Brazilian guidelines for the treatment of narcolepsy

Diretrizes brasileiras para o tratamento da narcolepsia

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Abstract

This manuscript contains the conclusion of the consensus meeting of the Brazilian Sleep Association with Brazilian sleep specialists on the treatment of narcolepsy based on the review of medical literature from 1980 to 2010. The manuscript objectives were to reinforce the use of agents evaluated in randomized placebo-controlled trials and to issue consensus opinions on the use of other available medications as well as to inform about safety and adverse effects of these medications. Management of narcolepsy relies on several classes of drugs, namely, stimulants for excessive sleepiness, antidepressants for cataplexy and hypnotics for disturbed nocturnal sleep. Behavioral measures are likewise valuable and universally recommended. All therapeutic trials were analyzed according to their class of evidence. Recommendations concerning the treatment of each single symptom of narcolepsy as well as general recommendations were made. Modafinil is the first-line pharmacological treatment of excessive sleepiness. Second-line choices for the treatment of excessive sleepiness are slow-release metylphenidate followed by mazindol. The first-line treatments of cataplexy are the antidepressants, reboxetine, clomipramine, venlafaxine, desvenlafaxine or high doses of selective serotonin reuptake inibitors antidepressants. As for disturbed nocturnal sleep the best option is still hypnotics. Antidepressants and hypnotics are used to treat hypnagogic hallucinations and sleep paralysis.

Descriptors: Antidepressants; Cataplexy; Stimulants; Narcolepsy; Excessive sleepiness

Resumo

Este artigo relata as conclusões da reunião de consenso da Associação Brasileira de Sono com médicos especialistas brasileiros sobre o tratamento da narcolepsia, baseado na revisão dos artigos sobre narcolepsia publicados entre 1980 e 2010. Os objetivos do consenso são valorizar o uso de agentes avaliados em estudos randomizados placebo-controlados, emitir recomendações de consenso para o uso de outras medicações e informar pontos importantes a respeito da segurança e efeitos adversos das medicações. O tratamento da narcolepsia é baseado em diversas classes de agentes, estimulantes para sonolência excessiva, agentes antidepressivos para cataplexia e hipnóticos para sono noturno fragmentado. Medidas comportamentais são igualmente importantes e recomendadas universalmente. Todos os ensaios clínicos terapêuticos foram classificados de acordo com o nível de qualidade da evidência. Recomendações terapêuticas individualizadas para cada tipo de sintoma e recomendações gerais foram formuladas pelos autores. Modafinila é indicada como a primeira escolha para o tratamento da sonolência diurna. Agentes de segunda escolha para o tratamento da sonolência excessiva são metilfenidato de liberação lenta seguido pelo mazindol. Reboxetina, clomipramina, venlafaxina, desvenlafaxina e os inibidores seletivos de recaptação de serotonina em doses altas são a primeira escolha para o tratamento da cataplexia. Hipnóticos são utilizados para o tratamento do sono noturno fragmentado. Antidepressivos e hipnóticos são igualmente utilizados para o tratamento das alucinações hipnagógicas e paralisia do sono.

***Descritores**: Antidepressivos; Cataplexia; Estimulantes; Narcolepsia; Sonolência excessiva*

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Introduction

The current paper presents the conclusions drawn by the sleep specialists attending the consensus meeting of the Brazilian Sleep Association in 2010. The conclusions reached for the treatment of narcolepsy are based on a review of the medical literature investigating narcolepsy published between 1980 and 2010.

The objectives of the consensus meeting were to assess the use of agents that have been tested in randomized placebo-controlled studies for the treatment of narcolepsy, to issue consensus recommendations for the use of alternative medications, and to provide information about important safety and adverse effects caused by such medications.

Goals of the treatment of narcoleptic symptoms

Treatment goals include the control of daytime and nighttime symptoms as well as psychosocial adaptation. Central nervous system (CNS) stimulating agents, antidepressants, hypnotic agents, sleep hygiene measures, and psychosocial and psychotherapy support are all ubiquitously employed in the treatment of narcolepsy.[1]

The treatment categories presented herein are based on the evaluation of the scientific evidence provided by clinical studies.[2] The classification of the types of clinical studies is shown in Table 1 and their findings are summarized in Table 2.

