Clinical experience suggests that modafinil is an effective and safe treatment for paediatric narcolepsy

Narcolepsy with cataplexy is a chronic, life-long, disabling condition that occurs during childhood in approximately one-third of subjects. It usually begins during the first or second decade of life, and symptoms may develop rapidly over a few weeks or months, with excessive daytime sleepiness (EDS) and cataplexy being the most dramatic and observable symptoms. Pharmacological treatments in children with narcolepsy are mostly based on empirical data and clinical experience; randomized clinical trials are lacking and treatment guidelines have not yet been established in narcoleptic children (Ivanenko *et al.*, 2003; Nevsimalova, 2009).

Based on the experience of all the undersigned, wake-promoting medications have significantly improved the symptoms and well-being of young patients with narcolepsy. However, all available treatments are delivered off-label in the paediatric population (Aran *et al.*, 2010; Peraita-Adrados *et al.*, 2011). Modafinil is a non-amphetamine type stimulant that acts as a wakefulness-promoting drug, and is approved for managing EDS due to narcolepsy in adults. Following the findings of a safety review, the European Medicines Agency has recently recommended that the use of medicines containing modafinil should be restricted to sleepiness associated with narcolepsy only, with all other indications to be removed from product information. In addition, the Committee for Medicinal Products for Human Use recommended that the product information carry a recommendation stating that modafinil should not be prescribed to children, as the risk of developing serious skin and hypersensitivity adverse reactions appears to be higher in this age group.

As an international group of paediatric sleep specialists with over two decades of experience using modafinil, we were surprised by this decision. Our concerns were that this decision might be based on the absence of safety data from well-conducted trials in children. This recommendation has the potential to adversely affect our ability to use of one of the few efficient and safe drugs available for the treatment of narcolepsy in children and adolescents.

Based on our clinical experience, we collected all cases providing here a description of efficacy and side-effects. Summarizing the data from all authors, 205 children and adolescents (99 M; 106 F) with narcolepsy were treated with modafinil; the age range was 4–18 years, and the prescribed dose of modafinil varied from 50 to 600 mg (Table 1). Patients have been treated for more than 10 years in the majority of the Centres, with the longest period of treatment of 19 years in France.

According to literature, increasing modafinil doses above 400 mg has not usually conferred any additional benefit, and most co-authors used a maximum daily dose of 400 mg. In the French paediatric cohort, the average daily dose of modafinil was 388 ± 140 mg. In some rare cases, and for adolescents over 16 years old, modafinil had progressively been titrated to twice-daily 300 mg doses. In these cases, increasing the dose was beneficial, safe and well tolerated.

We found modafinil to be effective in more than 85% of patients, and in the remaining cases lack of efficacy, habituation or mild adverse effects led to drug discontinuation.

The most frequent side-effects were represented by headache in 13.7% of cases, nervousness and irritability in 6.5%, and loss of appetite in only 2.2%. No severe hypersensitivity reactions were reported by any author, and particularly no serious skin reactions were recorded.

Although these data are based on clinical experience and cannot replace randomized studies, the number of patient-years we have accrued suggests modafinil can be used safely in children and adolescents.

Prior to this recommendation the major limitation for utilization of modafinil within different countries was related to the availability and price of the compound. For instance, in France, modafinil was used for decades as the first-line treatment for adults with narcolepsy before sodium oxybate was licensed. In Italy it is the only first-line treatment for narcolepsy in children, as methylphenidate is licensed only for attention deficit hyperactivity disorder. In Spain it is a high-cost treatment, as the public health system refunds only 60% of the price of modafinil. The Spanish Narcolepsy Association has lobbied both to the Health National Service and the Health Commission in Parliament without success.

A specific Working Group for Narcolepsy in Children has been recently constituted as part of the European Network of Rare Pediatric Neurological Diseases (http://*www.neuroped.eu*). Its far-reaching aims are to identify current research, treatment and patient care challenges, to develop a registry for observational and prospective studies, and to disseminate recommendations on diagnosis and treatment on narcolepsy in children. Although not specific for children, the European Narcolepsy Network (http://www.narcolepsy-network.eu) is another non-profit organization with the purpose of gaining a better insight into narcolepsy and related hypersomnias by pooling the resources of a variety of Sleep Centres, and creating an international database of patients with narcolepsy and hypersomnias. Together these initiatives will provide additional valuable information about the safety of modafinil.

Across our European Centres, both the young people we treat and their careers attest to the potential for modafinil to restore a high quality of alertness and attention throughout

