Sodium oxybate for the treatment of narcolepsy with cataplexy in adults

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Summary

- Narcolepsy is a disabling sleep disorder characterised by excessive daytime sleepiness. Patients are often unable to stay awake or asleep for long periods of time. Around 70% of people with narcolepsy also have cataplexy, which is a sudden loss of muscle tone triggered by strong emotions. Episodes can last from seconds to minutes and occur with varying frequency.
- Pharmacological treatments aim to manage the symptoms. Commonly used drugs include stimulants (e.g. modafinil, methylphenidate), SSRIs and tricyclic antidepressants.
- Sodium oxybate is the sodium salt of gammahydroxybutyric acid (GHB) and is licensed for the treatment of narcolepsy with cataplexy (Xyrem®, UCB Pharma). It is a schedule 2 controlled drug. NHS England currently commission sodium oxybate for treatment of narcolepsy with cataplexy in post-pubescent children aged ≤18 years.
- NETAG reviewed sodium oxybate in 2009 and did not recommend use, since it was considered unlikely to be cost effective. There is limited new evidence since that time.
- A meta-analysis and systematic review published in 2012 summarises all of the available randomised controlled trial evidence. The analysis demonstrates significant improvements in number of cataplexy attacks, wakefulness, number of sleep attacks and global clinician global impression of change associated with sodium oxybate.
- Adverse effects including gastrointestinal effects, dizziness and enuresis were more common with sodium oxybate than placebo. Discontinuation due to adverse effects occurred in 7-9% of patients.
- The cost of sodium oxybate varies with the dose, which ranges from 4.5 g to 9 g daily. This results in an estimated cost per patient of £6,500 to £13,100 per year. Mean doses used in practice are likely to be in the middle of that range.
- No cost-effectiveness studies were found. The number of patients eligible for treatment with sodium oxybate is expected to be low, both in terms of newly diagnosed adults and patients transitioning from paediatric services.

Introduction and background

Narcolepsy is a disabling sleep disorder characterised by excessive daytime sleepiness and abnormal rapid-eye-movement (REM) sleep manifestations including cataplexy, sleep paralysis, and sleep-onset hallucinations. Cataplexy frequently occurs with narcolepsy as a distinct entity. Cataplexy itself is defined as a sudden loss of muscle tone triggered by strong emotions such as laughter, excitement or fright. Cataplectic attacks are sometimes limited to facial muscles or limbs and may manifest as facial flickering, jaw tremor, head or jaw dropping, dropping of objects, or unlocking of the knees. Cataplectic episodes may last less than one second to several minutes and may occur with frequency of less than one per annum to several per day.[1,2]

Narcolepsy is often diagnosed either in adolescence or in middle age.[1,2] Narcolepsy with cataplexy is estimated to affect about 35 per 100,000 of the population.[1] 2 Transposing this rate to the population of the NTAG area yields an estimated adult (age ≥18 years) prevalence of 879, although a large proportion of these patients will be undiagnosed.

Narcoleptic patients generally do not spend much time asleep, even at night. Because they are unable to stay awake or asleep for long periods of time, nocturnal sleep is disrupted in a third of patients. Typically, patients fall asleep as soon as they get into bed but they wake up several times during the night.[1]

As might be expected, the condition often has a negative social impact, particularly with respect to driving, accident occurrence, and work-place and professional performance, with consequent effects on employment.[1,2]

There is currently no cure for narcolepsy and so treatment relies upon lifestyle changes and symptomatic therapies. A range of drug treatments is used in the management of narcolepsy with cataplexy and include sympathomimetic stimulants (mostly adrenergic) for daytime sleepiness and sleep attacks, antidepressants (mostly noradrenergic) for cataplexy and other REM-associated symptoms, and hypnotics for disturbed night-time sleep. Few drugs are actually licensed for narcolepsy with cataplexy, with dexamfetamine (a stimulant) and clomipramine (a noradrenergic antidepressant) being the only other drugs along with Xyrem®. Other drugs commonly used are summarised in table 1.[1-3]

Sodium oxybate (Xyrem®, UCB Pharma Ltd) is licensed for the treatment of narcolepsy with cataplexy in adult patients.[4] It has been available in the UK since 2006 and is a schedule 2 controlled drug.[5] Xyrem was a designated orphan drug when first licensed, but has since been removed from the register of orphan medicinal products.[6]