This treatment categorization was based on a literature search (Medline and Cochrane Controlled Trials Register) and on a systematic review of all relevant articles about narcolepsy treatments that were published between 1980 and 2010.

The guidelines are complemented by specific levels of recommendation, namely, "standard", "guideline", "optional", or "consensus". These recommendation levels have been incorporated into this document.[2-4] The three first recommendation levels represent articles with levels from I to III (Table 1).

Recommendations resulting from the consensus meeting

Whenever empirical data were limited or non-conclusive, the specialists would cast their vote for the most recommended treatment. When only class IV and V studies were available but not class I, II, and III, the recommendation was decided when the majority of the members of this consensus (> 80%) voted in agreement. In this way, the agreed recommendations took into account the scientific expertise and personal experience of each member of the consensus.[5]

Behavioral treatment

1. Adequate sleep hygiene

Recommendation level D with degrees of evidence IV and V.

Sleep hygiene measures increase the efficacy of the pharmacological treatment for excessive sleepiness[6-9] and consist of:

- maintenance of regular sleep and wake schedules;
- avoidance of alcohol and sedatives;
- avoidance of excess and/or abstinence of chocolate and caffeinated beverages;
- avoidance of sleep deprivation;
- tobacco abstinence; and
- avoidance of meals rich in carbohydrates.

2. Naps

Recommendation level B with degree of evidence III.

Scheduled morning and afternoon naps improve the level of alertness and allow for the reduction of stimulant dosage.[10-12]

3. Social measures

Recommendation level D with degree of evidence V.

Adaptation of work schedules to accommodate naps.[6-8]

4. Psychological support

Recommendation level D without support from publications.

Psychological support for the adaptation to and acceptance of sleepiness and cataplexy symptoms.[6-8]

5. Pharmacological treatment

Recommendation level A with degree of evidence I.

6. Excessive Sleepiness (ES) treatment

1) CNS stimulants (Table 3). CNS stimulants reduce the intensity of sleepiness to 65 - 90% of the pre-treatment level.[1,4,7,8,11,13]

Modafinil

Modafinil is currently classified as an atypical stimulant due to its chemical structure, its pharmacodynamic mechanisms of action, and its distinct neurobehavioral effects.

The primary cellular mechanisms of modafinil in CNS neurotransmission are:

1) Blockade of dopamine transporter (DAT) reuptake protein with low-affinity, which in turn enhances D1-D2 meso-cortico-limbic dopaminergic neurotransmission.[14-18]

2) Intensification of electrical synchronization of GABAergic gap-junctions of GABAergic cells within the cholinergic pedunculopontine nucleus. Such electrical synchronization leads to cholinergic and glutamatergic excitatory activity within the brain stem nuclei and cerebral cortex.[19-28]

3) hypocretin-dependent increase of histaminergic neurotransmission in the posterior tuberomammillary hypothalamic nuclei.[14,29]

1. Effects of modafinil on narcolepsy related to excessive sleepiness

Recommendation level A with degree of evidence I.

Two multicentric studies (US Modafinil in Narcolepsy Multicenter Study Group), which included 550 narcoleptic patients followed-up for 9 consecutive weeks, demonstrated that doses of 200 mg of modafinil once a day, or 400 mg divided in two doses, improved daytime sleepiness up to 71% from baseline, as measured by the

Table 1 - Classification of evidence

I - Randomized, well-designed trials with low alpha and beta error, or meta-analyses of randomized controlled trials with homogeneity of results
II - Randomized trials with high alpha and beta error, methodological problems, or high quality cohort studies
III - Nonrandomized concurrently controlled studies (case-control studies)
IV - Case-control or cohort studies with methodological problems, or case series
V - Expert opinion, or studies based on physiology or bench research

Table 2 – Levels of recommendations

Standard A
This is a generally accepted patient-care strategy that reflects a high degree of clinical certainty. The term standard generally implies the use of level 1 evidence, which directly addresses the clinical issue, or overwhelming level 2 evidence.
Guideline B
This is a patient-care strategy that reflects a moderate degree of clinical certainty. The term guideline implies the use of level 2 evidence or a consensus of level 3 evidence.
Option C
This is a patient-care strategy that reflects uncertain clinical use. The term option implies either inconclusive or conflicting evidence or conflicting expert opinion.
Consensus D
This is a recommendation based on the clinical experience of a panel of experts and approved by over 80% of the members of the panel.

