International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Review Article **CODEN: IJPNL6**

TREATMENT OPTIONS FOR NARCOLEPSY: A REVIEW

V. Bindu Praneeta*****, B. Sukanya Bai, V. Usha Vanya, M. Mahima Swaroopa

Pharm.D Interns, Kims College, Amalapuram, Andhra Pradesh, India

***Corresponding author e-mail:** vpraneeta92@gmail.com

Received on: 11-12-2015; Revised on: 04-02-2016; Accepted on: 05-03-2016

ABSTRACT

Narcolepsy is a chronic neurological disorder specifying the abnormal sleep manifestations which mainly impact the quality of life of narcolepsy patients. The exact cause is unclear but found significant evidences that orexin/hypocretin deficiency causes narcolepsy which regulates sleep. Treatment focuses on symptomatic relief throughout medication, education, and behavioral therapy. Stimulants are the first line treatment for the excessive daytime sleepiness. Modafinil, sodium oxybate, amphetamine, methylphenidate, and selegiline are effectual treatments for somnolence associated with narcolepsy. Tricyclic antidepressants and SSRIs are one of the best treatments for cataplexy, sleep paralysis, and hypnagogic hallucinations. Benzodiazepines are the best regimen for disturbed nocturnal sleep.

Keywords: Narcolepsy, Excessive daytime sleepiness(EDS), Tricyclic antidepressants(TCAs), Selective serotonin reuptake inhibitors (SSRIs), Gammahydroxybutyrate (GHB)

INTRODUCTION

Narcolepsy is a chronic disabling neurological sleep disorder characterized by the tetrad of symptoms excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations, and sleep paralysis, and the Other secondary symptoms include automatic behaviors and cognitive deficits, but only 10% of patients simultaneously exhibit all components of the tetrad. Narcolepsy with cataplexy is caused by sudden, short loss of muscle tone triggered by emotions mostly typical laughing or joking, abnormal rapid eye movement (REM) sleep manifestations, disturbed nocturnal sleep, sleep paralysis, hallucinations.[1,2]

There are three discrete forms of narcolepsy according to the international Classification of sleep disorders-Narcolepsy with cataplexy, Narcolepsy without cataplexy,Secondary narcolepsy -narcolepsy due to medical condition.[1] The etiology is not yet cleared, however researchers discovered that narcolepsy is caused by orexin/hypocretin deficiency producing neurons in the hypothalamus which regulates sleep, although this deficiency leads to immune system attacking parts of the brain that produce this chemical.[3-5] There is a association between narcolepsy and the HLA haplotype, a variant of the HLA-DQB1 gene located on the short arm of chromosome 64 and its symptoms which result in the destruction of the hypocretin-secreting neurons of the hypothalamus.[6] Low CSF hypocretin can be seen in 99% of patients cataplexy positive for HLA DQB1*0602.[7] The aim of the review is to provide the brief explanation of treatment options and lifestyle changes in narcolepsy patients.

PREVALENCE

Patients shows signs and symptoms between the first and second decade of life and the prevalence of narcolepsy in US affecting males and females identical 1 in 2000.[8] Though narcolepsy can begin at any age, majority of people shows symptoms at the age of 15-30 years,only 6% shows prior to 10 years of age and after the age of 40 narcolepsy rarely reported.[9]

Based on the incidence rates and prevalence of narcolepsy an estimated incidence of narcolepsy diagnosis with cataplexy is 0.74 per 100,000 individuals per year and 1.37 per 100,000 individuals per years for patients diagnosed narcolepsy with and without cataplexy.[10]Estimation of the prevalence of sleep paralysis affects 25% to 50% of individuals and one-third to 80% of individuals with hypnagogic hallucinations, where minority of individuals 10% to 25% suffer from the complete tetrad of symptoms.[11,12]

TREATMENT FOR EXCESSIVE DAYTIME SOMNOLENCE

Stimulants are psychoactive drugs that persuade short term improvements in either mental or physical functions or both. These medications are most effective for managing EDS, but do not provide relief from cataplexy.

