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Benefits and Risks of Pharmacotherapy for Narcolepsy

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Abstract

Narcolepsy is a life-long central nervous system (CNS) syndrome characterised by excessive sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations and disturbed night-time sleep. Unsuccessfully treated narcolepsy confers increased risks on patients and on society due to the patient's increased chance of becoming involved in vehicle crashes and workplace mishaps. The syndrome may be diagnosed by a clinical history positive for cataplexy and excessive daytime sleepiness and negative for other more common sleep disorders such as sleep apnoea and sleep deprivation. Night-time polysomnography and multiple sleep latency testing are helpful in differentiating narcolepsy from other sleep problems. Recent data from canine, murine, and human forms of narcolepsy indicate that genetically or developmentally mediated deficits in the hypocretin neurotransmitter system may cause some, but not all, forms of narcolepsy. Pharmacotherapy for narcolepsy is required to control symptoms and involves the use of

CNS stimulants or modafinil to control sleepiness and antidepressant medications or sodium oxybate to control cataplexy. Modafinil and sodium oxybate have been developed and approved specifically for the indication of narcolepsy based on large, double-blind, placebo-controlled, parallel group efficacy and safety studies. The efficacy of drugs in the treatment of narcolepsy is variable from patient to patient and usually associated with adverse effects that can limit patient compliance and, therefore, symptom control. Nevertheless, the benefits of pharmacotherapy are judged to outweigh the risks to the patient. The favourable benefit-risk ratio of pharmacotherapy is greater if one considers the reduced risk to society of vehicle crashes and workplace mishaps that might be precipitated by attentional lapses or sleep attacks in the untreated or under-treated patient with narcolepsy.

Narcolepsy is a life-long central nervous system (CNS) disorder characterised by potentially disabling symptoms of excessive sleepiness and cataplexy. The narcolepsy syndrome confers on patients and society increased risks for accidents in the workplace and while driving. Pharmacotherapy for narcolepsy is often required to reduce such risks. Pharmacotherapy can involve the use of schedule II stimulants as well as the off-label use of other prescription medications. This paper reviews the narcolepsy syndrome and assesses the benefits and risks of long-term pharmacotherapy for narcolepsy.

1. The Narcolepsy Syndrome

1.1 Overview

Narcolepsy, next to sleep apnoea,[1] is the most common diagnosis made in patients who complain of excessive sleepiness.[2] Descriptions of narcolepsy appeared as early as 1862. However, Gelineau first used the term, 'narcolepsy', in 1880 in reference to a syndrome comprised of four characteristic symptoms, known as the narcolepsy tetrad:[3-5]

- sleep attacks
- cataplexy
- hypnagogic hallucinations
- sleep paralysis.

With the advent of sleep laboratories that can perform all-night polysomnographic recordings, disturbed nocturnal sleep was recognised as a component of the clinical presentation in almost all patients with narcolepsy, and some authorities have suggested that disturbed nocturnal sleep should become the fifth symptom, comprising a narcolepsy pentad.[6]

Molecular studies such as human leucocyte antigen (HLA) typing and evaluation of hypocretin (orexin) related genes have yielded some laboratory findings that are quite specific to narcolepsy, especially narcolepsy with cataplexy.

1.2 Human Leucocyte Antigen (HLA) Findings

Japanese investigators were first to document a strong association between narcolepsy and certain HLA DR and DQ haplotypes.[7,8] In patients with an unambiguous history of cataplexy, other groups have confirmed this finding and extended its description.[9-11] In other series of patients with narcolepsy, particularly those in whom there is not a uniform presence of cataplexy, the HLA association is not as strong.[12,13] Nevertheless, the association between narcolepsy and HLA antigens has generated speculation that some forms of narcolepsy may be the result of some autoimmune process.[14] HLA-DR2, which is a supertype of HLA-DRB1*1501, is associated with autoimmune diseases which affect the CNS, including multiple sclerosis and optic neuritis. However, no abnormalities of immunological function have yet been identified in the human or canine forms of narcolepsy despite considerable research.[15] The haplotype HLA-DQB1*0602 is even more tightly asso-

ciated with the diagnosis of narcolepsy than is HLA-DRB1*1501.[16] In some ethnicities, the HLA-DQB1*0602 haplotype may also be associated with abnormal immune responses.[17,18]

1.3 Hypocretin (Orexin) Findings

The connection between defects in the hypocretin neurotransmitter system and narcolepsy was first described in dogs and, shortly thereafter, in mice developed with defects in the gene that produces hypocretin or the genes that produce hypocretin-related receptors.[19,20]

It is now generally accepted that syndrome of narcolepsy in *most* humans and animals stems from one or more defects in the functioning of the hypocretin neurotransmitter system.[21] The literature on narcolepsy in humans,[22,23] naturally occurring animal forms of narcolepsy,[19] and genetically engineered animal forms of narcolepsy,[20] collectively indicate that the hypocretin system becomes dysfunctional, giving rise to the symptoms of narcolepsy via genetic defects, genetic predispositions and developmental accidents. Hypocretin abnormalities, however, are not found in all patients with the diagnosis of narcolepsy. The hypocretin system may be normal in up to 20% of patients with narcolepsy with cataplexy – usually in those patients without the HLA DR and DQ markers. The hypocretin system is also normal in up to 100% patients without cataplexy.[24]

Narcolepsy has been described in a variety of non-human species, including canine, murine, equine, and bovine forms.[20,25-27] The above-referenced neurochemical and pharmacotherapeutic studies of human, canine, and murine narcolepsy suggest that several abnormalities are involved:

- low levels of hypocretin in the cerebrospinal fluid of humans with narcolepsy
- abnormal or non-functional hypocretin 2 receptor in dogs
- abnormal production of the parent molecule for hypocretin 1 and 2 in mice
- abnormal production of hypocretin 1 and 2 receptors in mice
- widespread under-release of dopamine in humans and dogs
- proliferation of muscarinic acetylcholine receptors and hypersensitivity to acetylcholine in the brainstem in humans and dogs.

