



Universiteit
Leiden
The Netherlands

Pharmacological management of narcolepsy in children and adolescents

Plazzi, G.; Pizza, F.; Lecendreux, M.; Gringras, P.; Barateau, L.; Bruni, O.; ... ; Bassetti, C.L.A.

Citation

Plazzi, G., Pizza, F., Lecendreux, M., Gringras, P., Barateau, L., Bruni, O., ... Bassetti, C. L. A. (2023). Pharmacological management of narcolepsy in children and adolescents. *Journal Of Sleep Research*. doi:10.1111/jsr.14055

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](https://creativecommons.org/licenses/by/4.0/)

Downloaded from: <https://hdl.handle.net/1887/3736507>

Note: To cite this publication please use the final published version (if applicable).

Pharmacological management of narcolepsy in children and adolescents

Dear Editor,

Narcolepsy is often a paediatric disorder with symptoms that can commence in early childhood, and new diagnoses that peak at 15 years of age (Postiglione et al., 2018). For this reason we need controlled safe and effective pharmacological treatments to manage narcolepsy symptoms in young people. This has been a continued struggle for paediatric patients with narcolepsy, who have been at risk of becoming therapeutic orphans, without considerable advocacy (Lecendreux et al., 2012).

In 2021 Claudio Bassetti with other narcolepsy experts including most of the authors of this letter, on behalf of European Academy of Neurology, European Sleep Research Society, and European Narcolepsy Network, published, in this Journal, the European guidelines on the management of narcolepsy in adults and children (Bassetti

et al., 2021). This document, based on the evidence available, reported that among drugs registered in many European countries for adults' narcolepsy symptoms, only one, sodium oxybate, had data supporting its use in paediatric patients and related European Medicine Agency (EMA) approval, while other drugs are used off-label on the basis of experts' opinion and clinical practice or under single Country approval (see Figure 1). Since the publication of these guidelines, other clinical controlled pharmacological trials in children with narcolepsy have also been conducted or are ongoing with results still unpublished.

Pitolisant, a selective antagonist/inverse agonist of the central nervous system H3 histamine receptor, already licensed to treat narcolepsy symptoms in adults, underwent efficacy and safety trials in paediatric patients (Dauvilliers et al., 2023).

Suggested clinical pathway for the pharmacological management of narcolepsy in children