Epworth Sleepiness Scale (a decrease from 18 to 12 points). The same studies also reported an increase of 40% in sleep latency recorded in the Multiple Sleep Latency Test (MSLT) and a 54% increase in sleep latency recorded in the Maintenance of Wakefulness Test (MWT).[29,30] A non-significant reduction of cataplexy attacks was also observed.[29,30] Additional randomized studies in which patients were followed-up for 40 weeks, and open studies wherein patients were followed for 136 weeks, produced encouraging results in the control of somnolence.[1,31-33]

2. Doses of modafinil for the treatment of sleepiness in narcolepsy

Pharmacologic treatment for narcolepsy consists of 100mg of modafinil in the morning, which is increased by 50 to 100 mg every five days. The safest dose of modafinil is 200mg in the morning, which can be increased over two weeks up to 200, 300, or 400mg per day in the morning if residual symptoms of sleepiness are still present.[1,31-34] The regimen in which the doses are divided into 200mg in the morning and 200mg in the afternoon is safer when compared to a single 400mg morning dose because it has been shown to be more efficient and to have fewer adverse effects, and it also prevents the resurgence of sleepiness towards the end of the day. The maximum safe dose of modafinil is 600mg per day.[1,31-34] Subpopulations of Caucasian narcoleptic women respond to lower doses of modafinil due to a sexual dimorphism of the gene that modulates catechol-O-methyl transferase (COMT), which metabolizes dopamine within the synaptic cleft.[35]

3. Clinical pharmacokinetics of modafinil

Modafinil is well absorbed orally, and the onset of its action occurs in approximately two hours after oral administration. The ingestion of food delays intestinal absorption of the drug by about one hour. The half-life of modafinil is between 9 and 14 hours, and the drug reaches a steady-state after 2 to 4 days of use.[36,37] Ninety percent of modafinil metabolization occurs with cytochrome CYP-450 yielding no CNS active metabolites.[36-38] The rate of renal excretion is reduced in up to 20% in patients over 65 years of age. The dose of modafinil must be reduced by half in cases of hepatic and renal failure.[38]

4. Drug interactions with modafinil

Modafinil reversibly inhibits the CYP2C19 isoenzyme of cytochrome CYP-450 and prolongs the half-life of calcium channel antagonists, as it does for statins, omeprazole, clomipramine, clozapine, selective serotonin reuptake inhibitors (SSRIs), buspirone, midazolam, diazepam, propranolol, phenytoin, and warfarin, the last of which requires blood testing to control prothrombin time.[38]

Modafinil induces the CYP3A4 isoenzymes responsible for the metabolism of ethinyl estradiol, which is an oral contraceptive agent, thus resulting in the reduction of the plasmatic concentration of estradiol for up to a month after the patient ceases taking modafinil.[38,39] An additional dose of at least 50µg of estradiol during the use of modafinil is clinically recommended. Also, two additional months of at least 50µg of estradiol after the patient has ceased taking modafinil is also a recommendation.

The co-administration of isoenzyme P450 inducers, such as carbamazepine, phenobarbital, and rifampcin, or inhibitors of the isoenzyme P450 such as ketoconazole, can affect the plasmatic concentration of modafinil.

Therapeutic doses of modafinil can be safely used along with all classes of monoamine oxidase inhibitors (MAOI). Studies with healthy volunteers demonstrated that there was no interaction between dextro-amphetamine, methylphenidate, and amphetamines and modafinil when acutely co-administered. Also, in cocaine-addicted individuals, there was no interaction between cocaine and modafinil, with no further risks of autonomic effects.[38,39] There are no studies evaluating the interaction between modafinil and alcohol.