Ultimately, molecular genetic analyses of patients with narcolepsy will probably provide foundations for more objective diagnostic methods and for rational segregation of narcolepsy patients into subtypes. It is expected that such subtypes will be important for more refined research techniques and subtype-specific treatments. Already, assaying cerebrospinal fluid for the finding of undetectably low levels of hypocretin has been suggested as a new diagnostic technique.[28]

1.4 Pathophysiology

These neurochemical abnormalities fit with current understanding of mechanisms that regulate wakefulness, sleep, and rapid eye movement (REM) sleep. Dopamine is thought to be important for ascending alerting pathways and for motor pathways that can indirectly influence alertness. Drugs that potentiate dopamine transmission lead to increased alertness and increased motor activity. Acetylcholine is important as an inhibitory transmitter in a pathway that descends from the forebrain through the pontine reticular formation into the spinal cord. Drugs that activate cholinergic transmission can bring about elements of sleep and, in particular, REM sleep. The motor inhibition of REM sleep and cataplexy are mediated at the spinal cord level through glycinergic interneurons.[29]

1.5 Epidemiology

The prevalence of narcolepsy in Western Europe and North America has been estimated at 0.03 to 0.06% (i.e. 30–60 per 100 000).[30] However, prevalence estimates can differ based upon whether or not the presence of cataplexy is required for the diagnosis of narcolepsy. A recent report from Olmsted County Minnesota[31] indicates that the prevalence for narcolepsy on January 1, 1985 was 56.3 per 100 000 persons. The prevalence estimate

for narcolepsy with cataplexy in this county was 35.8 per 100 000. While the diagnosis appears to be equally likely in men and women,[5] there may be a higher incidence in men[31] and/or a higher diagnostic rate in men.[32] The disease typically emerges in the second decade of life and increases in severity through the third or fourth decade.[33,34]

1.6 Clinical Presentation

Patients with narcolepsy experience episodes of unwanted or unintended sleep. The vast majority of patients report that they awaken feeling refreshed from such episodes of sleep. In fact, napping, if permitted by the patient's schedule and responsibilities, can reduce the need for pharmacotherapy.[35,36] The sleepiness of narcolepsy seems to involve dysregulation of wakefulness and sleep rather than true hypersomnolence. Patients with narcolepsy do not sleep more than normal controls.[37,38] Patients with narcolepsy also experience intrusion into wakefulness of components of REM sleep such as paralysis and hallucinations. Paralysis is due to the same central mechanisms that normally block muscle activity during REM sleep. Two distinct types of paralysis may occur:

- Cataplexy, characterised by sudden muscle weakness and partial or complete collapse during excitement or anticipation (e.g. telling a joke or catching a fish).
- Sleep paralysis, an often frightening inability to move just before falling asleep (hypnagogically) or just after awakening (hypnopompically). Sleep paralysis frequently is associated with, usually unpleasant, hallucinations. Hypnagogic paralysis and hallucinations are more specific to narcolepsy than are the hypnopompic varieties.

Such paralytic and hallucinatory experiences typically first occur early in a patient's life and, with delayed diagnosis and treatment, are left unexplained for years. These experiences can superimpose secondary psychological problems on the patient's clinical presentation and complicate the recording and evaluation of adverse effects of medications.

Narcolepsy is associated with an abnormal tendency to achieve REM sleep shortly after sleep onset. REM sleep normally first occurs approximately 80 to 100 minutes after sleep begins at night. Patients with narcolepsy have periods of REM sleep occurring immediately or within the first few minutes of sleep. This tendency is sometimes termed 'increased REM pressure'. The clinical use of the Multiple Sleep Latency Test (MSLT) derives, in part, from this feature of narcolepsy. In contrast to healthy controls, patients with narcolepsy tend to fall asleep quickly on the four or five 'naps' comprising an MSLT and to reach REM sleep within 15 minutes of sleep onset.[39]

2. Pharmacotherapy

2.1 Overview

Discussion of the various pharmacological treatments of the narcolepsy syndrome must first address what symptoms should be, and can be, treated. As was described above, narcolepsy is characterised by a variety of symptoms throughout the 24-hour day. Therefore it is important to decide when, during the 24-hour day, narcoleptic symptoms should be treated. Concerns for the safety of the patient and of others who share the road and the workplace with the patient[40-43] obligate clinicians to address the symptoms of sleepiness and cataplexy during the day. Questions have not been systematically addressed concerning the presence or significance of abnormal sleepiness during the night-time in patients with narcolepsy. While circadian effects and the effects of narcolepsy may be experimentally separable, clinical questions remain as to whether patients with narcolepsy are at special risk during night-time driving or shift work. It is clinically conservative to assume that patients with narcolepsy are more impaired by sleepiness during the night than are healthy controls. However, it is not documented that the pharmacotherapies used to control daytime sleepiness in narcolepsy are efficacious when given while the patient with narcolepsy is trying to stay awake and function at night.

Table I. Drugs marketed in the US that have narcolepsy as a clinical indication and are used to treat sleepiness

Tradename[a]	Generic name	Manufacturer
Adderall® tablets	Amphetamine (d and l)	Shire US
Dexedrine® spansule capsules	d-Amphetamine	GlaxoSmithKline
Dexedrine® capsules	d-Amphetamine	GlaxoSmithKline
DextroStat® tablets	d-Amphetamine	Shire US
Metadate™ ER tablets	Methylphenidate	Medeva
Methylin™ ER tablets	Methylphenidate	Mallinckrodt
Provigil® tablets	Modafinil	Cephalon
Ritalin® hydrochloride tablets	Methylphenidate	Novartis

a The use of tradenames is for product identification purposes only and does not imply endorsement.

ER = extended release.

Prior to the advent of night-time therapy with sodium oxybate for the reduction of cataplexy, the symptom of disturbed nocturnal sleep has generally not been treated on a nightly basis. Some clinicians have found occasional sedative hypnotics to be helpful.[44] It is not uncommon for physicians to prescribe, for night time use, sedative hypnotics with elimination half-lives short enough to minimise the chances of morning carry-over effects (e.g. triazolam, zolpidem, zaleplon, etc.).[45] Other clinicians believe that improvement in the night-time sleep duration and continuity with sedative hypnotics, seems to have minimal clinical benefit for patients with narcolepsy. In any case, it is rare for clinicians to prescribe sedative hypnotics on a long term nightly basis for any condition including narcolepsy.[46] However, as will be discussed, clinical trials with sodium oxybate have re-introduced the question of whether improvement of night time sleep continuity has a role in the control of sleepiness in narcolepsy.

Thus, by convention and by default, pharmacotherapy for narcolepsy focuses on daytime symptoms and is two-pronged: (i) the symptom of excessive sleepiness is reduced with psychomotor stimulant drugs; and (ii) the symptoms of cataplexy, hypnagogic hallucinations and sleep paralysis are controlled with antidepressant drugs or sodium oxybate. If the particular stimulant and antidepressant are chosen judiciously and taken at appropriate times of day, the two classes of drugs can work in concert to enhance wakefulness during the day, decrease cataplexy, and promote continuous sleep during the night. While the choices of drugs we have made for detailed discussion in this article were primarily based on each agent's Food and Drug Administration (FDA) and market status within the US, these drugs also have broad availability throughout the world.

2.2 Drugs for Sleepiness

Table I presents a list of drugs currently having narcolepsy as at least one clinical indication. The most recent addition to this list is modafinil, a non-amphetamine, alerting agent initially developed for the indication of narcolepsy. Several other drugs are frequently used in the treatment of narcolepsy on an 'off-label' basis. Most prominent among these are methamphetamine, pemoline and mazindol.