Amphetamines: The collective group of amphetamines includes dextro, levo-amphetamine, dextroamphetamine, and methamphetamine has been used for narcolepsy from past 1930.[13]When amphetamines are used at low doses, the neurotransmitters dopamine released and norepinephrine to a lesser extent through reverse efflux via monoaminergic, dopamine and norepinephrine transporters while at high doses monoaminergic reduction and inhibition of reuptake occurs. These medications can have side effects and substance abuse because of the noradrenergic Effects. Patients with hypertension, cardiac problems, symptomatic hyperthyroidism should use amphetamines with caution.[14] Amphetamine tolerance effect may develop in up to one - third of narcolepsy patients.[15] The adverse effects include irritability, anorexia, hyperactivity, palpitations, mood changes, headache, sweating, tremors, and insomnia but at high doses stimulants can also exacerbate more frequent hospitalizations, cardiac arrhythmias, co-morbid psychiatric complications such as anxiety, mania, and even psychosis.[16,17]

Methylphenidate: Methylphenidate persuade dopamine release yet does not have any major effect on monoamine storage. The action of methylphenidate is similar to that of amphetamines but have shorter elimination half - life 2 – 7 h and the day-to-day dose may be divided into two or three parts. In some cases a sustained release form is useful. Abuse potential is low in narcoleptic patients but tolerance may develop and it is contraindicated in pregnant women.[18]

Both Amphetamine and Methylphenidate the usual dosage is 10 to 60 mg per day, will depend on the formulation.[19]

Modafinil: Modafinil is a [(2 - [(diphenylmethyl) sulfi nyl] acetamide)] nonamphetamine psychostimulant approved by the United States Food and Drug Administration for the treatment of excessive daytime somnolence related with obstructive sleep apnea, narcolepsy and shift work sleep disorder.[20] Modafinil is an wake-promoting agent indicated to improve wakefulness and the mode of action is unclear but it's action may involve in increased catecholaminergic signaling and reduced gamma aminobutyric acid (GABA) release in hypothalamus.[21,22]

The therapeutic range of modafinil is 100 to 400 mg and the recommended daily dose is 200 mg, to be taken once in the morning,the dose up to 400 mg have been well tolerated in randomized placebo-controlled studies.[20] The most common adverse effects are headache, rhinitis, dry mouth, , nausea, and anxiety, Cardiovascular effects like tachycardia, palpitations, or chest pain can see in some cases. There can be serious dermatologic and hypersensitivity reactions, Neurocognitive complaints and have reports linking modafinil to visual hallucinations in mania.[20,23]

In patients with renal impairment Safety and efficacy have not been assessed and in severe hepatic impairment, decreased dose by 50%.[24] Modafinil is effective in 60% of narcolepsy patients and moderately effect in 20% of the patients. [25] The peak bioavailability of Modafinil reaches in 2 h and stable after 2 – 4 days. The elimination half -life is 9 to 14 h.

Armodafinil: *It* is the *R* - enantiomer of modafinil, particulary affects areas of the brain involved in controlling wakefulness. Both have similar half - lives, plasma concentration. Armodafinil administration is higher late in the day than that following modafinil administration, results in a more extended effect during the day and a potential improvement in sleepiness in the late afternoon in narcolepsy patients [26].

Mazindol: It is an imidazolidine derivative which is similar to the amphetamines, it blocks dopamine and norepinephrine reuptake with high affinity. The recommended dosage is 2 mg per day in patients with 40 kg of ample or less, 4 mg a day in patients with more of 50 kg of obese. washout period of mazindol is about 10hr.Adverse effects include dry mouth,

nervousness, gastrointestinal upset and headache, dizziness, tachycardia and excessive sweating. Pulmonary hypertension and cardiac valvular regurgitation have been reported in some cases due to this valvular abnormalities it has been withdrawn in several countries from the market but used as a third - line treatment and with close monitoring. Mazindol decreases EDS in 53-60% of patients.[27]

Selegiline: A selective irreversible inhibitor of Type B monoamine oxidase, metabolically converted to desmethyl selegiline, amphetamine, and methamphetamine but vary in omission half - life– 2.5 h for desmethyl selegiline, 18 h for amphetamine, and 21 h for methamphetamine. Selegiline binds to MAO-B within the nigrostriatal pathways which blocks microsomal metabolism of dopamine and increasing the dopaminergic activity in the substantial nigra. Selegiline may also enhance dopaminergic activity through mechanisms other than inhibition of MAO-B. At higher doses, selegiline can impede monoamine oxidase type A (MAO-A), allowing it to be used for the treatment of depression. The daily dose of selegiline is 10 – 40 mg and at dose of 20 mg per day have seen improvement of daytime sleepiness and also dose - dependent rapid eye movement (REM) sleep suppressing properties.[28] The use of selegiline is limited due to adverse effects and interaction with other drugs. Abuse potential is low and Co-administration of triptans and serotonin specific reuptake inhibitors is contraindicated.[29,30] It has wakefulness promoting properties and can also reduce cataplexy but a low tyramine diet is suggested with selegiline to avoid the risk of hypertensive reactions. Many medications, including antidepressants has been used to control cataplexy, required washout period earlier to initiating an MAOI.