Sodium oxybate is the sodium salt of gammahydroxybutyric acid (GHB). GHB had gained notoriety as a ‘rave drug’ and a ‘date rape’ drug but has since been legislated.[7] Its mode of action has not been fully elicited but at treatment doses it is believed to act as a central nervous system depressant which promotes slow wave (deep) sleep as well as other effects on sleep patterns and reduced sleep fragmentation.[1,4]

Table 1. Drugs used in the treatment of narcolepsy with and without cataplexy

Type	Examples	Indication/target symptoms
Sympathomimetic stimulant Principally adrenergic activity, also possible action on dopaminergic, GABA-ergic, and serotonergic systems.	Modafinil (Provigil®) Methylphenidate (Ritalin®, Equasym®, Concerta XL®). Dexamfetamine (Dexedrine®)	Excessive daytime sleepiness
SSRIs	Fluoxetine, italopram	Cataplexy and other REM-associated phenomena
Benzodiazepines and related hypnotics	Clonazepam, zolpidem, zopiclone	Adjuvant to aid night-time sleep
Tricyclic antidepressant acting on serotonin and noradrenaline pathways	Clomipramine (Anafranil®)	Cataplectic symptoms
SNRI	Venlafaxine (Efexor®)	Cataplectic symptoms
Noradrenergic reuptake inhibitor	Reboxetine (Edronax®) Atomoxetine (Strattera®)	Cataplectic symptoms

Sodium oxybate is distinguished from other drugs used in the treatment of narcolepsy with cataplexy as it is considered to be effective in controlling daytime sleepiness, cataplexy, and disturbed night-time sleep; i.e. it is used to control multiple symptoms whereas other drug treatments are usually targeted at a single symptomatic aspect.[1,3]

NETAG reviewed the evidence for sodium oxybate in December 2009, at which time the group did not recommend use. Although clinically effective, sodium oxybate was considered unlikely to be cost-effective, even if reserved for the most severe cases.[8]

This report is an update of the 2009 NETAG appraisal.[9] It will review evidence published since that date for the efficacy, safety and cost-effectiveness of sodium oxybate for the treatment of narcolepsy with cataplexy in adults.

Guidance and related advice

There are no UK guidelines on the management of narcolepsy. The European Federation of Neurological Societies published management guidelines in their Handbook of Neurological Management.[10] They make the following recommendations:

- The first line choice of drugs for excessive daytime sleepiness and irresistible episodes of sleep are not unequivocal.
- When the most troubling symptom is excessive daytime sleepiness, modafinil should be prescribed.
- When excessive daytime sleepiness is accompanied by cataplexy and poor sleep, sodium oxybate may be prescribed but should be carefully titrated. Sodium oxybate therapy may be supplemented with modafinil.

- Behavioural measures, such as good sleep hygiene and planned naps, are always advisable.
- Sodium oxybate is the first-line pharmacological treatment for cataplexy. Second-line options include antidepressants such as the tricyclics (particularly clomipramine) and SSRIs. Venlafaxine, reboxetine and atomoxetine are used, but have little published evidence.

NHS England commissions sodium oxybate for post-pubescent children weighing ≥40 kg and aged ≤18 years old, where attempts to control narcolepsy with cataplexy have failed.[11] The inclusion criteria are:

- Patients with narcolepsy with cataplexy according to International Classification of Sleep Disorders 3 (ICSD) criteria
- Adequately treated co-morbid sleep disorders (e.g. sleep apnoea, restless legs syndrome)
- Incomplete response to trials of >1 medication from each symptom group
    - Narcolepsy: methylphenidate, lisdexamfetamine, modafinil, atomoxetine
    - Cataplexy: venlafaxine, clomipramine and other SSRIs
- Significant adverse effects as a result of second line medication in each symptom group, AND
- Assessed as able to benefit from sodium oxybate by a properly constituted multidisciplinary team.

Patients are excluded from treatment if they have serious adverse effects (including respiratory depression) or evidence of incomplete response at 3 months.

The Scottish Medicines Consortium reviewed sodium oxybate in 2007 and did not recommend use.[12] The committee had concerns that the cost of treatment was not justified. The All Wales Medicines Strategy Group were unable to recommend use in 2008, as a submission was not made by the holder of the marketing authorisation.[13]

Clinical efficacy

The NETAG appraisal conducted in 2009 summarised the evidence from two randomised controlled trials (RCTs) and several smaller studies.[9] It concluded that sodium oxybate has clear clinical benefits and there is a clear dose-response relationship for both efficacy and adverse effects. Longer term data indicated continued gains in clinical efficacy for the first few months followed by maintenance of the effect, although this evidence was taken from open studies with smaller patient numbers.