5. Substitution of other stimulants for modafinil

The substitution of methylphenidate or amphetamine for modafinil must be done using meticulous clinical criteria, its use being

Table 3 – Stimulating agents used in the treatment of excessive somnolence

Agent	Therapeutic dose	Maximum dose	Half life
Dextro-Amphetamine/Amphetamine	5-60mg/day	100mg/day	16-30 h
Methylphenidate	10-60mg/day	100mg/day	2-5 h
Mazindol	2-8mg/day	12mg/day	10 h
Selegiline	10-40mg/day	50mg/day	1 h
Modafinil	200-600mg/day	400-800mg/day	12-14 h
Cafeine	100- 200mg/day	500-600mg/day	3-6 h

supported by the rationale that sympathomimetic drugs are less safe than modafinil. Switching from sympathomimetics to modafinil is accomplished with a slow reduction of the sympathomimetic stimulant and the gradual introduction of modafinil. The introduction of a specific anti-cataplectic agent or a dose increase of the anti-cataplectic already in use should be put into practice to avoid cataplexy episodes during the switching process, as modafinil is not particularly effective against cataplexy.[40-42]

6. Adverse and side effects of modafinil amongst the narcoleptic population

Side effects of modafinil in doses of up to 600mg/day occur in less than 5% of users. Headaches are most frequent (13%) and are limited to the first three weeks of treatment. Headaches are more commonly observed in association with a rapid increase in the modafinil dosage. This side effect may well be avoided by increasing the dose slowly. Nervousness (8%), diarrhea, nausea (5%), rhinitis symptoms, hypertension, appetite reduction, and weight reduction were additional side effects reported.[43]

Modafinil (up to 600mg/day) does not cause central and autonomic nervous system side effects in the narcoleptic population, such as psychomotor agitation, insomnia, anxiety, tolerance, and/or dependence.[29,30,32] There are no accounts of suicide attempts with modafinil.

7. Allergic reactions related to modafinil

Allergic reactions as angioedema and Stevens-Johnson syndrome were reported with the use of modafinil. However, such cases are quite uncommon and their occurrence is confounded by the prevalence of both conditions in the general population. Should an allergic reaction emerge in association with modafinil use, the clinical recommendation is to stop the treatment with modafinil promptly. Systemic inflammatory reactions in multiple organs, such as myocarditis, hepatitis, eosinophilia, leucopenia, thrombocytopenia, itching, and asthenia have been reported. There are no predictive clinical markers for these adverse effects.[38]

8. Effects of modafinil in the hypothalamic-pituitary-adrenal axis

Modafinil does not cause neuroendocrine alterations, such as activation of the hypophysis-pituitary axis. There is no increase in adrenocorticotropic hormones, cortisol, or changes in prolactin or growth hormone secretion.[29,30,32,38,39]

9. Metabolic changes caused by modafinil

Mild elevation of gamma-GT and alkaline phosphatase hepatic enzymes can occur.[29,30,32,38,39]

10. Modafinil contraindications[7,32,38,39]

- Age under 16;
- pregnancy;
- breast-feeding;
- uncontrolled arterial hypertension;
- hypertrophy of the left ventricle;
- ischemic ECG alterations;
- cardiac arrhythmias;
- typical or unstable angina;
- recent acute myocardial infarction; and
- mitral valve prolapse.

11. Modafinil abuse potential in narcoleptic populations

Evidence from preclinical animal studies and clinical human studies suggests that modafinil does not present risks for abuse and dependence when used in therapeutic doses in clinical populations not prone to abuse. This finding is contrary to those related to other sympathomimetic stimulants such as amphetamines, methylphenidate, and caffeine.[38,44-47]

Modafinil (up to 600mg/day) holds a low potential for abuse not only in narcoleptic populations but also in individuals with obstructive sleep apnea syndrome and shift workers.[29,30,32,43-45]

Modafinil is currently classified as a Schedule IV drug by the Food and Drug Administration (which indicates a low potential for abuse and a limited potential for physical and psychological dependence).[48] In Brazil, modafinil is classified by the Sanitary Vigilance Agency (ANVISA) as an A3 drug (yellow prescription form).