Pemoline: *It* is a stimulant drug of the 4-oxazolidinone class with prolong half-life of 12h and blocks dopamine reuptake and stimulates dopamine release feeble. It shows moderate improvement in sleepiness in 65% of narcoleptic patients. The side effects include dry mouth, reduction in appetite, high blood pressure, increased heart rate, constriction of smooth muscle, cardiac stress, dilated pupils, liver problems it has been withdrawn from the market almost due to lethal hepatotoxicity.[31]

Behavioural therapy: Behavioural treatment measures are always preferable. Beyond, the studies available support on the recommended systematic nocturnal sleep and design naps during the day, as naps temporarily reduced sleep propensity and shorten reaction time. Variation in performance demands and limitations on work or home times for taking them, naps are principal planned on a patient - by –understanding basis.[32,33]

TREATMENT FOR CATALEPSY, SLEEP PARALYSIS, AND HYPNAGOGIC HALLUCINATION

Sodium oxybate: Sodium oxybate is the sodium alkali of gammahydroxybutyrate (GHB) is an endogenous metabolite of gamma-aminobutyric acid approved by FDA for sleepiness and cataplexy is the only medication recommended for all the symptoms of narcolepsy.[34,35] Sodium oxybate, may act as neurotransmitter/neuromodulator which can act through its very own receptors and through stimulation of GABA - B receptors. GHB was useful to control catalepsy, decrease day time sleepiness, enhance night sleep in narcolepsy patients.[36]
The dose alignment from 3 to 9 g nightly, the dose starting at 4.5g per night divided in to two equal doses of 2.25g per night two increased by 1.5g at two weeks interval. Adverse effects were dose related and includes nausea, vomiting, dizziness, confusion, enuresis, anxiety, depressive symptoms, sleepwalking. Sodium oxybate is fastly absorbed through oral administration, reaches plasma peak within 25 – 75 min after ingestion and its half - life is 90 – 120 min. Overdosing of GHB can results CNS sedation, respiratory depression, bradycardia, and seizures.[37] Sodium oxybate should not be recommended during pregnancy.

Sodium oxybate plus venlafaxine (for cataplexy) or sodium oxybate plus modafinil (for EDS) is given in severe cases (cataplexy or EDS) until the sodium oxybate is effective and tapering of other medication done at that point. Patients who have cardiac problems, hypertension, or renal impairment may need caution while starting sodium oxybate earlier and patients with hepatic impairment should be started at one-half the usual dosage as It undergoes significant first pass metabolism in the liver. The efficacy of sodium oxybate, declining cataplexy attacks and EDS signify in pivotal clinical trials.[38-40] Sudden withdrawal of GHB can result in life-threatening conditions since its shared agonism with GABA, baclofen is very useful in the treatment of GHB withdrawal.[41,42] Sodium oxybate in combination with modafinil helps to improve the withdrawing symptoms of EDS.

Non - specific monoamine uptake inhibitors:
Tricyclic anti-depressants (TCAs) are monoamino reuptake inhibitors include protriptyline, desipramine, and imipramine, Clomipramine.

Clomipramine is a serotonergic reuptake inhibitor often results in substantial REM suppression. Declining severity and frequency of cataplexy at doses of 25-75mg and at low dose of 10-20mg daily are more effective. Adverse effects exist of anticholinergic effects including dry mouth, sweating, constipation, tachycardia, weight increase, hypotension, difficulty in urinating, and impotence. Rebound cataplexy may occur on withdrawal of TCAs causes increased in number and severity of cataleptic attacks.[43]

Selective serotonin reuptake inhibitors: Selective serotonin reuptake inhibitors (SSRIs) are more selective than TCAs, inhibit presynaptic serotonin reuptake and also nocturnal REM sleep. Escitalopram, reduces the number of cataplectic attacks but excessive daytime sleepiness remained unchanged.[44] Adverse effects are less noticeable than tricyclics, they include CNS excitation, gastrointestinal upset, movement disorders, and sexual difficulties. The risk of cataplectic attacks has been documented after with drawal of SSRIs.[45]

Norepinephrine reuptake inhibitors: Viloxazine at a dose of 100-300 mg per day, the main advantage is adverse effects are limited.[46] Reboxetine at a dose of 2-10mg and adverse effects include sedation, cardiovascular effects.[47]
Atomoxetine at a dose of 40-60mg per day, adverse effects include tachycardia, hypotension.[48]

Norepinephrine/ serotonin reuptake inhibitors: Venlafaxine at a dose of 150-375mg/day. The main adverse effects are gastrointestinal problems and less frequently asthma, hypotension Increased heart rate and blood pressure may be seen at doses of 300 mg or more.

