRS. But they also used the modified Ashworth scale (MAS) to measure spasticity, which is generally seen as less sensitive to changes in MS spasticity compared to NRS (17). They found that 50% of participants receiving Sativex experienced at least 20% improvement on this scale, compared to 23.5% of participants receiving placebo. The mean improvement from baseline was also significantly greater. The Sativex group achieved a reduction of -21.73 compared to -5.99 for placebo (18).

Another study used visual analogue scales (VAS) for participants' primary symptom they identified as most troublesome, including spasticity, spasms, bladder problems, tremor or pain. Sativex reduced spasticity scores significantly compared to placebo and also improved participants' quality of sleep (19).

A different study also found that Sativex significantly improved spasm frequency, sleep disruption and participants' ability to carry out daily living tasks compared to placebo (16).

You can find more information about the clinical trials in the Appendix, where we've put together a table with key information on the methods, findings and limitations of all clinical trials included in the NICE's guideline.

Real-world research

Along with clinical studies that can tell us about the efficacy of a drug in controlled conditions, we also need to look at studies that were run under real-world circumstances. They can tell us how effective Sativex may be in a clinical setting.

One of those studies included a cohort of 1,432 participants from 30 MS centres in Italy. 70.5% of participants achieved a reduction in spasticity NRS score of ≥20% when using Sativex as an add-on treatment. As well as reducing NRS scores, the study also found that 43.8% of responders showed a meaningful improvement in at least one spasticity-related symptom. For example, they experienced improved bladder control, sleep quality, pain and/or mood (14).

Interestingly, around 20% of participants who didn't experience ≥20% reduction in spasticity NRS still felt benefits and had an improvement in at least one spasticity-related symptom (14). This means that in a real world, clinical setting, even patients who would have been considered "non-responders" in RCTs could benefit from Sativex.

Research has also shown that reduced spasticity symptoms due to Sativex are linked to improvements in people's quality of life and activities of daily living, such as getting dressed or moving. These effects are also maintained over time (15).

The findings of the RCTs and real-world studies are very encouraging. They provide strong evidence that Sativex could be an effective add-on treatment for those who have not found relief through other treatments alone.

Is Sativex safe?

Sativex is generally safe and well-tolerated. Adverse events as a result of the treatment tend to be mild and temporary. Common ones include dizziness, sleepiness and nausea. More serious adverse events are rare. Sativex also hasn't been linked to any of the serious side effects that can occur with recreational cannabis use, such as mental health or cognitive issues.
At very high doses, Sativex can cause mild euphoria, but only in a small number of people. Even though Sativex is cannabis-based, the abuse potential for Sativex is low. It has not been shown to cause dependence or a withdrawal syndrome, even in people with heavy and regular previous cannabis use.

Adverse events

In all studies, Sativex was generally well-tolerated and the adverse events (AEs) that participants experienced were mostly mild and short-lived. Common AEs that participants reported in clinical trials were dizziness, fatigue, sleepiness, vertigo and nausea (11, 12, 13, 16, 18, 19).

Few more serious treatment-related AEs were reported in the clinical trials, such as one case of vomiting (11). But severe AEs were very rare and could be resolved.

Since Sativex is a cannabis-based treatment, it's understandable that some people may also be worried about negative effects that are normally associated with regular recreational use. But even though smoking cannabis regularly has been linked to mental health (20) and cognitive issues (21), this is not the case for Sativex.

In a study looking into the effects Sativex has on people's mental health and thinking more specifically, researchers found that Sativex didn't cause the onset of psychotic or anxiety symptoms. It also didn't impair participants' thinking abilities, as normally linked to smoking cannabis (22).

The difference between Sativex and cannabis is likely due to the combination of THC and CBD in Sativex (23). CBD seems to counteract the effects of THC, but more research is needed to fully understand how the different cannabinoids interact.

What about psychoactive effects?

Some symptoms characteristic of a 'cannabis high' have been reported in isolated cases in clinical trials, however, this is rare (23). In clinical trials, the number of participants who experienced feelings of intoxication or euphoria has been very low (24).

For example, in one clinical trial less than 4% of subjects on Sativex reported feeling euphoric and mean intoxication scores (from 0, no intoxication, to 10, extreme intoxication) stayed below 2 (11). Feelings of mild intoxication or euphoria while receiving Sativex treatment are likely to be uncommon and mild.