A systematic review and meta-analysis, which considered all of the trial reports discussed in the 2009 NETAG appraisal, was published in 2012.[14] Articles were identified for inclusion via searches of databases including Medline, Embase, CINHAL, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov. Included studies were randomised controlled trials of sodium oxybate in people diagnosed with narcolepsy with cataplexy. Two reviewers independently screened

the search results, assessed study quality and extracted data using a standardised extraction form. When assessed for bias none of the included studies had adequate sequence generation or concealment of treatment allocation. Blinding, accounting for incomplete data and freedom from selective reporting were generally good. Pooled estimates of treatment effects were derived using a random effects model.

Study characteristics are summarised in table 2. Patients with other sleep disorders other than narcolepsy were excluded.

Table 2. Characteristics of studies included in meta-analysis

Article	Type	n	Setting	Duration in weeks (longest follow-up)
Xyrem Int. Group, 2005[15]	RCT	228	42 sleep clinics in USA, Canada, Europe	8 (8)
Xyrem Int. Group, 2004[16]	RCT	55	14 clinical sites	2 (2)
US Xyrem Multicentre Study Group, 2002[17]	RCT	136	18 clinical sites	4 (4)
Black et al, 2006[18]	RCT	278	44 clinical sites in USA, Canada, Europe	4 (8)
Lammers et al, 1993[19]	Crossover RCT	24	1 site, Netherlands	4 (4)
Scrima et al, 1989[20]	Crossover RCT	20	1 site. USA	4 (12)

All of the efficacy outcomes reported favoured sodium oxybate (see table 3) and all were statistically significant, with the exception of the proportion of REM sleep. However, sample sizes for some comparisons were very small, and confidence intervals were wide in several cases, limiting the precision of these estimates of treatment effect.

Table 3. Efficacy outcomes from meta-analysis of sodium oxybate

Outcome	Participants		Treatment difference (95% CI)
	Oxybate	Placebo	
Mean weekly cataplexy attacks	53	71	-8.46 (-15.27 to -1.64)
Maintenance of wakefulness	84	108	5.18 (2.59 to 7.78)
Mean sleep attacks	93	110	-9.65 (-17.72 to -1.59)
Clinician global impression of change “much” or “very much” improved	132	148	2.42 (1.77 to 3.32)
Percentage of REM sleep	21	22	-0.49 (-3.90 to 2.92)

NB: all outcomes except percentage of REM sleep favour sodium oxybate.

No other new trials of sodium oxybate were found. However, several new post-hoc analyses of older trials have been published.

The 4 week trial (n=136) published in 2002 compared sodium oxybate to placebo for the primary outcome of number of cataplectic attacks.[17] The trial had a 12 month open-label extension, which found extended treatment led to further reduction in cataplectic attacks and improvement in quality of life.[21] In the new analysis, Bogan et al examined data from the trial and extension to determine the mean time to treatment response.[22] A total of 86 patients were treated with sodium oxybate in both the original trial and the extension. Of these, 78% were considered responders using the Epworth Sleepiness Scale (ESS, see appendix 1) and 91% were cataplexy responders.

The median time to ESS response was 37 days (95% CI 31-50) and maximum ESS response was achieved in 106 days (95% CI 85-164 days). First cataplexy response was observed at 25 days (95% CI 17-29 days) and maximum response was achieved at 213 days (95% CI 94-279 days).

The 8 week trial (n=228) published in 2005 compared several doses of sodium oxybate to placebo for the primary outcome of change in sleepiness, as measured using ESS.[15] Bogan et al published a further analysis in 2016 which assessed the impact on quality of life, as measured using the Medical Outcomes Survey short form 36 (SF-36) questionnaire. The questionnaire was administered at baseline, and at weeks 4 and 8 and a change of 5 points was considered to represent the minimum clinically important difference.

The analysis found that all doses of sodium oxybate (4.5 g, 6 g or 9 g daily) were associated with significant improvements in the physical components of quality of life ($p<0.05$). However, only the 9 g dose exceeded the minimum clinically important difference, with a change from baseline of 6.3 ±9.1 points. In contrast, only the 6 g dose was associated with a significant improvement in the mental components of quality of life (3.8 points, $p<0.05$ vs. baseline).