12. Symptoms of modafinil withdrawal in narcoleptic populations

There are no accounts of abstinence or withdrawal syndrome due to the sudden discontinuation of modafinil used in therapeutic doses.[38,39,45] Rebound excessive sleepiness can occur after sudden discontinuation of 400mg/day doses.[29,32]

13. Armodafinil

Armodafinil is the R-enantiomer of modafinil, and it has a half-life of approximately 15 hours.[49] Armodafinil is not available in Brazil.

Amphetamine-like stimulants

1. Amphetamine

In usual clinical therapeutic doses, amphetamines are potent sympathomimetic drugs that enhance dopaminergic and noradrenergic neurotransmission in the nervous system.[14,16,50]

2. Cellular mechanisms of amphetamine action

Amphetamines block the dopamine transporter (DAT) and noradrenaline (NAT) reuptake proteins with high affinity. This leads to the following:

1) increased activation of D1-D2 meso-cortico-limbic receptors;[14,16,50]

2) increased noradrenergic neurotransmission within the *locus coeruleus;*[14,16,50]

3) increased pre-synaptic dopaminergic and noradrenergic release into the synaptic cleft; and

4) monoamine oxidase (MAO) inhibition with supra-therapeutic doses of amphetamine.[14,16,50]

3. Types of amphetamines

Dextroamphetamine and dextromethamphetamine are more potent than the other known isomers.[14,16,50]

Dextromethamphetamine is more lipophilic and acts more rapidly and efficiently with less peripheral effects, but has a higher potential for abuse and dependence that renders it unsafe for clinical use.[14,16,50]

4. Methylphenidate and amphetamines

Recommendation level B with degree of evidence III.

The mechanism of action of methylphenidate is similar to that of amphetamines.[14,16,50]

Table 4 - Adverse effects of sympathominetic stimulants

Autonomous	Motor	Mental
High Blood Pressure	Gilles de la Tourette's	Insomnia
Taquicardia	Tremors	Emotional Labiality
Anorexia	Convulsive seizures	Irritability
Reduction of libido	Vertigo	Mania
Impotence	Bruxism	Anxiety-agitation
Nausea and vomit	Tics	Depression
Dizziness	Flushing	Aggressive behavior
Headaches	Muscular weakness	Psychosis and paranoia
Dry mouth		Tolerance and dependency

The onset of the action of methylphenidate occurs one hour after the oral administration, and its half-life ranges from three to four hours, requiring the use of more than one dose per day.[14,16,50]

Eighty percent of methylphenidate is metabolized by the liver producing an inactive metabolite.[14,16,50] Amphetamines and methylphenidate have been found to improve narcolepsy baseline sleepiness up to 65-85%.[51,52] The maximum daily dose of methylphenidate recommended by the American Academy of Sleep Medicine and by the European Federation of Neurological Societies is 100mg per day.[1,8,9]

5. Stimulant contraindications

Amphetamines and methylphenidate are not recommended for patients with glaucoma, anxiety disorders, tics, or a history of Giles de la Tourette's syndrome.[14,51,52] Also, amphetamines and methylphenidate are contraindicated for patients with arterial hypertension, thoracic pain, cardiac arrhythmias, mitral prolapse, ventricular hypertrophy, angina, and acute myocardial infarction.[49,50,52]

Patients with depression, psychosis, epilepsy, and cardiovascular comorbidity must be carefully evaluated when the use of methylphenidate is under consideration.[14,51,52]

6. Adverse effects of stimulants

Psychiatric side-effects are uncommon in the narcoleptic population, but systemic arterial hypertension can occur with use of therapeutic doses.[14,51-54]

7. Abuse and tolerance

Sympathomimetic stimulants are classified as Schedule II in the Controlled Substance Act due to their high potential for abuse and tolerance.[9] Abuse and dependence are uncommon and occur in 1-3% of narcoleptic patients.[14,50,55,56]

Mazindol

Recommendation level A with degree of evidence I.