Research has also found that in the small percentage of people who do experience intoxication, these effects decrease significantly with continuing use of Sativex. In a 2013 study, participants reported their intoxication levels using a 100 mm visual analogue scale. The mean intoxication score two hours after taking Sativex decreased from 12.4/100 (SD=18.9) at the first ever dose to 3.1/100 (SD=8.3) after continuous (>4 weeks) exposure (25).

Based on these findings we can be confident that symptoms similar to a 'high' are likely to be uncommon and mild. In those who do experience intoxication, these effects seem to decrease with continued Sativex use.

Could Sativex be abused and lead to dependence?

Along with adverse events, previous research has also looked into the abuse potential of Sativex. This includes the potential for people to become dependent on Sativex.

Since effects similar to a cannabis 'high' tend to be uncommon and mild, Sativex is not likely to be abused. Also, in a cohort of participants who regularly use cannabis recreationally, low doses (4 sprays) of Sativex were not found to have a higher abuse potential compared to placebo.

Medium (8 sprays) and high doses (16 sprays) showed some evidence of abuse potential compared to placebo. But Sativex' abuse potential was significantly lower than for another

cannabis-based treatment (Dronabinol, a synthetic form of THC licensed in other countries as a treatment for nausea and vomiting caused by cancer chemotherapy).

The abuse potential is expected to be lower if Sativex is taken throughout the day, as recommended, rather than in a single dose, as in the trial (26).

It's also important to keep in mind that the trial specifically looked at people who used cannabis on a frequent basis. In the sample, about 78% of participants smoked cannabis at least once a day in the 12 weeks leading up to the study (26). People with previous regular recreational experience are most likely to abuse a drug once it's on the market (26), so the abuse potential of Sativex is likely to be lower in people with less frequent or no prior cannabis use.

Along with the low abuse potential, research also indicates that Sativex does not cause dependence. Several studies looked at how people react when Sativex is suddenly stopped, after long-term use. Some mild and temporary symptoms, such as mild sleep, mood and appetite disturbances were seen in a small number of participants (24).

For example, in one study, the most common symptoms included interrupted sleep (16% of participants), hot and cold flushes (16% of participants), tiredness (16%) and low mood (12%) (27). In another study, only 2% of participants experienced low mood (28). But all of these symptoms were mild and temporary and no withdrawal syndrome has been found (24).

Research has also not found evidence to suggest that patients build up a tolerance to Sativex and need to increase the dose. In fact, in a long-term safety study, the mean dose of Sativex tended to decrease over time (27).

The spasms steadily got worse to mean that Sheila couldn't sleep in a bed, then couldn't sleep in a reclining chair. When Roy raised the foot rest she was in too much pain to continue. She ended up sleeping on her commode but that led to pressure sores.

She was waking up up to seven times a night and Roy had to try to make her more comfortable before they both tried to get more sleep before being woken again. Neither of them had much sleep for months.

Sheila no longer gets any spasms. In the past if she moved her arm she would get leg spasms. It got to the stage that she was worried about moving at all because of the consequences. After Sativex she can move and do more as there isn't the fear that it will set spasms off. And Sheila had such a lot of pain with the spasms.

"Sativex has made life possible for us again. Before we weren't functioning, we were barely existing. We weren't sleeping, but that has all changed. Sativex has been life changing."

– Sheila, living with secondary progressive MS, and Roy, her husband

"Before I started on Sativex all my symptoms were getting worse. I had spasms and muscle cramping every night. It was a case of when I would wake up, not if. I hadn't had a full night's sleep in 10 years, and neither had my wife.

It was incredibly painful with my body trying to do things it really couldn't do as a result of the spasms. I would often cramp into a foetal position.

After starting on the Sativex I had the first good night's sleep in 10 years. I didn't suffer with MS fatigue, but I hadn't realised how much I was running on fumes due to a lack of sleep until I had some sleep. I didn't realise how tough it was until it stopped.

I usually take four doses a day. I can tell if I only have three. But I have a spray of Sativex and it gets rid of the spasms within 10 minutes."

– Neil, 61, living with secondary progressive MS

Is Sativex cost effective?

Based on their cost-effectiveness analysis, NICE have concluded that the incremental cost-effectiveness ratio (ICER) for Sativex was £19,512 per QALY gained, which is within their willingness-to-pay threshold (£20,000/QALY to £30,000/QALY). Based on their analysis, Sativex is a cost-effective add-on treatment for people with moderate to severe spasticity caused by MS.