The 4 week trial (n=278) published in 2006 recruited patients already taking modafinil.[18] Participants were then randomised to receive sodium oxybate monotherapy, modafinil monotherapy, sodium oxybate + modafinil combination therapy or placebo. Black et al published a further analysis of this trial in 2016 which examined the outcomes in patients with and without cataplexy.[23] Cataplexy was not an inclusion criterion, but 95 participants with a diagnosis of narcolepsy with cataplexy were retrospectively identified. Results in patients with and without cataplexy were compared using the ESS, maintenance of wakefulness test (MTW, see appendix 2) and clinician's global impression of change.

Patients were taking modafinil prior to the trial starting, so patients in the modafinil arm generally did not see any significant change in symptoms. Sodium oxybate was generally associated with improvements regardless of presence of cataplexy, as was the combination of sodium oxybate with modafinil (see table 4).

Table 4 Change from baseline in patients with and without cataplexy (post-hoc analysis)

Patients with or without cataplexy	Placebo	Sodium oxybate	Modafinil	Oxybate + modafinil
Sleepiness (ESS, see appendix 1) Reductions in score represent less sleepiness				
Cataplexy	0.8	-2.9 (p=0.01)	0.7 (p=0.7)	-3.8 (p=0.002)
Without cataplexy	0.8	-3.0 (p=0.02)	0.3 (p=0.8)	-2.8 (p=0.015)
Maintenance of wakefulness (MWT, see appendix 2) Increases in score represent more wakefulness				
Cataplexy	-2.58	0.90 (p=0.1)	0.4 (p=0.05)	3.34 (p<0.001)
Without cataplexy	-2.9	0.45 (p=0.007)	-1.2 (p=0.04)	2.16 (p<0.001)
Clinician global impression of change (% of patients “much” or “very much” improved)				
Cataplexy	18.8	69.2 (p=0.004)	20 (p=0.9)	59.1 (p=0.001)
Without cataplexy	28.6	44.1 (p=0.3)	19.4 (p=0.5)	41.4 (p=0.7)

NB: patients were taking modafinil prior to randomisation in this study. All p values are comparisons with placebo.

Safety

The meta-analysis reported on several safety outcomes (see table 5). Serious adverse effects were rare. Nausea, vomiting, dizziness and enuresis were all found to be more common with sodium oxybate than placebo, and the difference was statistically significant for all comparisons except vomiting. As with the efficacy outcomes, wide confidence intervals limit the precision of these estimates.

Discontinuation due to adverse effects was reported for two of the trials, and occurred in 7% of patients in one compared to 9% in the other.[15,18]

Table 5. Safety outcomes from meta-analysis of sodium oxybate

Outcome	Participants		Risk ratio (95% CI)
	Oxybate	Placebo	
GI effects/nausea	145	450	7.74 (3.15 to 19.05)
Vomiting	90	94	2.87 (0.84 to 9.80)
Dizziness	88	90	11.83 (1.56 to 89.43)
Enuresis	145	150	4.32 (1.14 to 16.41)

NB: all outcomes favour placebo.

Sodium oxybate is contraindicated in patients with major depression or succinic semialdehyde dehydrogenase deficiency, and in those taking opioids or barbiturates.[4] It should be used with caution in patients with underlying respiratory disorders, including sleep apnoea, and in patients taking substances which increase

the risk of respiratory depression. Caution is also required in patients taking substances known to increase plasma GHB concentrations, such as valproate and topiramate.

Dosage and administration

Sodium oxybate is available as a licensed oral 500 mg/mL oral solution (Xyrem®, UCB Pharma).[4] The recommended starting dose is 4.5 g/day in two equal doses, to be taken upon getting into bed and again 2.5-4 hours later. Both doses should be made up at the same time, upon retiring, to facilitate ease of administration. The dose should be titrated to response based on efficacy and tolerability, to a maximum of 9 g/day.

Cost analysis

Xyrem costs £360 per £180 mL bottle (excl VAT). Cost per patient varies with the required dose, ranging from £504 to £1008 per 28 days (£6,500 to £13,100 per year) based on a daily dose of 4.5 to 9.0 g.

In studies of longer term use the mean daily doses of sodium oxybate were found to be 6.5 g (n = 117 with 12 months follow-up) and 6.8 g (n = 55 with 21 months follow-up, range 7 to 44 months).[16,21] Median doses were found to be 6 g and 7.5 g, respectively. Therefore, it is assumed that a 'typical' or 'average' dose for cost analyses is 7 g daily although it should be noted this does not correspond to an actual licensed dose. The annual cost of treatment at this dose is about £10,000 (£12,000 incl VAT).