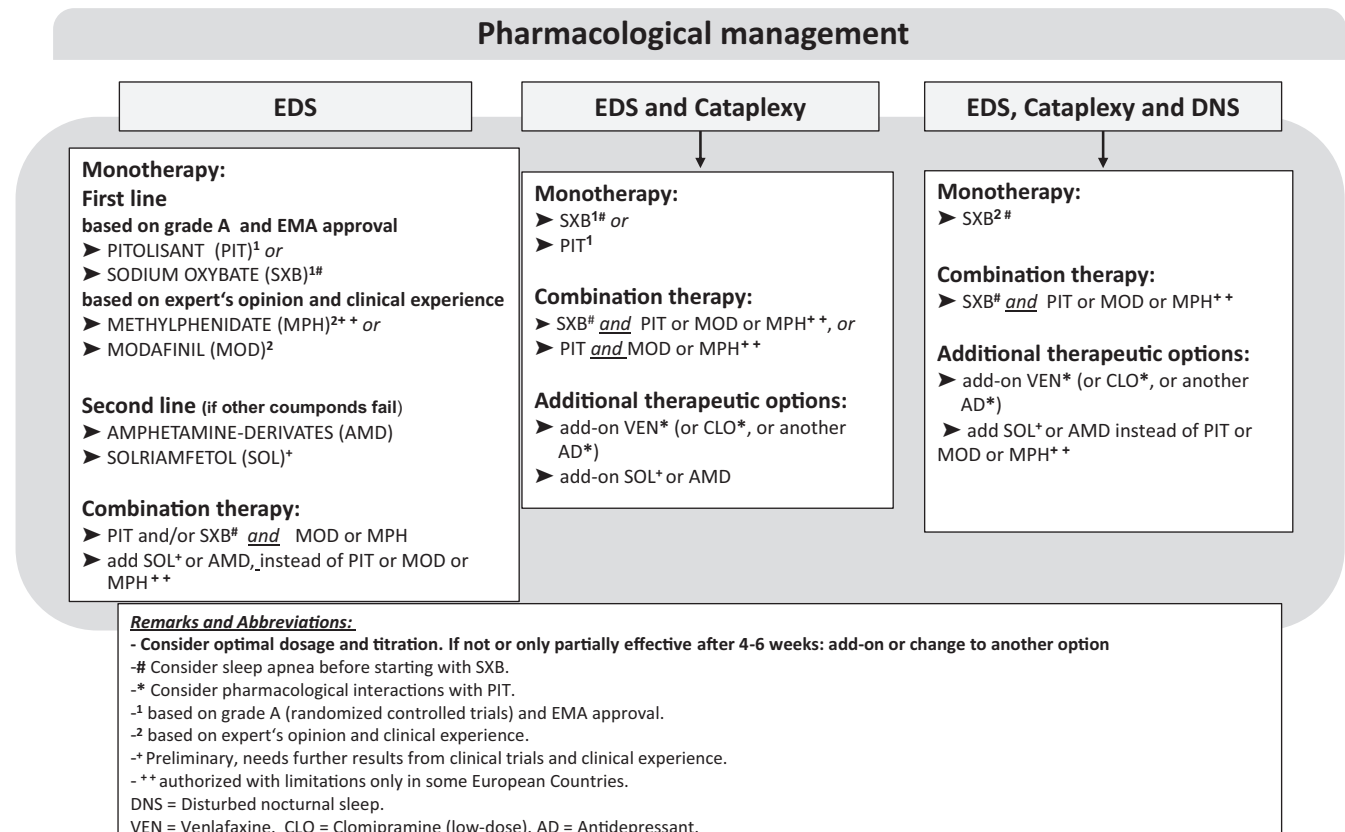


FIGURE 1 Suggested clinical pathway for the pharmacological management of narcolepsy in children.

The seminal double-blind, randomised, placebo-controlled study (Dauvilliers et al., 2023) involved 11 sleep centres in five European countries and enrolled 110 paediatric patients (mean age 12.9 ± 3.0 years), most of them (82%) with type 1 narcolepsy. Significant improvements, compared with placebo, of the Ullanlinna Narcolepsy Scale (UNS) total score, UNS-cataplexy sub-score, and Paediatric Daytime Sleepiness Scale (PDSS) showed that pitolisant was safe and effective in treating the main symptoms of narcolepsy. This trial found a similar favourable safety profile to the adult trials, with a similar prevalence of treatment-emergent adverse events in the pitolisant (31%) and in the placebo (34%) groups. The most frequently reported adverse events in children and adolescents were headache and insomnia, as in adults.

Based on these data, in February 2023 the EMA approved pitolisant for the treatment of narcolepsy with or without cataplexy of children and adolescents from the age of 6 years. The drug's efficacy, safety, and potential was also confirmed by a real world study (Triller et al., 2023). Further studies are planned to confirm its long-term efficacy and safety in children and adolescents.

While awaiting results from new clinical trials, the above recent studies now place pitolisant within the “first-line” registered drugs for the treatment of both daytime sleepiness and cataplexy in paediatric patients with narcolepsy (see Figure 1). The dearth of significant side effects is reassuring for physicians who know that early appropriate patient-centred multimodal treatment of narcolepsy will reduce later physical, learning, and social consequences (Plazzi et al., 2018).

AUTHOR CONTRIBUTIONS




Giuseppe Plazzi: Conceptualisation; writing – original draft; supervision; validation. **Fabio Pizza:** Validation; Conceptualisation; writing – original draft; supervision. **Michel Lecendreux:** Supervision; validation; Conceptualisation; writing – original draft. **Paul Gringras:** Conceptualisation; supervision; validation; writing – original draft. **Lucie Barateau:** Conceptualisation; validation; supervision; writing – original draft. **Oliviero Bruni:** Conceptualisation; writing – original draft; validation; supervision. **Patricia Franco:** Supervision; validation; Conceptualisation; writing – original draft. **Alex Iranzo:** Supervision; Conceptualisation; writing – original draft; validation. **Poul Jennum:** Supervision; validation; Conceptualisation; writing – original draft. **Ramin Khatami:** Supervision; Conceptualisation; writing – original draft; validation. **Stine Knudsen-Heier:** Validation; supervision; Conceptualisation; writing – original draft. **Silvia Miano:** Validation; supervision; Conceptualisation; writing – original draft. **Lino Nobili:** Conceptualisation; writing – original draft; validation; supervision. **Markku Partinen:** Supervision; validation; Conceptualisation; writing – original draft. **Paul Reading:** Conceptualisation; writing – original draft; validation; supervision. **Karel Sonka:** Conceptualisation; writing – original draft; validation; supervision. **Attila Szakacs:** Conceptualisation; writing – original draft; validation; supervision. **Massimo Zenti:** Supervision; validation; Conceptualisation; writing – original draft. **Ulf Kallweit:** Conceptualisation; writing – original draft; validation; supervision. **Gert J. Lammers:**