How is cost effectiveness calculated?

Cost-effectiveness describes whether a treatment or intervention provides good value for money. If a treatment offers increased effectiveness against an illness or symptom at a reasonable cost, it is considered cost-effective. If it offers increased effectiveness and is cheaper than standard treatments or saves money in other ways (for example by reducing management costs), it is cost-saving, also called dominant.

The NICE model estimated cost-effectiveness by producing the incremental cost-effectiveness ratio (ICER). It's defined by the difference in cost between the old and new treatment, divided by the difference in their effect.

The ICER is expressed as cost per quality-adjusted life year (QALY) gained. QALY is a concept that's based on the idea that a person's health state can be summarised as a utility, with 1 meaning perfect health and 0 meaning death. QALYs are then worked out by multiplying the sum of a person's health state utility with the length of time the health state lasts.

For example, two years spent in a state with a utility of 0.8, followed by 6 months in a state with utility 0.4 would result in 1.8 QALYs [(2 years x 0.8) + (0.5 years x 0.4)]. The change in utility as a result of a treatment response is worked out by comparing quality of life before and after.

Cost-effectiveness can be worked out through different types of analyses, but the most common approach is modelling. The goal is to create a model of the clinical situation that is

specific enough to closely represent reality and to do so over a long enough period of time to find out the most important outcomes and costs.

In practice, this means creating a model that includes all important information available about patient populations, treatment effects and more. So that we can be confident that the model is fairly accurate and can show us the effect the treatment will have in terms of costs.

Because modelling is always uncertain and based on assumptions, different assumptions are tested. In the base case analysis, researchers run the model with the assumptions that they think best represent reality. In sensitivity analyses, the model stays the same, but one assumption is changed for each analysis. This allows us to see how the assumptions affect cost-effectiveness (29).

Cost-effectiveness models can be really useful, but it's important to keep in mind that all models are based on assumptions and rely on the information available at the time. All models simplify reality and no model can ever perfectly represent reality. You can learn more about cost-effectiveness and how to judge whether an analysis or model is reliable here.

The NICE economic model

NICE created an economic model that explored the cost-effectiveness of Sativex as an add-on treatment for people with MS who experience moderate to severe spasticity and who haven't responded well to other treatments alone. The model included data from all relevant trials, longer-term registry data and data on adverse events that was available at the time.

The analysis was run from the perspective of the NHS and Personal Social Services (PSS) in the UK and only included costs and outcomes that were relevant to this perspective. Because of this focus, unpaid carer's QALYs and patients' productivity losses caused by the effect of spasticity on people's ability to work, for example, were not taken into account.

The model structure reflected the research available and adopted a 4-week treatment cycle length. The time horizon for the base case analysis was 5 years, with longer time horizons being explored in the sensitivity analyses.

In the model, a treatment response (meaning that the treatment is working for the patient) is defined as a reduction of spasticity of >30% on the spasticity numerical rating scale (NRS). But it's also estimated that 10% of non-responders would continue treatment. This is because in a real-world scenario, patients who experience a reduction in spasticity of less than 30% might still continue taking Sativex.

The model is based on assumptions taken from research, including clinical trials. All assumptions were decided by the clinical committee for the guideline and in some cases the estimates from other studies were changed to align with the clinical opinion of the committee.

Some of the key assumptions are summarised in Table 2 and Figure 2 to give a general overview of the model. The full list of assumptions and the analyses that were run to determine them is described in the **NICE guideline, Appendix M: Economic model** (30).

Table 2: Key cost assumptions in the NICE economic model

Treatment costs	Cost
Sativex (first pack free under NHS Pay for Responders scheme)	£300 per pack (270 doses)
Standard of Care (SoC)	£0 (since SoC treatment was received by both groups)
Average adverse events costs	
Non-serious event (including dizziness, dry mouth, fatigue, headache and nausea)	£18.50 each
Serious adverse event	£686.31 each
Average spasticity management costs	
Responders	£138.72 per 4-week cycle
Non-responders	£473.09 per 4-week cycle