With the exception of modafinil, the agents most often used to treat excessive somnolence are psychomotor stimulants. Psychomotor stimulants may be defined as drugs that produce behavioural activation and increased arousal, motor activity and alertness. Psychomotor stimulants may be divided into three classes: (i) direct acting sympathomimetics, such as the α_1 adrenergic stimulant, phenylephrine; (ii) indirect acting sympathomimetics such as methylphenidate, amphetamine, mazindol, and pemoline; and (iii) stimulants that are not sympathomimetics and have different mechanisms of action, such as caffeine. For the

most part, indirect sympathomimetics have been the stimulants of choice for the treatment of narcolepsy.

Some CNS stimulant drugs (e.g. dextroamphetamine and methylphenidate) have FDA approval for the indication of narcolepsy. Other amphetamine-based drugs are used for the treatment of narcolepsy on an off-label basis (e.g. methamphetamine).

Amphetamine, racemic B-phenylisopropylamine, is a powerful CNS stimulant which was first used in the 1930s as a bronchodilator, respiratory stimulant and analeptic. Several preparations of amphetamine have been developed as oral preparations which vary in terms of the concentration of the dextro-isomer and whether a phosphate or sulphate salt is used.

Methylphenidate, a piperidine derivative, was introduced in the 1950s as a milder CNS stimulant.

Modafinil (2-[(diphenylmethyl)sulfinyl] acetamide), a racemic compound unrelated to the amphetamines, cannot be categorised as a psychostimulant. Modafinil began to appear on the world market for the indication of narcolepsy and CNS hypersomnia in the early 1990s. Modafinil was discovered and developed for narcolepsy by Laboratoires Lafon in France and subsequently taken worldwide by Cephalon, Inc. in the US. The first placebo-controlled crossover studies on the effect of modafinil in narcolepsy appeared in the mid 1990s.[47-49] Longest term follow up data on the use of modafinil date back to this period. The largest double-blind, placebo-controlled studies of this compound were completed in Canada and the US.[50-52]

Pemoline (2-amino-5-phenyl-2-oxazolin-4-one) is an oxazolidine compound that was introduced as a mild CNS stimulant. Since the introduction of pemoline, significant potential for hepatotoxicity has been documented.[53-55] The need to perform regular and frequent liver function testing has limited the overall acceptance of this agent as a pharmacotherapy for narcolepsy.

Table II. Drugs marketed in the US commonly used to treat cataplexy

Tradename	Generic name	Manufacturer
	Clomipramine	Geneva; Mylan; Watson
Effexor®	Venlafaxine	Wyeth-Ayerst
Prozac®	Fluoxetine	Lilly
Vivactil®	Protriptyline	Merck
Xyrem®	Sodium oxybate	Orphan Medical US

2.3 Drugs for Cataplexy

Table II presents a list of drugs commonly used to treat the cataplexy of narcolepsy. Most of the drugs in table II have depression and/or obsessive compulsive disorder as their clinical indication.

Numerous antidepressants are prescribed on an off-label basis for treatment of cataplexy.

Clomipramine (3-chloro-5-[3(dimethylamino) propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride) is an example of a tricyclic antidepressant.

Venlafaxine [(R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)] cyclohexanol hydrochloride] is a novel antidepressant whose action is thought to derive from reuptake blockade of serotonin, norepinephrine (noradrenaline) and, to some extent, dopamine.

Fluoxetine (±-*N*-methyl-3-phenyl-3-[(α,α,α-trifluro-p-toly)oxy]propylamine hydrochloride) is an example of a specific serotonin reuptake inhibitor.

Protriptyline (*N*-methyl-5H dibenzo[a,d]-cyclohepten-5-propanamine hydrochloride) is an example of a heterocyclic antidepressant.

Sodium oxybate (sodium 4-hydroxbutyrate) is not an antidepressant and is the only drug in table II that has narcolepsy as a clinical indication.

3. Risks of Pharmacotherapy

A consideration of the relative risks and benefits of pharmacotherapeutic agents for narcolepsy is complicated by several inter-related factors:

- There are currently only two agents, modafinil and sodium oxybate, that have been developed and undergone US FDA evaluation for the indi-

cation of narcolepsy. Other agents commonly prescribed for narcolepsy were initially developed for various indications and were approved for market at a time when different guidelines for the evaluation of safety and efficacy of therapeutic agents prevailed.

- Published information on the efficacy and adverse effects of agents prescribed for narcolepsy is often not specific to the doses and populations that are relevant to the population of patients with narcolepsy.

Table III presents, for drugs commonly used to treat narcolepsy, the generic name, FDA and the Drug Enforcement Agency (DEA) status, dose range usually used, and adverse effects. The organisation of table III is based on adaptations of entries from the Coding Symbols for Thesaurus of Adverse Reactions Terms (COSTART) dictionary that subdivides CNS effects and lists any concerns about risks of abuse and diversion. Information on adverse events was obtained from package labels and from American Hospital Formulary Service (AHFS) Drug Information of 2002. Adverse events are listed if they were reported to occur in at least 1% of the patients sampled. It cannot be stated, however, that the surveillance and detection mechanisms for adverse events listed are comparable from drug to drug. The drugs in tables I, II and III differ in terms of their primary indications, the patient populations in which they are used and the FDA regulations and policies applicable at the time of their introduction to the US market. The importance of the dissimilarities in the regulatory histories of the drugs listed in tables I, II and III should not be underestimated. For example, while the adverse effects of modafinil tabulated in table III may not appear to be qualitatively dissimilar to those of amphetamine-like drugs, modafinil is widely regarded as less prone to use-limiting adverse effects and to abuse than are the amphetamines. One indication of these differences is the schedule IV DEA status of modafinil versus schedule II for the amphetamines.

In addition to the adverse effects tabulated for antidepressant agents, it should be noted that evaluations of patients taking drugs in this class often disclose increased levels of periodic limb movements during sleep (sometimes referred to as nocturnal myoclonus).[56-58] The clinical significance for the treatment of narcolepsy of this observation is unknown and especially difficult to appreciate because periodic limb movements during sleep is a well recognised feature of unmedicated patients with narcolepsy.[59] Nevertheless, in patients with narcolepsy who have markedly disrupted nocturnal sleep, sleep specialists often consider the possibility of antidepressant-induced or antidepressant-exacerbated periodic limb movements during sleep.

4. Benefits of Pharmacotherapy

As was mentioned earlier, pharmacotherapy for narcolepsy addresses the symptom of excessive daytime sleepiness and, if necessary and in a separate fashion, the symptom of cataplexy. Because of the dangers and discomforts associated with impaired alertness in narcolepsy, control of excessive sleepiness is focused on daytime alertness and performance and is mandated by patient needs and by societal needs for safety on the highways and in the workplace. Therefore, benefits of stimulant or alerting drugs should be evaluated in terms of how well both types of needs are served.