Writing – original draft; Conceptualisation; validation; supervision.

Yves Dauvilliers: Conceptualisation; validation; writing – original draft; supervision. **Claudio L. A. Bassetti:** Conceptualisation; writing – original draft; validation; supervision.

DATA AVAILABILITY STATEMENT

No data reported.

Giuseppe Plazzi^{1,2} 
 Fabio Pizza^{1,3}
 Michel Lecendreux^{4,5}
 Paul Gringras⁶
 Lucie Barateau^{7,8}
 Oliviero Bruni⁹ 
 Patricia Franco^{10,11}
 Alex Iranzo¹²
 Poul Jennum¹³
 Ramin Khatami^{14,15}
 Stine Knudsen-Heier^{16,17}
 Silvia Miano¹⁸ 
 Lino Nobili^{19,20} 
 Markku Partinen^{21,22}
 Paul Reading²³
 Karel Sonka²⁴
 Attila Szakacs^{25,26}
 Massimo Zenti^{27,28}
 Ulf Kallweit^{29,30} 
 Gert J. Lammers^{31,32}
 Yves Dauvilliers^{7,8}
 Claudio L. A. Bassetti^{33,34}

¹IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

²University of Modena and Reggio Emilia, Modena, Italy

³Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, Bologna, Italy

⁴Pediatric Sleep Disorders Center, AP-HP, Robert Debre Hospital, Paris, France

⁵National Reference Centre for Orphan Diseases, Narcolepsy, Idiopathic Hypersomnia and Kleine-Levin Syndrome, Paris, France

⁶Children's Sleep Medicine Kings College, London, UK

⁷National Reference Centre for Orphan Diseases, Narcolepsy, Idiopathic Hypersomnia, and Kleine-Levin Syndrome, Gui-de-Chauliac Hospital, CHU Montpellier, Montpellier, France

⁸Institute of Neurosciences of Montpellier, University of Montpellier, INSERM, Montpellier, France

⁹Department of Developmental and Social Psychology, Sapienza University, Rome, Italy

¹⁰Pediatric Sleep Unit and National Reference Center for Narcolepsy, Mother-Children's Hospital, Hospices Civils de Lyon & U1028, Lyon Neuroscience Research Center (CRNL), University Lyon 1, Lyon, France

¹¹National Reference Centre for Orphan Diseases, Narcolepsy, Idiopathic Hypersomnia, and Kleine-Levin Syndrome Lyon, Lyon, France