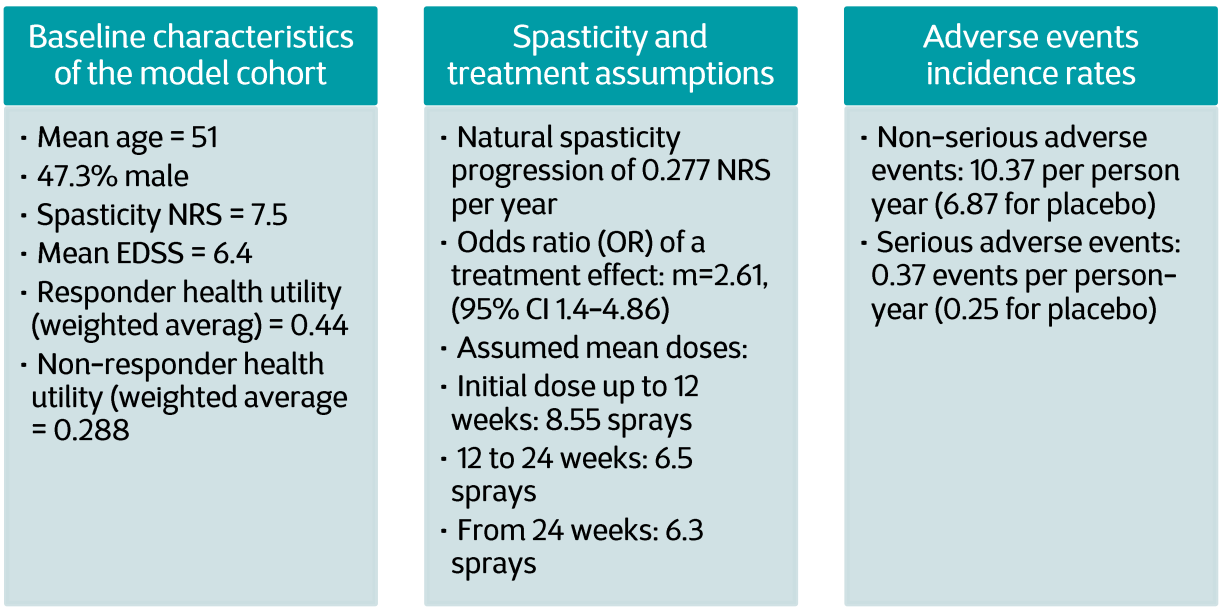

Figure 2: Key assumptions of the NICE economic model

What does the NICE model tell us about Sativex' cost-effectiveness?

Over the 5-year time horizon of the economic model, Sativex as an add-on treatment resulted in higher treatment and adverse events costs, but also added cost-saving of £2,460 by reducing the need for other spasticity management. Overall, compared to SoC alone, Sativex cost £1,580 more, but also produced 0.081 more QALYs, equivalent to about 30 days of perfect health, over the 5 years. This means that the ICER for Sativex was £19,512 per QALY, which is below both the £20k/QALY and £30k/QALY thresholds. You can find relevant costs and savings in Table 3.

Table 3: Estimated costs and cost-effectiveness of Sativex as an add-on treatment

	SoC	Sativex + SoC	Incremental
QALYs	1.286	1.367	0.081
Total costs	£30,630	£32,210	£1,580
Treatment cost	£0	£3,377	£3,377
Adverse events cost	£1,345	£2,008	£663
Management cost	£29,284	£26,825	–£2,460
ICER			**£19,512**

Along with the base case analysis, NICE tested the model with different assumptions through many sensitivity analyses. In most of the analyses, the ICER stayed in or below the range of £20-30,000/QALY gained. This range is normally seen as cost-effective by NICE's advisory committees.

The sensitivity analyses also showed that the model was most sensitive to assumptions related to treatment effects (odd ratios), the dosage of Sativex and patients' quality of life.

For example, the base case assumed that there is no correlation between spasticity NRS scores and EDSS scores. Changing this assumption to assume that NRS and EDSS are correlated at 0.17 (meaning that a reduction in spasticity NRS would also lead to a reduced EDSS score) increased the QALYs gained over the 5 year horizon to 0.125 and lowered the ICER to £12,670.

Also, adjusting the odds ratios so they're based on the two clinical studies that didn't allow participants to go over the licensed dosage (13, 16), increased the QALY gained to 0.111 and led to a much lower ICER of £6.260 per QALY.

What does other research show?

The cost-effectiveness of Sativex has also been estimated for the contexts of other European countries and healthcare systems.

These studies conclude that Sativex seems to be cost-effective for other European countries, as well. The ICER when compared to SoC has been estimated as £10,891/QALY for Wales (published in 2016, (31), 4,968€/QALY (equivalent to £4,289/QALY) for Italy (year of costing: 2013, (32), 11,060€ (£9,549, published in 2013) or 11,214€/QALY (£9,682, year of costing: 2010) in Germany (33, 34) and dominant in Spain, estimated to produce cost savings of 3,496€ (equivalent to £3,018) per patient over 5 years (year of costing: 2010, (34).