The mechanism of action of mazindol is similar to that of amphetamines.[6]

The dose peak occurs in one to two hours, and the drug has a 10-hour-long half-life. Prescribed doses range from 1 to 4mg/day, starting with low doses.[1,8,9] Mazindol reduces ES in 53% to 60% of patients and it also has anticataplectic effects.[14,50,55-59] Mazindol is metabolized in the liver into inactive compounds with kidney and fecal excretion.

Selegiline

Recommendation level C with degree of evidence IV.

Selegiline is a selective, reversible, potent inhibitor of MAO-B enzyme when used in doses of 5 to 20mg/day.[14,16,50] However, in doses over 20mg, selegiline fails to retain its properties as a selective MAO-B inhibitor, thus requiring a tyramine-poor diet. Selegiline is metabolized in the liver into amphetamine and methamphetamine contributing to the reduction of daytime sleepiness.[14,50]

Selegiline is usually better tolerated than amphetamine-like drugs and possesses a clinically relevant anti-cataplectic effect. However, its use is limited by its sympathomimetic effects and its interactions with other drugs.[60,61]

Pemoline

Pemoline is no longer available due to its hepatotoxic effects, which, although rare, are potentially lethal.[62,63] It is not available in Brazil.

Caffeine

Recommendation level C without support from publications.

High doses (> 450mg/day) of caffeine improve alertness but can produce tremors, irritability, gastrointestinal symptoms, and excessive dieresis.[14,50,64]

Treatment of refractory excessive sleepiness or excessive sleepiness relapse

1. Combination of stimulant agents

Recommendation level C with degree of evidence IV.

Approximately 65% to 85% of patients respond satisfactorily to stimulants.[53,55] In the refractory cases, modafinil can be used (400mg to 600mg/day, 400mg in the morning plus 200mg after lunch). Alternatively, in addition to modafinil doses of 200 to 300mg/day, 5 to 10mg of rapid onset-of-action methylphenidate can be added under judicious clinical care.[1] There are no studies evaluating the safety of the association of different types of stimulants in the treatment of narcoleptic patients (methylphenidate and modafinil, amphetamine and modafinil, and amphetamine and methylphenidate).

2. Agents chosen for the treatment of ES

Recommendation level A with degree of evidence I.

The first-choice treatment for ES is modafinil 200-400mg/day,[1,6-9,14,29-33,50] since doses over 600mg/day are not considered safe. The second choice is slow-release methylphenidate in doses up to 120mg/day[1,6-9,14,29-33,50] (Table 5). Methylphenidate has been found to be safer than mazindol and amphetamines.[6-9,14,29-33,50]

Cataplexy treatment

Sympathomimetic stimulants reduce the frequency and intensity of cataplexy attacks.[1,6-9] Modafinil, however, has not been found to improve cataplexy.[29-33] The recommended treatment for cataplexy is based on antidepressants.[65]

Antidepressants

1. Tricyclic Antidepressants (TCA)

Recommendation level B with degree of evidence III for cataplexy.

Recommendation level C with degree of evidence IV for sleep paralysis and hypnagogic hallucinations.

TCA are effective in the treatment of cataplexy. However, their side effects may pose a limitation to their use.[1,6-9,64,65] TCA used in the treatment of cataplexy include nortriptyline (25-200mg/day), clomipramine (25-150mg/day), and imipramine (10-100mg/day).[65,66]

2. SSRI antidepressants

Recommendation level B with degree of evidence III for cataplexy.

Recommendation level C with degree of evidence III for sleep paralysis and hypnagogic hallucinations.

SSRIs such as fluoxetine (20-80mg/day),[67] paroxetine (20-60mg/day),[68] sertraline (50-150mg/day),[65] and citalopram (20mg)[69] are less efficient than TCA and noradrenaline selective reuptake inhibitors (NSRIs) in the treatment of cataplexy. Equivalent or even higher doses of SSRIs than those used in the treatment of depression are required to control cataplexy.[65,66]

3. Serotonin and Noradrenaline Reuptake Inhibitor (SNRI) antidepressants

Recommendation level B with degree of evidence III for cataplexy.