Psychostimulants have been used for centuries in tonics and other preparations to allay fatigue and treat a variety of ailments (for reviews see Haddad[60] and Angrist and Sudilovsky[61]). Coffee along with leaves of sage or rosemary was prescribed as early as 1672 for disorders associated with sleepiness. The Indians of Peru and Bolivia used cocaine, a crystalline alkaloid derived from the leaves of the coca plant, for pleasure and to increase stamina. From 1886 to 1905, cocaine was an ingredient in Coca-Cola. The medicinal use of cocaine was advocated by Freud.[62] However, the profound potential of cocaine for abuse and addiction soon limited the role of this stimulant in modern medicine.

In the early 1930s, Doyle and Daniels,[63] Janota,[64] and Daniels[65] described the use of ephedrine to treat sleepiness. After 1956, methyl-

Table III. Drugs commonly used to treat narcolepsy. Information on adverse events was obtained from package labels and from the American Hospital Formularly Service Drug Information (2002)

	Treatment for sleepiness				Treatment for cataplexy				
	d-amphetamine	methylphenidate	pemoline	modafinil	clomipramine	venlafaxine	fluoxetine	protriptyline	sodium oxybate
FDA-approved indication	ADHD, narcolepsy	ADHD, narcolepsy	ADHD	Narcolepsy	OCD	Depression	Depression, OCD, bulimia	Depression	Narcolepsy
DEA schedule status	II	II	IV	IV					III
Dose range (mg/day)	5-60	5-60	18.75-150	100-400	25-75	25-75	5-60	5-60	3-9 g/day
Societal/legal abuse potential	High, amphetamine is among the most abused drugs with high addiction potential	High, methylphenidate is considered to be an abused drug with high addiction potential	NA	Moderate, produces euphoria, self-reinforcing in monkeys	NA	NA	NA	NA	Low. While sodium oxybate is one of a family of molecules that contains or is metabolised into GHB, which is CNS depressant that is abused, there are less expensive sources of GHB
Societal/legal diversion potential	High, substantial risk of fraudulent prescriptions and illicit sale of medication	High, substantial risk of fraudulent prescriptions and illicit sale of medication	NA	Moderate, little illicit diversion	NA	NA	NA	NA	Low. While sodium oxybate is one of a family of molecules that contains or is metabolised into GHB, which is CNS depressant that is diverted and sold illicitly, there are less expensive sources of GHB
Adverse effects as grouped under symptom or system/event category									
Body as a whole	NA	Headache	Headache	Headache, chest pain, neck pain, chills, rigid neck, fever	Headache, migraine	Headache, asthenia, infection, chills, chest pain, trauma	Headache, asthenia, flu syndrome, fever	Headache, fatigue, perspiration	Asthenia, fever, flu syndrome, headache, infection, viral infection, pain, chest pain
Cardiovascular system	Palpitations, tachycardia, elevation of blood pressure, cardiomyopathy	Fever; palpitations; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; cerebral arteritis and/or occlusion; leucopenia and/or anaemia	NA	Hypotension, hypertension, vasodilation, arrhythmia, syncope	Orthostatic decrease in blood pressure, tachycardia, flushing, palpitations, chest pain, syncope, ECG abnormalities, general oedema	Vasodilatation, hypertension, tachycardia, postural hypotension	Vasodilatation, palpitation	Myocardial infarction, stroke, heart block, arrhythmias, hypotension, tachycardia, palpitation, flushing	Palpitation

CNS: psychological, psychiatric	Psychotic episodes at recommended doses (rare), overstimulation, restlessness, insomnia, euphoria, dysphoria	Nervousness, insomnia, drowsiness, toxic psychosis, depressed mood	Hallucinations; mild depression, increased irritability, and insomnia	Nervousness, depression, anxiety, insomnia, emotional lability	Hypomania, mania, anxiety, reduced libido, insomnia, confusion, psychosomatic disorder, depersonalisation, aggressive reaction, asthenia, dream disorder	Nervousness, anxiety, abnormal dreams, decreased libido, agitation, confusion, abnormal thinking, depersonalisation, depression	Insomnia, anxiety, nervousness, somnolence, abnormal dreams	Confusional states, hallucinations, disorientation, delusions, anxiety, restlessness, increased or decreased libido, agitation, hypomania, exacerbation of psychosis, insomnia, panic, nightmares	Anxiety, abnormal dreams, hallucinations, sleep disorder, somnolence, abnormal thinking
CNS: neurological	Dizziness, dyskinesia, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome	Dizziness, dyskinesia, Tourette's syndrome, NMS	Seizures; Tourette's syndrome; dyskinetic movements of the tongue, lips, face, extremities; nystagmus oculogyric crisis; dizziness	Dizziness, cataplexy, paresthesia, dyskinesia, hypertonia, confusion, amnesia, ataxia, tremor	Seizures, tremor, myoclonus, hypertonia, diaphoresis, shivering, fever, mental status changes, diarrhoea, somnolence, dizziness	Somnolence, dry mouth, dizziness, insomnia, tremor, hypertonia, paresthesia	Dizziness, tremor, decreased libido	Seizures, incoordination, ataxia, tremors, peripheral neuropathy, numbness, tingling, paresthesias, extrapyramidal symptoms, drowsiness, dizziness, weakness, syndrome of inappropriate ADH secretion, tinnitus, altered EEG patterns	Amnesia, confusion, dizziness, hyperkinesia, hypesthesia
Digestive system	Dry mouth, unpleasant taste, diarrhoea, constipation, other gastrointestinal disturbances	Anorexia, nausea, abdominal pain, abnormal liver function	Hepatic dysfunction, ranging from asymptomatic reversible increases in liver enzymes to hepatitis, jaundice and fatal hepatic failure	Nausea, diarrhoea, dry mouth, anorexia, abnormal liver function, vomiting, mouth ulcer, gingivitis, thirst	Dry mouth, nausea, dyspepsia, diarrhoea, abdominal pain, taste perversion, flatulence, stomatitis, oesophagitis	Nausea, constipation, anorexia, diarrhoea, vomiting, dyspepsia, flatulence	Nausea, diarrhoea, anorexia, dry mouth, dyspepsia, flatulence, vomiting	Paralytic ileus, constipation, dry mouth and sublingual adenitis, nausea, vomiting, epigastric distress, diarrhoea, peculiar taste, stomatitis, abdominal cramps, black tongue, jaundice, altered liver function, parotid swelling	Diarrhoea, dyspepsia, nausea, vomiting
Haematological/ lymphatic system	NA	NA	Isolated reports of aplastic anaemia	Eosinophilia	Purpura, anaemia	NA	NA	Agranulocytosis, bone marrow depression, leucopenia, thrombocytopenia, purpura, eosinophilia	NA
Musculoskeletal	NA	Arthralgia	NA	Joint disorder	Myalgia, back pain, arthralgia, muscle weakness	NA	NA	NA	Myasthenia