Monoamino oxidase type-A inhibitors: MAOIs act by inhibiting the activity of monoamine oxidase, thus preventing the breakdown of monoamine neurotransmitters and thereby increasing their availability. Adverse effects include impotence, orthostatic hypotension, weight gain, edema, but these drugs are not using any more.

Others- Mazindol, Selegiline: Both the drugs have anticatapleptic effects and stimulant properties.

Behavioural therapy: Cataplexy is highly linked to strong, particularly positive, emotions, the most important causating factor is social contact so there is no particular behavioral treatment expect avoiding or reducing social withdrawal which helps in reducing cataplexy

TREATMENT FOR DISTURBED NOCTURNAL SLEEP

The standard treatment of disturbed nocturnal sleep is hypnotics. Benzodiazepines and non-benzodiazepines, which may delay the awakening during night time.

LIFE STYLE MODIFICATIONS

- Practice Good Sleep Hygiene to impose and strengthen a regular sleep/wake cycle.
- Limit Consumption of stimulating foods, beverages, alcohol and tobacco, especially several hours before sleep and naps.
- Exercise to develop strength and endurance and improve metabolism. All of these help to reduce and combat sleepiness and helps a person to get better quality sleep.
- Let Natural and/or Simulated Sunlight Work for You. Modern science has devised special lights that simulate sunlight, stimulating the brain to produce serotonin and norepinephrine, brain chemicals that give us a positive feeling and promote wakefulness.
- Schedule Naps, Work and Activities to maintain regularity in your life.
- Keep a To-Do List to stay organized.
- Seek support through Support Groups and Narcolepsy Network's Online Community to share issues, coping mechanisms, stories, information and to feel accepted.
- Try other Tips for Wakefulness published by former Narcolepsy Network Board of Trustees Member and Sleep Activist Ann Austin.

CONCLUSION

Narcolepsy is an sleep disorder due to loss of hypocretin neurons which manage sleep. Stimulants are the primary treatment for the excessive daytime sleepiness. Modafinil, sodium oxybate, amphetamine, methylphenidate, and selegiline are effectual treatments for somnolence associated with narcolepsy. Tricyclic antidepressants and SSRI are one of the best treatments for cataplexy, sleep paralysis, and hypnagogic hallucinations. Benzodiazepines are the best treatment for disturbed nocturnal sleep.

ACKNOWLEDGEMENTS

Author thank B. Sukanya, V. Usha vanya, M. Mahima, J. Vasantha for providing their immense support and cooperation.