Recommendation level C with degree of evidence IV for sleep paralysis and hypnagogic hallucinations.

1) Venlafaxine

Venlafaxine (75-225mg/day) is clinically effective in the treatment of cataplexy, hypnagogic hallucinations, and sleep paralysis.[65,66,70] The noradrenergic effect of venlafaxine can increase the autonomic effect of sympathomimetic drugs upon the systemic arterial pressure and the heart rate of the patient.[14,50,54] Thus, the arterial blood pressure must be monitored when venlafaxine is combined with other stimulants.

2) Desvenlafaxine

Desvenlafaxine is a hepatic metabolic sub-product of venlafaxine. Desvenlafaxine presents a milder array of side-effects in comparison to venlafaxine. It is therefore a suitable alternative to venlafaxine and other antidepressants used for the treatment of cataplexy. However, there are no studies on the effects of desvenlafaxine in narcolepsy. Arterial blood pressure must be monitored when desvenlafaxine is combined with other stimulants.

Table 5 - Consensual conclusion about the pharmacological treatment of excessive somnolence

Agents	Recommendation level
Modafinil	A
Slow release Methylphnidate	B
Mazindol	A
Amphetamine	B
Selegiline	C

4. NSRI antidepressants

Reboxetine

Recommendation level B with degree of evidence III for cataplexy.

Recommendation level C with degree of evidence IV for sleep paralysis and hypnagogic hallucinations.

One study involving 12 patients treated with up to 10mg/day of reboxetine demonstrated a 48% reduction in the Epworth Sleepiness Scale, a 54% reduction in the sleep latency on the MSLT, and a significant reduction in cataplexy attacks.[71]

5. Conclusions concerning the treatment of cataplexy with antidepressants

The most effective antidepressants for the treatment of cataplexy are reboxetine, venlafaxine, clomipramine, nortriptyline, and combinations of these antidepressants (Table 6).[1,6-9,24,50,65,66] Tolerance to the anticataplectic effects has been described, and increments of the dose or medication change may be necessary in these cases.

6. Other antidepressant agents

Irreversible MAO-A and -B inhibitor agents can be used in the treatment of cataplexy;[14,50] however, there is no scientific evidence on the efficiency and safety of this drug class in the treatment of cataplexy.[14,50]

Other agents used to treat cataplexy

Selegiline and mazindol can be used in cases of cataplexy resistant to the agents mentioned above.[6,8,50,60,61,65,72] The use of selegiline is limited by its potential of interaction with other drugs and with tyramine, which could cause severe hypertensive crises.[50,72]

Gamma-hydroxybutyrate (GHB)

GHB belongs to a distinct drug category, partly due to its therapeutic effects in cataplexy, in sleepiness, and in fragmented nocturnal sleep.[73-77] GHB is not available in Brazil.

Anticataplectic agent withdrawal, rebound, and *status cataplecticus*

The sudden withdrawal of anticataplectic antidepressants can cause cataplexy rebound or *status cataplecticus*, which is characterized by an increase in the length, frequency, and intensity of the cataplectic episodes.[7,65]

The intensity of the *status cataplecticus* as well as the intensity of the rebound phenomenon are directly proportional to the clinical pharmacological strength of the anticataplectic agent, as well as to its sudden discontinuation.

Contraindicated drugs for the narcoleptic population with cataplexy

Anti-hypertensive agents that reduce the central adrenergic

Table 6 - Consensual conclusion about the pharmacological treatment of cataplexy

Agents	Recommendation level
Clomipramine	B
Nortriptiline	C
SSRI Antidepressants	B
Reboxetine	B
VenlafaxinE/DesvenlafaxinE	B

neurotransmission, such as prazosin and clonidine, worsen cataplexy seizures.[50]

Medication interactions during the treatment of narcolepsy

The combination of multiple agents for the treatment of narcolepsy is not uncommon along the treatment of this condition. No reports exist of significant and unsafe clinical pharmacokinetic interactions between methylphenidate and modafinil or between dextroamphetamine and modafinil.[14,50,55,78]

Conversely, there are potential significant interactions between tricyclic antidepressants, SSRIs, selegiline, modafinil, amphetamines, and prazosin. These interactions are not generally clinically important, but the attending physician should be aware of them (Table 7).[14,50,54,78,79]

Sleep paralysis and hypnagogic hallucinations

Recommendation level C without support from publications.