Table III. Contd

	Treatment for sleepiness				Treatment for cataplexy				
	d-amphetamine	methylphenidate	pemoline	modafinil	clomipramine	venlafaxine	fluoxetine	protriptyline	sodium oxybate
Nutritional/ metabolic	Anorexia, bodyweight loss	Bodyweight loss	Anorexia, bodyweight loss, nausea, stomach ache	Hyperglycaemia, albuminuria	Bodyweight gain, bodyweight loss, thirst	Bodyweight loss	Bodyweight loss	Elevation or depression of blood sugar levels, anorexia, weight gain or loss	NA
Respiratory system	NA	NA	NA	Rhinitis, pharyngitis, lung disorder, dyspnoea, asthma, epistaxis	Pharyngitis, rhinitis, cough, sinusitis, yawning, bronchospasm, epistaxis, dry and sore throat	Yawning	Pharyngitis, sinusitis, yawning	NA	NA
Skin/ appendages	Urticaria	Hypersensitivity (including skin rash, urticaria, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotising vasculitis, thrombocytopenic purpura)	Skin rash	Herpes simplex, dry skin	Increased sweating, rash, pruritus, dermatitis, acne, dry skin, abnormal skin odour, urticaria	Sweating, rash, pruritus	Sweating, rash, pruritus	Petechiae, rash, urticaria, itching, oedema, alopecia	Increased sweating
Special senses	NA	NA	NA	Amblyopia, abnormal vision	Abnormal vision, abnormal lacrimation, mydriasis, conjunctivitis, anisocoria, blepharospasm, ocular allergy, tinnitus, otitis media	Blurred vision, taste perversion, tinnitus, mydriasis	Abnormal vision	Blurred vision, disturbance of accommodation, increased intraocular pressure, mydriasis	Amblyopia, tinnitus
Urogenital system	Impotence, changes in libido	NA	Isolated acid phosphatase elevation	Abnormal urine, urinary retention, abnormal ejaculation	Erectile failure in males, ejaculatory failure, anorgasmy, micturition disorder, urinary retention, dysmenorrhoea, vaginitis, leucorrhoea, amenorrhoea	Abnormal ejaculation/orgasm, impotence, urinary frequency, impaired urination, menstrual disorder	Erectile failure in males, abnormal ejaculation	Urinary retention, delayed micturition, nocturia, dilatation of the urinary tract, impotence, gynecomastic in the male, breast enlargement and galactorrhoea in the female, testicular swelling	Dysmenorrhoea, urinary incontinence

ADH = antidiuretic hormone; **ADHD** = attention deficit hyperactivity disorder; **DEA** = Drug Enforcement Agency; **ECG** = electrocardiogram; **EEG** = electroencephalogram; **FDA** = US Food and Drug Administration; **GHB** = gamma hydroxybutyrate; **NA** = not applicable; **NMS** = neuroleptic malignant syndrome; **OCD** = obsessive-compulsive disorder.

phenidate came into broad use as suggested by Daly and Yoss.[66]

The treatment of narcolepsy underwent a dramatic change with the introduction of ephedrine. Despite its clinically noteworthy efficacy, it was soon apparent that adverse effects, incomplete patient acceptance, rapid development of tolerance, and cost limited its usefulness. In 1935, Prinzmetal and Bloomberg[67] suggested that amphetamine sulphate would be appropriate treatment for narcolepsy because of its close relationship to ephedrine and epinephrine (adrenaline), its low toxicity and low cost, its prolonged action, and its lack of pronounced sympathomimetic adverse effects. In their first report, nine patients noted complete relief from sleep attacks and practically complete relief from cataplexy. They noted that insomnia and restlessness were potential problems and that the medication should not be given late in the day. They recommended 10mg doses initially with a gradual increase until an optimal effect was obtained. Subsequent reports described the benefits of dextroamphetamine and methamphetamine, and the use of up to 80mg of amphetamine sulphate to achieve control of sleepiness. By 1949, amphetamines, in one or another of the several oral preparations as a phosphate or sulphate, had become the treatment of choice for excessive sleepiness, with a typical initial treatment of 10mg three times daily, followed by gradual increases until sleepiness was controlled.[68]

Adverse effects of amphetamines were readily noted in the clinical literature. Shapiro[69] noted that two of 15 patients treated with amphetamine sulphate experienced adverse effects. Young and Scoville[70] noted psychotic symptoms in three patients with narcolepsy and suggested that amphetamine sulphate may have 'precipitated the psychotic reaction' in two of them; the patients showed 'a great apprehension' amounting to panic, confusion and bewilderment. By 1949 there were at least four reports of an association between narcolepsy and paranoid psychosis (reviewed by Sours[68]).

In the mid-1950s, Daly and Yoss[66] introduced methylphenidate as a treatment for narcolepsy by reporting their experience in using daily doses of methylphenidate ranging from 20 to 200mg. As their patients were assessed before polysomnography was developed and sleep apnoea was discovered, their series and other early series of patients with narcolepsy may have included patients with other sleep disorders. The use of high doses of methylphenidate may have been partly motivated by the report of Yoss et al.[71] of reversal of pupillographic abnormalities in patients with narcolepsy by methylphenidate 120 mg/day. For patients who did not respond well to methylphenidate, Daly and Yoss[72] subsequently recommended methamphetamine up to 40mg daily dose. In the 1974 summary by Daly and Yoss,[72] of their experiences, they advocated that patients be given initial trials of low to moderate dosages of methamphetamine or methylphenidate with gradual increases in doses to as much as 200mg of either drug if needed to control sleep attacks.

In the mid-1960s, the use of stimulants was often supplemented by antidepressants to treat cataplexy.[73,74] While the efficacy of antidepressants in reducing narcolepsy is readily appreciated by patients and clinicians, troublesome adverse effects are frequently reported including dry mouth, urinary retention, impaired sexual activity and cardiac arrhythmias. The well-recognised anticholinergic properties of tricyclic antidepressants are generally thought to be responsible for these types of adverse effects. However, it can be seen that these adverse effects are also reported for anti-depressants outside the tricyclic class.

In the mid-1970s, gamma hydroxybutyrate (GHB) was introduced on an experimental basis as a novel pharmacotherapeutic approach to narcolepsy uncomplicated by the abuse and diversion potentials of the amphetamines or the adverse effect problems of the antidepressants. The groups of Broughton and Mamelak,[75] Scharf et al.[76,77] and Scrima et al.[78,79] were first to describe the anticataplectic effects of the sodium oxybate formulation of GHB.