Table 1 Cases of narcolepsy treated with modafinil reported by each author

	Total	*M*	*F*	*Age range (years)*	*Min/*max dose (mg)*	*Nervousness, %*	*Headache, %*	*Loss of appetite, %*	*Severe reactions*	*Note*
Bruni	10	7	3	4–18	100–300	20	20	10	No	First-line treatment in Italy for EDS in narcolepsy; interrupted in one case for loss of appetite.
Gringras	4	2	2	10–15	200–400	0	25	0	No	First-line treatment for children in UK is often slow-release methylphenidate.
Lecendreux, Konofal, Franco	68	32	36	6–17	100–600	12	12	4	No	Modafinil interrupted in 20/68 patients due to lack of efficacy, habituation or mild adverse effects.
Nevsimalova	27	12	15	6.5–18	100–400	0	18.5	0	No	Well-tolerated, safe, better effect compared with methylphenidate.
Paiva	5	3	2	6–17	100–400	0	0	0	No	Well tolerated.
Partinen	23	11	12	6–17	50–400	13	26.1	0	No	Modafinil interrupted in 7/23 due to lack of efficacy. Urticaria in one girl related to concomitant antibiotic (amoxicillin) treatment. No skin reaction when modafinil was restarted.
Peeters	10	4	6	4–17	100–300	0	10	0	No	Well-tolerated, definite effect EDS, in all patients still on modafinil treatment, no discontinuation.
Peraita- Adrados	12	6	6	6–17	200–400	16.6	16.6	0	No	Well tolerated.
Plazzi, Poli	46	22	24	4–17	50–400	15.2	8.7	6.5	No	First-line treatment in Italy for EDS in narcolepsy. Interrupted in four children due to lack of efficacy or habituation.
Total	205	99	106	4–18	50–600	8.5	15.2	2.3	No	

*The approximate mean duration of modafinil treatment was about 7 years.
EDS, excessive daytime sleepiness.

the day. Very few therapeutic alternatives are available for children, and in practice modafinil may show lower potential abuse than amphetamine-based stimulants, as reported in the adult population (Heinzerling *et al.*, 2010).

We have a limited repertoire of therapeutic interventions for young people with this devastating, life-long neuroimmunological disorder. Modafinil is an important agent to promote daytime wakefulness and we have shown that, according to our collective clinical experience, it can be a successful and safe treatment in children and young people with narcolepsy.

We urgently need robust controlled clinical trials in the paediatric population of active medications both against placebo, and equivalence trials, to accurately inform our knowledge, and that of the regulators about the safety and efficacy of these medications in this important but poorly served group of patients.

CONFLICT OF INTERESTS

Oliviero Bruni participated in the Cephalon's trial 'Modafinil as treatment for excessive sleepiness associated with narcolepsy and other types of hypersomnia mainly obstructive sleep apnoea in children and adolescents: a 6-month open-label study'. He has no shares and no conflicts of interests with Cephalon, Teva or Midy.

Patricia Franco has no shares and no conflicts of interests with Cephalon, Teva or Midy, and is working as a consultant and received honoraries for lecturing from UCB Pharma.

Paul Gringras has no conflicts of interest.

Michel Lecendreux is a consultant for UCB Pharma, Bioprojet and Shire. He has participated as an investigator in Cephalon's trial 'Modafinil as a treatment for excessive sleepiness associated with narcolepsy and other types of hypersomnia mainly obstructive sleep apnoea in children and adolescents: a 6-month open-label study'. He has no shares and no conflicts of interests with Cephalon, Teva or Midy.

Eric Konofal has served on advisory boards for Shire Pharmaceuticals, UCB and Vifor. He has consulted for Shire Pharmaceuticals. He has served as a medical writer for Remidica and Janssen-Cilag. He has served on the speaker's bureau of UCB, and served as a principal investigator in clinical trials supported by Eli Lilly and Janssen-Cilag, and has been co-investigator in studies sponsored by Glaxo-SmithKline, Cephalon, Eli Lilly and Shire Pharmaceuticals. He serves as a consultant for Shire Pharmaceuticals, Pharmacosmos, Pierre Fabre Medicament and Vifor. Dr Konofal is inventor of mazindol combination in the treatment of ADHD (WO/2007/116076).

Sona Nevsimalova participated in Cephalon's trial 'Modafinil as treatment for excessive sleepiness associated with narcolepsy and other types of hypersomnia mainly obstructive sleep apnoea in children and adolescents: a 6-month

open-label study', and Actelion Pharmaceuticals CZ – participant of the 'Registry for patients with Niemann-Pick type C disease'.

Teresa Paiva has no conflicts of interest.

Markku Partinen has been working as a consultant for UCB Pharma, Bioprojet and Leiras. He has received honoraries for lecturing and travel grants from Cephalon, GlaxoSmithKline, Leiras, MSD and Servier. He has been involved in open or randomized clinical trials on narcolepsy supported by Bioprojet, Cephalon and UCB Pharma. He is Chairman of the Board of the Finnish Narcolepsy Research Centre, Helsinki Sleep Clinic, and member of the Board in the Finnish Sleep Federation and Finnish Sleep Research Society. M. Partinen has no shares in any of these companies, and has no conflicts of interest with Teva or Midy.

Els Peeters has no conflicts of interest.

Rosa Peraita Adrados participated in Cephalon's trial 'Modafinil as treatment for excessive sleepiness associated with narcolepsy and other types of hypersomnia mainly obstructive sleep apnoea in children and adolescents: a 6-month open-label study'.

Giuseppe Plazzi has been consultant for UCB Pharma, Cephalon. He has received honoraries for lecturing and travel grants from Cephalon. He is/has been involved in randomized clinical trials on narcolepsy supported by Bioprojet, and post-marketing studies by Cephalon and UCB Pharma. In particular he has participated in Cephalon's trial 'Modafinil as treatment for excessive sleepiness associated with narcolepsy and other types of hypersomnia mainly obstructive sleep apnoea in children and adolescents: a 6-month open-label study'.

Francesca Poli has no conflicts of interest.

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doi: 10.1111/j.1365-2869.2011.00991.x

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