REFERENCES

1. American Academy of Sleep Medicine. The International Classification of Sleep Disorders, Diagnostic and Coding Manual. 2nd ed. Westchester, IL: 2005.
2. Morrish E, King MA, Smith IE, Shneerson JM. Sleep Med, 2004; 5(1): 37–41.
3. Peyron C, Faraco J, Rogers W, et al. Nat Med, 2000; 6: 991-7.
4. Thannickal TC, Moore RY, Nienhuis R, et al. Neuron, 2000; 27: 469-74.
5. Crocker A, Espana RA, Papadopoulou M, et al. Neurology, 2005; 65: 1184-8.
6. Viorritto EN, Kureshi SA, Owens JA. Curr Neurol Neurosci Rep, 2012; 12: 175–81.
7. Mignot E, Chen W, Black J. Sleep, 2003; 26: 646-9.
8. Guilleminault C, Cao MT. Narcolepsy: Diagnosis and management. In: Kryger MH, Roth T, Dement WC, eds. Principles and Practice of Sleep Medicine, 5th ed. St. Louis, Missouri: Elsevier's Saunders, 2011; 957-68.
9. Dauvilliers Y, Arnulf I, Mignot E. Lancet, 2007; 369: 499-511.
10. Silber MH, Krahn LE, Olson EJ, Pankratz VS. Sleep, 2002; *25:* 197-202.
11. Narcolepsy fact sheet by National Institute of Neurological Disorders and Stroke (NINDS). http://www.ninds.nih.gov/disorders/narcolepsy/detail_narcolepsy.htm
12. Mamelak M. Prog Neurobiol, 2009; 89: 193-219.
13. Prinzmetal M,Bloomberg W. JAMA, 1935; 105: 2051-4.
14. Prescribing Information" sheet (PDF) for Adderall XR by Shire US Inc., http://www.adderallxr.com
15. Guilleminault C. Sleep, 1993; 16: 199 – 201.
16. Mitler MM , Aldrich MS , Koob GF , Zarcone V . Sleep, 1994; 17: 352-71.
17. Auger RR, Goodman SH, Silber MH, Krahn LE, Pankratz VS, Slocumb NL .Sleep, 2005; 28: 667–72.
18. Parkes JD.Dahlitz M. Sleep, 1993; 16.201-3.
19. Thorpy M.Sleep Med, 2007; 8: 427-40.
20. Cephalon "Prescribing Information" Sheet (PDF) for Provigil. https://www.provigil.com/hcp/default.aspx
21. Lin J-S, Hou Y, Jouvet M. Proc Natl Acad Sci USA, 1996; 93: 14128–14133.
22. Ludorff LE, Jonsson BH, Sjogren P. Palliat Med, 2009; 23(8): 731–738.
23. Morganthaler TI, K apur VK, Brown TM, Swick TJ, Alessi C, Aurora RN, et al. Sleep, 2006; 29: 1415-9.
24. Thomson Reuters (Healthcare) Inc.: Modafinil: Drug information. In: PDR_ Electronic Library. www.thomsonhc.com
25. Billiard M,Nicolet A,Dauvilliers Y et al. Modafinil: the european experience.In Bassetti C,Billiard M,Mognot E,(eds) Narcolepsy and Hypersomnia. Newyork.Informa Healthcare, 2007, pp. 561-9.
26. Darwish M , Kirby M , Hellriegel ET , Robertson P Jr. Clin Drug Investig, 2009; 29: 613 – 23.
27. Shindler J,Schachter M,Brincat S,et al. BM, 1985; 290: 1167-70.
28. Mayer G , Meier - Ewert K . Clin Neuropharmacol, 1995; 18: 306 – 19.
29. Hublin C , Partinen M , Heinonen E , Puuka P , Salmi T . Neurology, 1994; 44: 2095–101.
30. Mayer G , Meier - Ewert K .Clin Neuropharmacol ,1995; 18: 306–19.
31. Honda Y , Hishikawa Y . Curr Ther Res, 1980; 27: 429 – 41.
32. Rogers AE,Aldrich MS,Lin X. Sleep, 2001; 24: 385-91.
33. Broughton RJ,Murray BJ. The behavioral management of narcolepsy.In Bassetti C,Billiard M,Mignot E.(eds) Narcolepsy and hypersomnia Newyork.Informa-Healthcare, 2007 p. 497-512.
34. Billiard M, Bassetti C, Dauvilliers Y, Dolenc-Groselj L, Lammers GJ, Mayer G,et al. Eur J Neurol, 2006; 13:1035–48.
35. Morgenthaler TI, Kapur VK, Brown T, Swick TJ, Alessi C, Aurora RN, et al. Sleep, 2007; 30: 1705–11.
36. Broughton R, Mamelak M. Can J Neurol Sci, 1979 ; 6:1-6.
37. Prescribing Information Sheet (PDF) for Xyrem by Jazz Pharmaceuticals. ttp://www.xyrem.com/healthcareprofessionals/*prescribing-information.php*
38. The US XyremMulti-Center Study Group. Narcolepsy. Sleep, 2002; 25: 42–9.
39. Xyrem International Study Group. Narcolepsy. J Clin Sleep Med, 2005; 1: 391–7.
40. Black J,HoughtonWC. Sleep , 2006; 29: 939–46.
41. Wojtowicz JM, Yarema MC, Wax PM. CJEM , 2008; 10: 69-75.
42. LeTourneau JL, Hagg DS, Smith SM. Neurocrit Care, 2008; 8: 430-3.
43. Martinez-Rodriguez J,Iranzo A,Santamaria J,et al. Neurologia, 2002; 17: 113-6.
44. Sonka K , Kemlink D , Pretl M . Neuroendocrinol Lett, 2006; 27: 174– 6.
45. Poryazova R , Siccoli M , Werth E , Bassetti C . Neurology, 2005; 65: 967– 8.
46. Guilleminault C,Mancuso J,Quera-Salva MA,et al . Sleep, 1986; 9: 275-79.
47. Larrosa,dela Llave Y,Bario S et al. Sleep, 2001; 24: 282-5.
48. Niederhofer H. Sleep, 2005; 28: 1189.