5. Efficacy in Excessive Sleepiness

The literature on the use of stimulants in narcolepsy has been reviewed.[80-82] Prior to the introduction of modafinil and sodium oxybate, there have been few available data on the efficacy of pharmacotherapeutics for narcolepsy. Several, small, double-blind, placebo controlled clinical trials have been reported.[6,83] Objective measures of daytime alertness and ability to perform monotonous tasks in sedentary situations were used. Because these studies involved cross-over designs with less than 10 to 15 patients per drug, they did not provide the level of benefit/risk assessment that would meet present standards for approval of a clinical indication. Nevertheless, these trials did show that dexamphetamine, methamphetamine, methylphenidate and pemoline reduced sleepiness and enhanced performance in patients with narcolepsy in a dose-dependent fashion such that placebo conditions could be statistically distinguished from active medication conditions. These studies also underscored the profound sleepiness and impaired performance of patients with narcolepsy relative to healthy controls, even when optimal treatment is instituted. Figure 1 is redrawn from a 1993 study of methamphetamine in narcolepsy.[83] These data exemplify the efficacy of amphetamine in reducing daytime sleepiness in narcolepsy as measured by the tendency to fall asleep in the daytime on the MSLT.[39] Note also the inter-subject variability in response to the drug and the residual sleepiness of treated patients with narcolepsy relative to control subjects.

5.1 Sustained-Release Versus Standard Formulations

The objective efficacy studies of stimulants were not designed to address the advantages or disadvantages of sustained-release formulations, such as those available for methylphenidate and several amphetamine molecules. While it is understandable that cross-over study designs with small numbers of subjects are not adequate for this purpose, clinicians are, nevertheless, without objective data to inform their decision to prescribe or not prescribe a stimulant in a sustained-release formulation. Reasoning pharmacokinetically, the effect of a 20mg dose of methylphenidate in standard form and a 20mg dose of methylphenidate in sustained-release form should have different time courses. For example, on average, initial effects of the sustained-release form of the drug should be lower than those for the standard formulation. However, one should expect variability from patient to patient in rate of absorption and metabolism as well as in needs for alerting effects. In practice, physicians try to time stimulant dosing and selection of drug formulation so that, for any particular patient, alerting effects occur during key hours of the day (e.g. commuting to work, at work and commuting from work). To optimise symptom control throughout the day, combinations of standard and sustained-release formulations are often used. Also, combinations of two or more agents with different durations of action are often used. Decisions about such regimens are made on a patient-by-patient basis.

The series of clinical trials associated with the development of modafinil for the indication of narcolepsy, in contrast to studies of other stimulants, are extensive. Published work on modafinil comprises an order of magnitude more subjects as well as placebo-controlled, parallel groups designs.[50-52] Collectively, these studies document modafinil-related to: (i) reductions of daytime sleep tendency as measured by the MSLT;[39] and (ii) increases in ability to remain awake during the day as measured by the Maintenance of Wakefulness Test (MWT),[84] in several hundred patients with narcolepsy. Figure 2 depicts the dose-dependent increase in MWT sleep latencies that approach, but do not uniformly reach normal levels.

The literature on modafinil in the treatment of narcolepsy has been separately reviewed, with the conclusions that modafinil is a useful alternative to traditional CNS stimulants that is well tolerated and may be taken in combination with anticataplectic medications.[86-88] Modafinil seems to

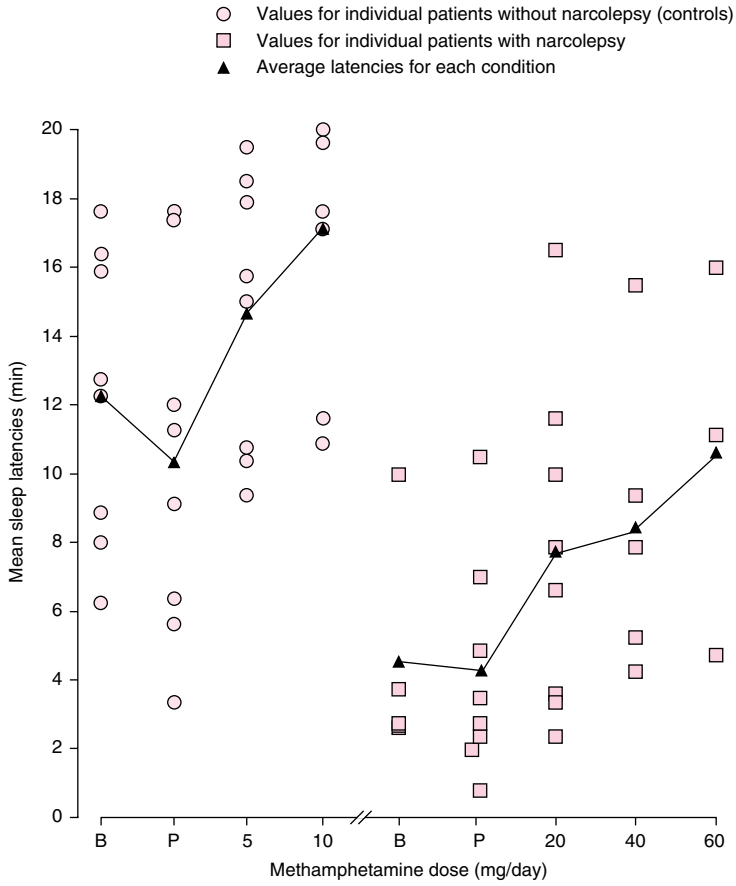

Fig. 1. Mean sleep latencies on the Multiple Sleep Latency Test (MSLT) as a function of dose level of methamphetamine in healthy controls and patients with narcolepsy. The horizontal axis represents conditions in a cross-over design. For eight controls, the conditions were: B = baseline, P = placebo, low dose (5mg), and high dose (10mg). For eight patients with narcolepsy, the conditions were: B = baseline, P = placebo, low dose (20mg), and high dose (40 or 60mg). There was a significant effect of active medication versus baseline and placebo in both groups. Sleep latency increased in every subject treated with methamphetamine. However, the mean sleep latencies of three patients with narcolepsy remained low, minutes even, at doses of 40 or 60mg (see lower right portion). Furthermore, the slopes of the regression lines for controls and patients with narcolepsy are significantly different, suggesting a greater sensitivity to methamphetamine in control subjects.

be an appropriate choice for the treatment of sleepiness in children with narcolepsy.[89]

5.2 Relative Efficacy

There are no head-to-head comparisons of the efficacies of the drugs used to control excessive sleepiness. Thus, it is impossible to rank such drugs in terms of efficacy or potency. Our group did a survey of ten polysomnographic studies on the pharmacological treatment of the sleepiness of narcolepsy.[90] Three studies employed the MSLT and seven employed the MWT as their polygraphic measure of sleep tendency. Statistically and clinically significant therapeutic changes were apparent for pemoline, modafinil, dexamphetamine and methylphenidate.