- ¹²Neurology Service, Sleep Disorders Centre, Hospital Clinic Barcelona, Universitat de Barcelona. IDIBAPS, CIBERNED: CBO6/05/0018-ISCIII, Barcelona, Spain
- ¹³Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, Copenhagen, Denmark
- ¹⁴Center for Sleep Medicine, Sleep Research and Epileptology, Clinic Barmelweid AG, Barmelweid, Switzerland
- ¹⁵Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland
- ¹⁶Norwegian Center for Neurodevelopmental Disorders and Hypersomnias – NevSom, Department of Rare Disorders, Oslo University Hospital, Oslo, Norway
- ¹⁷Institute of Clinical Medicine, University of Oslo, Oslo, Norway
- ¹⁸Neurocenter of Southern Switzerland, Faculty of Biomedical Sciences, Università della Svizzera Italiana, Sleep Medicine Unit, Civic Hospital, Lugano, Switzerland
- ¹⁹Child Neuropsychiatry Unit, IRCCS Istituto G. Gaslini, Genoa, Italy
- ²⁰Department of Neuroscience – Rehabilitation – Ophthalmology – Genetics – Child and Maternal Health (DINOGLI), University of Genova, Genoa, Italy
- ²¹Department of Neurosciences, Clinicum, University of Helsinki, Helsinki, Finland
- ²²Helsinki Sleep Clinic, Terveystalo Healthcare, Helsinki, Finland
- ²³Department of Neurology, The James Cook University Hospital, Middlesbrough, UK
- ²⁴Department of Neurology and Center for Clinical Neuroscience, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic
- ²⁵Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
- ²⁶Department of Pediatrics, Halmstad County Hospital, Halmstad, Sweden
- ²⁷Associazione Italiana Narcolettici e Ipersonni, Florence, Italy
- ²⁸European Narcolepsy Alliance for Patients, Brussels, Belgium
- ²⁹Center for Narcolepsy and Hypersomnias, Professorship for Narcolepsy and Hypersomnolence Research, Department of Medicine, University Witten/Herdecke, Witten, Germany
- ³⁰Center for Biomedical Education and Research (ZBAF), University Witten/Herdecke, Witten, Germany
- ³¹Stichting Epilepsie Instellingen Nederland (SEIN), Sleep-Wake Center, Heemstede, Netherlands
- ³²Department of Neurology, Leiden University Medical Centre, Leiden, Netherlands
- ³³Medical Faculty, University of Bern, Bern, Switzerland
- ³⁴Department of Neurology, University Hospital (Inselspital), Bern, Switzerland

Correspondence

Giuseppe Plazzi, Ospedale Bellaria, Padiglione G, Primo Piano, Via Altura 3, 40,139, Bologna, Italy.
Email: giuseppe.plazzi@isnb.it

ORCID

Giuseppe Plazzi  <https://orcid.org/0000-0002-1051-0472>

Oliviero Bruni  <https://orcid.org/0000-0003-2207-1398>

Silvia Miano  <https://orcid.org/0000-0003-4475-3947>

Lino Nobili  <https://orcid.org/0000-0001-9317-5405>

Ulf Kallweit  <https://orcid.org/0000-0003-1975-6919>

REFERENCES

- Bassetti, C. L. A., Kallweit, U., Vignatelli, L., Plazzi, G., Lecendreux, M., Baldin, E., Dolenc-Groselj, L., Jennum, P., Khatami, R., Manconi, M., Mayer, G., Partinen, M., Pollmächer, T., Reading, P., Santamaria, J., Sonka, K., Dauvilliers, Y., & Lammers, G. J. (2021). European guideline and expert statements on the management of narcolepsy in adults and children. *European Journal of Neurology*, 28, 2815–2830.
- Dauvilliers, Y., Lecendreux, M., Lammers, G. J., Franco, P., Poluektov, M., Caussé, C., Lecomte, I., Lecomte, J.-M., Leheret, P., Schwartz, J.-C., & Plazzi, G. (2023). Safety and efficacy of pitolisant in children aged 6 years or older with narcolepsy with or without cataplexy: A double-blind, randomised, placebo-controlled trial. *Lancet Neurology*, 22, 303–311.
- Lecendreux, M., Bruni, O., Franco, P., Gringras, P., Konofal, E., Nevsimalova, S., Paiva, T., Partinen, M., Peeters, E., Peraita-Adrados, R., Plazzi, G., & Poli, F. (2012). Clinical experience suggests that modafinil is an effective and safe treatment for paediatric narcolepsy. *Journal of Sleep Research*, 21(4), 481–483.
- Plazzi, G., Clawges, H. M., & Owens, J. A. (2018). Clinical characteristics and burden of illness in pediatric patients with narcolepsy. *Pediatric Neurology*, 85, 21–32.
- Postiglione, E., Antelmi, E., Pizza, F., Lecendreux, M., Dauvilliers, Y., & Plazzi, G. (2018). The clinical spectrum of childhood narcolepsy. *Sleep Medicine Reviews*, 38, 70–85.
- Triller, A., Pizza, F., Lecendreux, M., Lieberich, L., Rezaei, R., Pech de Laclause, A., Vandì, S., Plazzi, G., & Kallweit, U. (2023). Real-world treatment of pediatric narcolepsy with pitolisant: A retrospective, multicenter study. *Sleep Medicine*, 103, 62–68.