Sodium oxybate is currently protected by several active patents, however generics are expected to enter the market in Europe starting in January 2020 which may alter costs.[24] A once-nightly preparation is currently being studied in a phase III trial, which is expected to be completed in July 2017.[25]

The prevalence of narcolepsy has been estimated at roughly 35 per 100,000, although a large proportion of these may be undiagnosed.[1] Approximately 70% of people with narcolepsy also experience cataplexy. The population of the North East & Cumbria is approximately 3.1 million, of which approximately 2.5 million are aged over 18 years.[26] These figures suggest that there may be approximately 880 adults with narcolepsy in the North East and Cumbria, of whom 615 would be expected to experience cataplexy. This is roughly in line with patient numbers reported by consultant neurologists in the region.[27]

Sodium oxybate would be expected to be reserved for patients with severe cataplexy who have not responded to first line stimulants. [redacted] NHS England estimates that there are currently 10 children treated with sodium oxybate nationally,

with a further 10 waiting for treatment. They also estimate that 10 children each year may be diagnosed with severe narcolepsy with cataplexy and qualify for sodium oxybate treatment.[11]

No cost-effectiveness studies were found. In 2007 the SMC published brief details of a cost-utility analysis provided by the manufacturers of Xyrem.[12] The analysis compared sodium oxybate to clomipramine in patients diagnosed with narcolepsy with cataplexy, and found that the cost per QALY ranged from £65,980 for 6g daily dosing to £49,590 for the 9g daily dose. Sensitivity analyses found that the model was sensitive to utility values and drug costs. The price for Xyrem has not changed in the intervening time, but the utility values used in the model are not presented and could not be assessed.

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References

1. Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. Lancet 2007;369:499-511.
2. Kotagal S, Pianosi P. Sleep disorders in children and adolescents. BMJ 2006;332:828-32.
3. Wise MS, Arand DL, Auger RR et al. Treatment of narcolepsy and other hypersomnias of central origin. Sleep 2007;30:1712-27.
4. Summary of product characteristics: Xyrem 500 mg/ml oral solution, UCB Pharma Limited. Date of revision of the text: 20/01/2017. https://www.medicines.org.uk/emc/medicine/17364.
5. British National Formulary. Online edition. April 2017. Accessed via www.medicinescomplete.com.
6. European Medicines Agency. Xyrem. Sodium oxybate. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000593/human_med_001163.jsp&mid=WC0b01ac058001d124 Accessed 23/05/17.
7. Stell JM, Ryan JM. Ecstasy and neurodegeneration. gamma-Hydroxybutyrate is a new recreational drug that may lead to loss of consciousness. BMJ 1996;313:424.
8. North East Treatment Advisory Group. Treatment appraisal: decision summary. Sodium oxybate in the management of narcolepsy with cataplexy. January 2010. http://ntag.nhs.uk/docs/rec/NETAG-decision-summary-notice-Sodium-oxybate-Xyrem.pdf 2009.
9. North East Treatment Advisory Group. Appraisal Report: Sodium oxybate (Xyrem®) in the management of narcolepsy with cataplexy. http://ntag.nhs.uk/docs/app/Sodium%20Oxybate%20(Xyrem)%20NETAG-Appraisal-Report.pdf 2009.
10. European Federation of Neurological Societies. Chapter 38: Management of narcolepsy in adults. In: Gilhus NE, Barnes MR, Brainin M, editors. European Handbook of Neurological Management. p. 513-28.
11. NHS England. Clinical Commissioning Policy: Sodium oxybate for symptom control of narcolepsy with cataplexy (children). Reference 16065/P. December 2016. https://www.england.nhs.uk/wp-content/uploads/2016/12/clin-comm-pol-16065P.pdf.
12. Scottish Medicines Consortium. Sodium oxybate 500 mg/ml oral solution (Xyrem). September 2007. https://www.scottishmedicines.org.uk/files/sodium_oxybate_500mg_ml_oral_solution__Xyrem__Resubmission_FINAL_August_2007_for_website.pdf.
13. All Wales Medicines Strategy Group. Sodium oxybate (Xyrem®) Reference No. 279. http://www.awmsg.org/awmsgonline/app/appraisalinfo/279.
14. Alshaikh MK, Tricco AC, Tashkandi M et al. Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis. J Clin Sleep Med 2012;8:451-8.
15. Xyrem International Study G. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. J Clin Sleep Med 2005;1:391-7.
16. Group USXMS. Sodium oxybate demonstrates long-term efficacy for the treatment of cataplexy in patients with narcolepsy. Sleep Med 2004;5:119-23.
17. Group USXMS. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. Sleep 2002;25:42-9.
18. Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep 2006;29:939-46.