The American Academy of Sleep Medicine and the European Federation of Neurological Societies list the antidepressant agents for the treatment of sleep paralysis and hypnagogic hallucinations.[1,6-9]

Aside from these recommendations, hypnotic agents that consolidate fragmented sleep, such as zolpidem, zopiclone, benzodiazepines, and clonidine can be used.[1,6-9,14]

Nocturnal fragmented sleep treatment

Recommendation level D with degree of evidence IV.

Zolpidem and triazolam can be used to consolidate nocturnal sleep.[14,80]

Treatment of REM sleep behavior disorder and narcolepsy

Recommendation level D with degree of evidence IV.

Clonazepam is the first-choice treatment for REM sleep behavior disorder, but about 10% of the cases do not respond to the drug.[81] Treatment alternatives are melatonin, agomelatine, ramelteon, and pramipexole. Melatonin in doses between 3 and 13mg was shown to be effective in 57% of the cases.

Treatment of narcolepsy during pregnancy and lactation

Methylphenidate and modafinil are class C category agents for teratogenicity.

There are no studies on the use of stimulants and anticataplectic agents during pregnancy and lactation in narcoleptic patients.[14,82]

The only classes of agents in categories below C for teratogenicity are pemoline (which has been discontinued since 2005 due to hepatotoxicity) and GHB (which is class B but not available in Brazil). A safer alternative is to discontinue the use of the medication.[14,82] Gradual discontinuation is recommended to avoid the recurrence of cataplectic seizures.

When risks related to the symptoms are higher than the teratogenic risks, such as cataplexy accompanied by frequent falls or accidents due to sleepiness, fluoxetine and/or tricyclics are the recommended options. In these cases, special attention must be given to changes in arterial pressure caused by stimulants during pregnancy.[14,82]

Cesarean sections are also recommended due to the risk of *status cataplecticus* during delivery. There are no studies on the safety of stimulants during lactation. It is not known whether modafinil is excreted in the mother's milk.

Compliance in the treatment of narcolepsy

About 50% of patients with narcolepsy do not comply completely with the treatment and either reduce the dose of the drug or discontinue the medication altogether.[55,56,83] There are no reports of clinical risk factors for low compliance rates. A suspicion of non-compliance should always be considered in cases in which the patient is resistant to the treatment.

Conclusion

The individual therapeutic recommendations for each symptom as well as the general recommendations set forth herein were formulated by the authors. It was agreed among the sleep specialists attending the 2010 consensus meeting of the Brazilian Sleep Association of 2010 that modafinil is the first choice for the treatment of daytime sleepiness. Second-choice agents for the treatment of ES are slow-release methylphenidate and mazindol. Reboxetine, clomipramine, venlafaxine, desvenlafaxine, and high doses of SSRIs were agreed as being the first choice of treatment for cataplexy. Hypnotics, in turn, were recommended for the treatment of nocturnal fragmented sleep. Finally, antidepressants and hypnotics were recommended to be equally utilized in the treatment of hypnagogic hallucinations and sleep paralysis.

This article attempted to objectively characterize the individualized treatment of narcolepsy in Brazil. The authors trust it will serve its purpose well, which is to offer a form of reference to sleep professionals throughout the country.

Table 7 – Pharmacological interactions

Drug associations	Effect
TCA + Amphetamine or Methylphenidate	Hypertensive crises
TCA + SSRI	Serotoninergic syndrome
TCA + sedatives	Over-sedation
ChlomipraminE + modafinil (inhibition of P450)	TCA intoxication
MAOI + Methylphenidate/TCA/SSRI/ IRNS	Hypertensive crises
IMAO + Selegiline	Hypertensive crises
SSRI + Selegiline	Serotoninergic syndrome
TCA + Selegiline	TCA intoxication

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** Modest*
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**** Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
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For more information, see Instructions for Authors.

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