There was one previous cost-effectiveness study in 2012 for the UK (35), which found Sativex not to be cost-effective. However, the study only used the very limited data available at the time and also didn't take into account all spasticity management costs.

Only drug costs and clinic visits were considered, but other management costs (including hospital admissions, occupational therapy, disability equipment, and more) that add a lot of management costs weren't included. Cost estimations have a big impact on cost-effectiveness analyses and this could explain why this early study didn't estimate Sativex as cost-effective.

The general consensus in the context of different European countries is that Sativex is a cost-effective treatment option. As Sativex becomes established and is prescribed to more and more patients, more real-world data will become available. This will give us an even clearer picture of the benefits and savings that Sativex provides.

Some limitations to keep in mind

All cost-effectiveness models include a certain level of uncertainty and they can only be based on the data that's available at the time, resulting in limitations that we need to keep in mind.

One important limitation of NICE's economic model is the estimation of spasticity management costs. The costs were taken from a survey of 221 MS healthcare professionals who were asked about the amount and types of care their patients required due to spasticity and how this differed by spasticity severity (8).

But NICE's clinical committee for the guideline were of the opinion that the resource use estimations of the survey (for example wheelchair use) were not due to spasticity alone, especially in patients with high levels of disability. As a result, NICE reduced the estimated resource use by 50% in the model, leading to a 50% reduction in management costs estimated in the survey. But, as NICE themselves state in their guideline, their estimation was very uncertain.

The sensitivity analysis showed that using the estimations from the survey (8) would mean that there is a cost saving of £879 per QALY gained compared to SoC treatment. This would make Sativex a cost-saving treatment option.

The actual costs of spasticity management are uncertain and difficult to estimate perfectly. However, Sativex remains a cost-effective or even cost-saving option with both Stevenson et al.'s and NICE's estimations.

Conclusion

Spasticity is a common and very disabling symptom, especially if it's not managed well. It has a big impact of the lives of people with MS and their friends, families and carers. It also adds a lot of costs to the health and social care systems and society. Because of this, any treatment that is effective and cost-effective needs to be made accessible.

Based on the research of the last two decades, we come to the conclusion that Sativex is safe, effective and likely to be cost-effective. As recommended in NICE's guideline, Sativex should be offered to people with moderate to severe MS related spasticity where other drugs have not worked or caused severe side effects.

At the moment, thousands of people are missing out on a treatment that has the potential to hugely improve their lives.

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Appendix: Key information from the clinical studies

Study	Population	Sample	Methods	Primary findings	Limitations
Collin 2007 **UK, Romania** **Parallel RCT**	Patients with spasticity due to MS in at least 2 muscle groups with an Ashworth score of ≥2 whose current therapy failed to provide adequate relief. Stable disease for at least 3 months before the study. On stable treatment for at least 30 days before entry and during the study	**Sample size** Total: 189 Sativex: 124 Placebo: 65 **Demographic characteristics** 60.3% female Mean age: 49.1 **Baseline mean NRS:** Sativex: 5.49 Placebo: 5.39	Randomized, double-blind placebo-controlled, parallel-group study. 2-week titration phase, initial dose (1 spray) was increased to a maximum 48 sprays per day. The maintenance dose was sustained for 4 weeks. Follow-up: 2 and 6 weeks after beginning treatment	**Mean dose (sprays per day)** Sativex: 9.4 (SD: 6.4) Placebo: 14.7 (SD: 8.4) **Proportion of treatment responders (≥30% NRS reduction)** Sativex: 40% of participants Placebo: 21.9% of participants Difference: 18.1% (95% CI: 4.73, 31.52; p= 0.014) 17.5% of participants in the Sativex group (9.4% placebo) experienced a ≥50% reduction in NRS spasticity (Difference = 8.1%; 95% CI: -1.73, 17.98; P = 0.189). **Mean change in spasticity** Sativex: NRS decrease of 1.18 points Placebo: NRS decrease of 0.63 points Difference = 0.52 points (statistically significant at P = 0.048)	Maximum dose was above the recommended maximum in the SPC (summary of product characteristics) for Sativex of 12 sprays per day