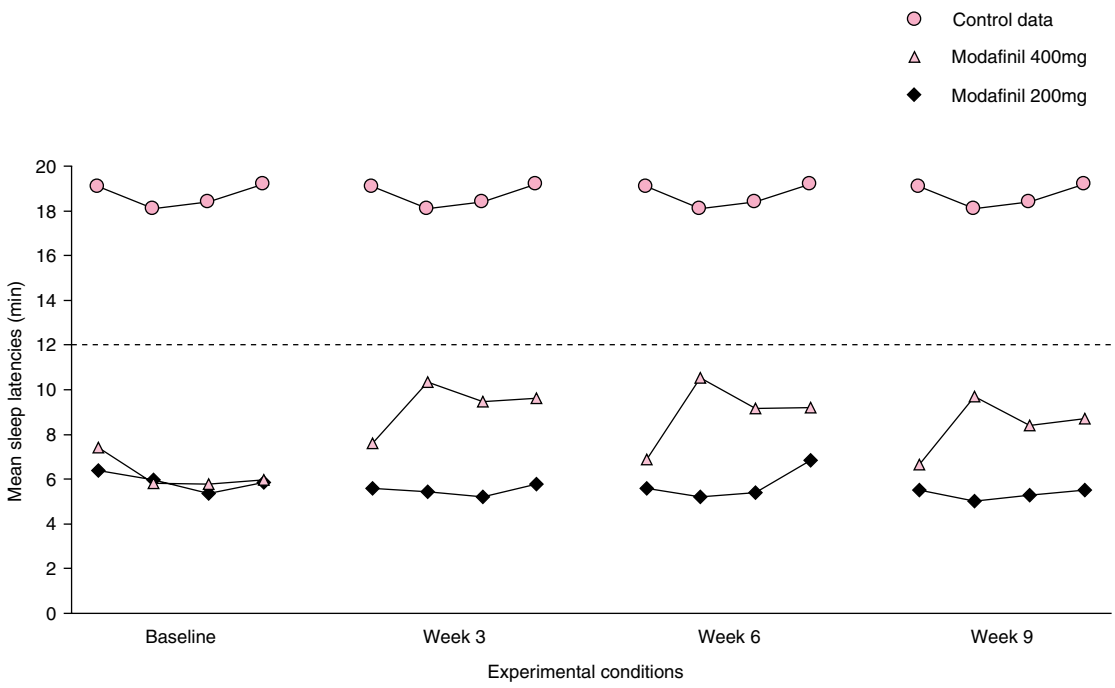

Fig. 2. This figure presents changes in the ability of patients with narcolepsy to stay awake on the Maintenance of Wakefulness Test (MWT),[84,85] as a function of treatment with modafinil. The MWT measures the time to fall asleep at 10:00, 12:00 14:00 and 16:00 hours when the subject is instructed to stay awake while seated comfortably in bed. The figure presents averages for each of the four MWT trials through the day. Data for narcolepsy patients were drawn from two 9-week long multicentre studies.[51,52] These studies evaluated modafinil at 200mg (n = 178) and 400mg (n = 172) doses versus placebo (n = 180) in a parallel -group, double-blind design. Administration was within an hour of getting up in the morning. Patients were tested at baseline and after 3, 6 and 9 weeks of treatment. For patients with narcolepsy, only the placebo and 400mg dose groups are displayed. The control data (top curve) is from the separate, MWT normative study (n = 64)[85] and are replotted above each of the treatment conditions of the modafinil study. The ability to remain awake on the MWT is significantly enhanced by modafinil and, by the 12:00 MWT trial, approaches the lower limits of the normal range as defined by the 5th percentile (horizontal dashed line drawn at 12 minutes). There was no evidence of a response to placebo or of a drop in treatment response with daily use over the 9-week period.

5.3 Abuse and Diversion

The abuse and diversion risks are judged to be significant for the amphetamines and methylphenidate. Such risks are judged to be moderate to low for pemoline and modafinil. Pemoline is a schedule IV controlled substance, but is not a common drug of abuse. Modafinil is classified as a schedule IV controlled substance and as such does not require the augmented administrative burdens on physicians, pharmacists and patients of dealing with a schedule II substance such as the amphetamines and methylphenidate. In addition, modafinil has low potential for abuse or diversion.[91,92]

6. Efficacy in Cataplexy

While not the most disabling symptom of narcolepsy, cataplexy can lead to falls and injuries as well as marked social discomfort. Therefore, in those patients for whom cataplexy is a common occurrence, efficacious anticataplectic treatment is desirable. The drugs used to reduce sleepiness listed in table I generally have not been found

to satisfactorily control cataplexy as monotherapies.[6,86,87,89,93]

Prior to the introduction of sodium oxybate as an anticataplectic agent, there had been several studies on the efficacy of anticataplectic pharmacotherapies. One study examined both the alerting and the anticataplectic effects of protriptyline at doses ranging from 5 to 60 mg/day.[6] The alerting effects were not found to be clinically significant. However, there were statistically significant anticataplectic effects as measured by the Narcolepsy Clinical Status Questionnaire[94] as shown in figure 3.

Similar levels of efficacy in reducing cataplexy have been reported for viloxazine[93] and for fluoxetine.[95]

As discussed earlier, sodium oxybate was introduced in the mid 1970s as a therapeutic agent for controlling cataplexy. Sodium oxybate is metabolised to GHB. The GHB molecule, occurs naturally *in vivo* as a metabolite, as well as a precursor, of gamma amino butyric acid (GABA).[96,97] The mechanism of action of sodium oxybate in patients with narcolepsy is not completely understood and most probably involves systems other than central GABAergic systems.[96,97] Sodium oxybate has undergone multicentre clinical trials and is now marketed for the indication of cataplexy in narcolepsy. One set of data demonstrating the efficacy of sodium oxybate is presented in figure 4. While there was a primary focus on the anticataplectic properties of sodium oxybate in the clinical trials, the drug may also enhance daytime alertness, as evidenced by self-determined and self-reported reduction of stimulant medication in patients on sodium oxybate therapy.