19. Lammers GJ, Arends J, Declerck AC et al. Gammahydroxybutyrate and narcolepsy: a double-blind placebo-controlled study. Sleep 1993;16:216-20.
20. Scrima L, Hartman PG, Johnson FH, Jr. et al. Efficacy of gamma-hydroxybutyrate versus placebo in treating narcolepsy-cataplexy: double-blind subjective measures. Biol Psychiatry 1989;26:331-43.
21. A 12-month, open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. Sleep 2003;26:31-5.
22. Bogan RK, Roth T, Schwartz J et al. Time to response with sodium oxybate for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. J Clin Sleep Med 2015;11:427-32.
23. Black J, Swick T, Bogan R et al. Impact of sodium oxybate, modafinil, and combination treatment on excessive daytime sleepiness in patients who have narcolepsy with or without cataplexy. Sleep Med 2016;24:57-62.
24. Insight A. http://adisinsight.springer.com/. Accessed 24/05/17.
25. ClinicalTrials.gov. Sodium Oxybate for Treatment of Excessive Daytime Sleepiness and Cataplexy in Narcolepsy. NCT02720744. https://clinicaltrials.gov/ct2/show/NCT02720744.
26. Office for National Statistics. Clinical Commissioning Group Mid-Year Population Estimates. Mid-2015. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/clinicalcommissioninggroupmidyearpopulationestimates.
27. Personal communication, April 2017. .

Appendix 1: The Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire with eight items each with a score from 0 to 3, so that the range for overall scale is 0 to 24. Each of the eight item-scores of the ESS provides a measure of one situational sleep propensity: the habitual tendency to doze or stay awake in that situation as part of daily life. The ESS relies on subjective and retrospective reports of dozing behaviour such as a nodding head and lapses of attention, and measures sleep propensity. Having a high sleep propensity (i.e. excessive daytime sleepiness) means having a history of dozing in situations that have a relatively low soporific nature in which normal subjects seldom doze. A normal score is considered to be between 0 and 10 points.

Sample of the ESS

Score: 0 = would never doze; 1 = slight chance of dozing;
2 = moderate chance of dozing; 3 = high chance of dozing.

Situation:

1. Sitting and reading
2. Watching TV
3. Sitting, inactive in a public place (e.g. a theatre or a meeting)
4. As a passenger in a car for an hour without a break
5. Lying down to rest in the afternoon when circumstance permit
6. Sitting and talking to someone
7. Sitting quietly after a lunch without alcohol
8. In a car, while stopped for a few minutes in the traffic

Johns MW. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. Sleep 1991;14(6):540-5

Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth sleepiness scale: Failure of the MSLT as a gold standard. Journal of Sleep Research 2000;9:5-11

Appendix 2: The Maintenance of Wakefulness Test (MWT)

The MWT measures a subject's ability to stay awake in a quiet, non-stimulating situation for a given period time. It may be used to evaluate the response to therapy for individuals in whom conditions causing daytime sleepiness have been diagnosed. The test is conducted using an assortment of quantitative instruments that can objectively detect sleep, including the type/stage/depth of sleep. The duration of the MWT can vary but it is recommended that 40 minutes duration is used. Four 20-minute tests, each two hours apart, were used in the study of sodium oxybate and modafinil.[18] Patients are required to sit or lie still and remain in a dark and silent room for the duration of the test. They are not permitted to use any physical technique to assist in staying awake (e.g. pinching themselves). The test is repeated, usually four times, with the mean sleep latency time in minutes taken as the result.

Mean sleep latency of less than eight minutes is taken to be abnormal, whereas staying awake for all four trials of a 40 minute test provides the strongest support of an individual's ability to stay awake. Values between 8 and 40 minutes are of uncertain significance. There are no established cut-off values for a change in mean sleep latency when used to evaluate a response to treatment.

Sullivan SS, Kushida CA. Multiple sleep latency test and maintenance of wakefulness test. Chest 2008;134:854-61