Collin 2010 **(multicentre – 15 in UK, 8 in Czech Republic)** **Parallel RCT**	Patients who had spasticity due to MS for at least 3 months and had a mean daily NRS spasticity score of at least 4 throughout the 6-day baseline period. Patients had to have stable treatment for at least 30 days before study entry.	**Sample size** Total = 337 Sativex: 167 (150 after withdrawn) Placebo: 170 (155 after withdrawn) **Demographic characteristics** 61% female Mean age: 47.5 **Baseline mean EDSS**: 6.0 (SD 1.53) **Baseline mean NRS:** Sativex: 6.84 Placebo: 6.49	Randomized, double-blind placebo-controlled, parallel-group study. 1-week baseline and 14-week treatment period Self-titration to optimal dose with a maximum of 24 sprays per day. No information on length of the titration phase. Follow-up at 2, 6, 10 and 14 weeks after starting treatment	**Mean dose (sprays per day)** Sativex = 8.5 (range: 1–22) Placebo = 15.4 (range: 2–23) **Proportion of treatment responders (≥30% NRS reduction)** Sativex: 36% of participants Placebo: 24% of participants Difference: 12% (p=0.040, 95% CI: 1.024– 2.960) **Mean change in spasticity** Sativex: NRS decrease of 1.30 points Placebo: NRS decrease of 0.84 points Difference: 0.46 points (statistically significant at p=0.035)	Maximum dose was above the recommended maximum in the SPC (summary of product characteristics) for Sativex of 12 sprays per day. But the mean dose for the Sativex group was lower (8.5). While the per-protocol (PP) analysis showed a statistically significant treatment difference in favour of Sativex, the Intention-to-treat (ITT) analysis was not statistically significant.
Leocani 2015	Patients with progressive primary or secondary MS for	**Sample size** Total: 34 Sativex: 15 Placebo: 19	Randomized, double-blind, placebo-controlled, crossover study.	**Mean dose (sprays per day)** Sativex: 7 Placebo: 10	Limited sample size – aim of 40 participants was not reached.

(Italy) **Cross-over RCT**	at least 12 months with moderate to severe spasticity as defined by a Modified Ashworth Scale score of at least 1+ in 1 limb. Patients were 18 years or older with an EDSS score of 3.0-6.5.	**Demographic characteristics** 44% female Mean age: 48 **Baseline mean NRS:** 7.1 **Baseline mean modified Ashworth scale (MAS) score: 9.7**	First treatment period: 4 weeks (including 2 weeks titration) Wash up period: 2 weeks Second treatment period: 4 weeks (including 2 weeks titration) During 2-week titration phase the initial dose was increased by 1 spray per day up to the optimal dose. Maximum dose was 12 sprays per day. Follow up at week 4, 6 and 10.	**Proportion of responders (≥20% improvement on the modified Ashworth scale)** Sativex: 50% Placebo: 23.5% Difference: 26.5% (statistically significant at p=0.041) **Mean change in spasticity (modified Ashworth scale)** Sativex: Improvement of 21.73% Placebo: Improvement of 5.99% Difference: 15.74% (statistically significant at p=0.006) **Mean change in spasticity (NRS)** Sativex: NRS decrease of 2.58 points Placebo: NRS decrease of 1.15 points Difference: 1.43 (not statistically significant, p=0.63)	Relatively short treatment period of 4 weeks.
Markova et al. 2018 **(Multiple sites – 14 in**	Patients with MS-related spasticity symptoms for at least 12 months with moderate to severe spasticity,	**Sample size** Total: 106 Sativex: 53 Placebo: 53	**Phase A**: eligible patients received Sativex for 4 weeks to identify initial responders [≥20% improvement in	**Mean dose (sprays per day)** **Proportion of responders (≥30% NRS improvement) at 12 weeks** Sativex: 77.4%	Demographic and clinical characteristics provided for all Phase A participants (n=191),