Sodium oxybate is judged to have moderate potential for abuse and diversion. One of the troublesome properties of GHB is its capacity to produce anaesthesia and the associated illegal use, alone and in combination with other agents, to produce amnesia in intended rape victims. The sodium oxybate molecule is transformed to GHB which can influence the levels of GABA which, in turn, is a naturally occurring neurotransmitter that has been

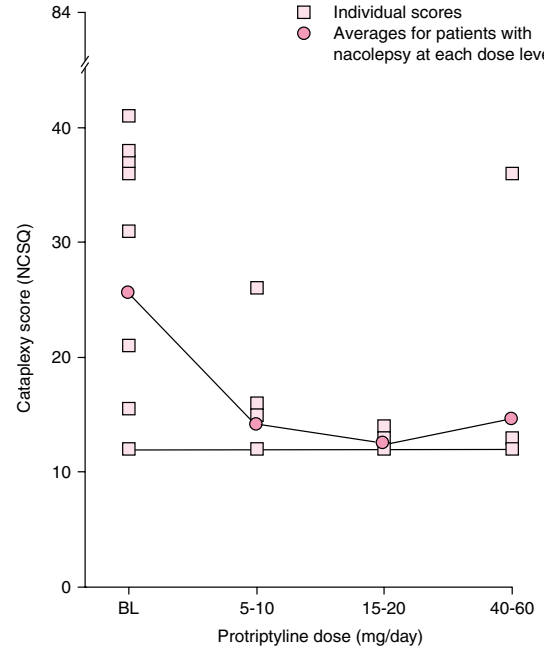

Fig. 3. Efficacy of protriptyline in the treatment of cataplexy as measured by the Narcolepsy Clinical Status Questionnaire (NCSQ).[94] The questionnaire quantifies changes in five major symptoms of narcolepsy: sleepiness, sleep attacks, cataplexy, hypnagogic hallucinations and sleep paralysis. Patients rate the severity of their symptoms on a 7-point Likkert scale from (1 = almost never to 7 = very often), basing responses on how much each of the symptoms has troubled them over the past 7 days, while engaging in the following 12 activities: (1) working, (2) driving, (3) sitting quietly, (4) reading, (5) watching television, (6) exercising, (7) lying in bed, (8) excited, (9) bored, (10) angry, (11) sad, (12) tense or under pressure. The score for each symptom can range from 12 to 84. The figure is redrawn from the data of Mitler et al.[6] on ten patients treated for narcolepsy versus nine healthy controls. The controls uniformly denied cataplexy yielding an average score of 12. The drop in symptom severity between baseline and the three dose levels is statistically significant.

classified as a schedule I controlled substance.[99] No cases of abuse were reported in sodium oxybate clinical trials.[100] There are other, more freely available and inexpensive sources of GHB precursors or analogues than prescription sodium oxybate. For example, gamma butyrolactone (GBL), 1,4-butanediol (1,4-BD) or gamma valerolactone (GVL) are metabolised *in vivo* to GHB or share

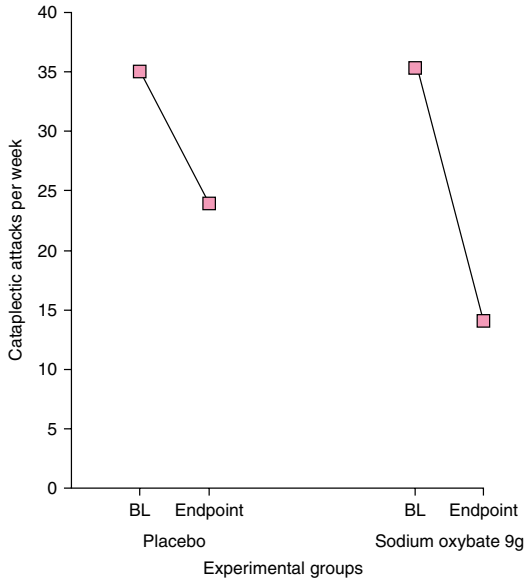

Fig. 4. Sodium oxybate in several, multicentre, randomised, placebo-controlled, parallel-group clinical trials has be shown to reduce the frequency of cataplexy. This figure presents the number of cataplectic attacks per week and is drawn from one such study in which four groups of patients were given either placebo, 3, 6 or 9g of sodium oxybate nightly for up to 4 weeks. This figure depicts the baseline and endpoint data for the placebo and the 9g groups (n = 33 and 33, respectively).[98] While there appears to be a response to placebo, there is a statistically and clinically greater response to active medication.

very similar CNS properties with GHB. Since 2000, the reported illicit usage, emergency room overdose cases and fatalities associated with GBL and especially 1,4-BD have risen sharply.[101]

7. Compliance

Compliance issues arise frequently in the pharmacotherapy of narcolepsy. But, over use and abuse of the medications discussed here is rare in patients with narcolepsy. On the contrary, available evidence suggests that patients frequently under comply with their prescribed medication regimens, either by reducing the daily dosage, by avoiding medication on some days, or both. This is true for use of alerting medications[102,103] and for use of anticataplectic medications.[77,98,104] The reasons for noncompliance are probably multifaceted and complex, involving patient finances, difficulty obtaining prescriptions for controlled substances, adverse effects, etc. Since public safety on the highways and the workplace is a concern in the management of narcolepsy, it is wise to monitor patients for under use of medications. While it is recognised that there is wide variability in local laws governing patient privacy vis-à-vis the prescribing physician, in locations where it is practical to do so, patients who do not properly take their prescribed alerting drugs should be reported to the appropriate authorities and such patients' driving privileges should then be reviewed.

8. Benefits Versus Risks

As is detailed in the forgoing discussions, narcolepsy is a disabling, life-long condition. The symptoms of narcolepsy adversely affect the quality of life of patients and represent safety risks for society in general.

The medications commonly used to treat the symptoms of narcolepsy have significant adverse effects. Some have potential for abuse and diversion. However, the efficacies of the drugs discussed here have been established by multiple clinical trials and reported in peer reviewed literature.

In general, experienced clinicians judge the risks of pharmacotherapy for narcolepsy to be acceptably low and the benefits of pharmacotherapy to be significant,[80-82] even for children.[89] The benefits of pharmacotherapy comprise, not only relief of the patient's disability and inconvenience, but also improved public safety on the highways and in the workplace, in so far as pharmacotherapy increases the ability of the patient to maintain alertness and operate vehicles and/or machinery.

9. Other Forms of Excessive Somnolence

The focus of this review has been narcolepsy. However, other disorders and diseases lead to excessive somnolence and can be confused with narcolepsy. Multicentre surveys based on standardised diagnostic techniques and criteria indicate

that more than 80% of individuals who present this symptom have sleep apnoea, narcolepsy, idiopathic hypersomnia, or insufficient sleep.[2,105]

The sleepiness associated with sleep apnoea resolves or improves with effective treatment of the apnoea, and that associated with insufficient sleep syndrome improves with increased amounts of sleep. However, for many patients with sleepiness due to a disorder other than narcolepsy, controlling excessive sleepiness is important to allow adequate functioning at home, while driving, or in the workplace. The benefit/risk discussion that applies to narcolepsy cannot be uniformly applied to other diseases and conditions. Nevertheless, the drugs used to control sleepiness in narcolepsy are often used in such cases. As is the case with narcolepsy, clinicians must weigh the patient's need for adequate treatment and the personal and social risks of inadequate treatment against the potential for adverse effects and abuse.

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