the Czech Republic, 1 in Austria) **Parallel RCT**	defined by a NRS score greater than 4.	**Demographic characteristics** (n=191, includes all participants in Phase A) 70.2% female Mean age=51.3 (SD 10.2) **Baseline mean NRS score** 6.4 (SD 1.2)	NRS score]. Following washout, eligible initial responders were randomised to receive Sativex or placebo for 12 weeks (double-blinded, Phase B). Dose was titrated up during the single-blind 4-week trial period (Phase A) to a maximum of 12 sprays per day. Follow up: 12 weeks	Placebo: 32.1% Difference: 45.3% (statistically significant at p<0.0001) **Proportion of initial responders (≥20% NRS improvement) at 4 weeks** Sativex: 81.1% of participants Placebo: 45.3% of participants Difference: 35.8% (statistically significant at p=0.0007) **Mean changes in spasticity (NRS)** Sativex: NRS decrease of 3.5 points Placebo: NRS decrease of 1.6 points Difference: 1.9 points (statistically significant at p<0.0001)	but not for Phase B participants (n=106) seperately. Enriched enrolment study. Patients were only included in the RCT phase of the trial if they showed a minimum 20% improvement in spasticity during the single-blind phase of the trial.
Novotna et al. 2011 **(UK, Spain, Poland, Czech Republic, Italy)**	Patients with a diagnosis of MS for at least 6 months and moderate to severe spasticity due to MS (defined by an NRS score of 4 or	**Sample size** Total: 241 Sativex: 124 Placebo: 117 **Demographic characteristics** 60% female Mean age: 48.6 (9.33 SD)	**Phase A**: initial 4-week single-blind treatment period including a 10-day self-titration period (max. 12 sprays per day) Participants with a ≥20% response to	**Mean dose (sprays per day) Phase B** Sativex: 8.3 Placebo: 8.9 **Proportion of initial responders in Phase A (≥20% reduction in NRS)** Sativex: 47.5% **Mean change in spasticity (NRS)**	Enriched enrolment study. Patients were only included in the RCT phase of the trial if they showed a minimum 20% improvement in spasticity during the single-blind

Parallel RCT	higher) for at least 3 months. Patients had to have at least a 20% reduction in spasticity during phase A.	**Baseline mean EDSS**: 6.0 (SD: 1.45) **Baseline mean spasticity NRS:** 7.0 (SD: 1.39)	Sativex were included in Phase B **Phase B**: 12-week double-blind, randomised, placebo-controlled, parallel-group study Final follow-up visit 2 weeks after completion of treatment	**Phase A:** Sativex: NRS decrease by 3.01 points **Phase B:** Sativex: Further decrease by 0.04 points, to a total decrease of 3.05 points Placebo: Deterioration of 0.81 points Difference: 0.84 (statistically significant at p=0.0002)	phase (Phase A) of the trial. This may increase efficacy and reduce the incidence of adverse events. No evidence of a wash-out period between Phase A and Phase B.
Wade et al. 2004 **(three clinical centres in the UK)** **Parallel RCT**	Patients with a diagnosis of MS and 1 of 5 target symptoms at a sufficient level of severity (spasticity, spasms, bladder problems, tremor, pain other than musculoskeletal).	**Sample size** Total: 160 Sativex: 80 Placebo: 80 Participants with spasticity as their primary symptom: 39 **Demographic characteristics** Sativex 58.8% female Mean age: 51	Six-week randomised, placebo-controlled, double-blind parallel group trial Self-titration with guidelines for increments and a 2-week follow up visit to review dosing and AEs. Maximum dose was set at 120 mg	**Mean dose (sprays per day)** Not reported **Proportion of responders** Not clear **Mean change in spasticity (visual analogue scale VAS)** Participants on active treatment with spasticity as their primary symptom showed a significant reduction in comparison with placebo. Sativex: -31.20 Placebo: -8.40	Maximum permitted dose was above the recommended maximum in the SPC (summary of product characteristics) for Sativex of 12 sprays per day. Mean dose is also not reported. Five primary symptoms were studied, and consequently, the

		Placebo 65% female Mean age: 50.4 **Baseline mean Ashworth score** Sativex: 5/20 Placebo: 4.6/20 **Mean Barthel ADL Index** Sativex: 14.2/20 Placebo: 15.7/20	THC and 120 mg CBD (about 44 sprays per day) At follow up, standardised measures and visual analogue scale (VAS) scores of the primary symptoms were assessed Follow up: 6 weeks. All patients then offered Sativex for 4 further weeks.	Difference: -22.79 (statistically significant at p=0.001)	number of patients with each individual symptom was small.

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MS National Centre 020 8438 0700
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Online
mssociety.org.uk www.
facebook.com/MSSociety
twitter.com/mssocietyuk

MS Society Scotland
0131 335 4050
msscotland@mssociety.org.uk

MS Society Northern Ireland
028 9080 2802
nireception@mssociety.org.uk

MS Society Cymru
mscymru@mssociety.org.uk

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