few days, she could walk without assistance. Four weeks after withdrawal of the drug, she had slight rigidity and mild bradykinesia. Treatment with 300 mg of L-dopa and 30 mg of carbidopa failed to further improve her motor function. Thus, it was unlikely that she had Parkinson's disease. A rechallenge procedure with milnacipran was not done, for she was no longer depressive. Because the temporal relation between the ingestion of milnacipran and the occurrence of parkinsonism was so noticeable, it is highly probable that milnacipran caused the severe parkinsonism. Because milnacipran is not metabolised by the hepatic cytochrome P450 system,[1] it is unlikely that concurrent use of etidronate disodium and calcitriol affected plasma concentration of milnacipran.

Although several lines of evidence suggest that dopamine release in the striatum is regulated by serotonin, the effects of serotonin and SSRI on dopamine release in the striatum of normal animals are disputed. Some studies have demonstrated that stimulation of the 5-HT(1A) receptors inhibits dopamine release and tyrosine hydroxylation in the striatum. In the striatum of the animals with nigrostriatal dopaminergic denervation, 5-HT(1A) receptor density was upregulated.[4] The density of dopamine D2 receptors in the striatum was increased after repeated administration of milnacipran.[5] Infarcts in the basal ganglia might have impaired such adaptive changes in the dopaminergic system, rendering the patient susceptible to milnacipran induced parkinsonism. To my knowledge, this is the first reported case of parkinsonism associated with the use of SNRI. Clinicians should be aware that not only SSRI but SNRI can cause severe parkinsonism.

**M Arai**

Department of Neurology, Seirei Mikatahara General Hospital, Mikatahara-cho 3453, Hamamatsu, Shizuoka 433-8558, Japan

Correspondence to: Dr M Arai; arai-m@sis.seirei.or.jp

Competing interests: none declared.

## References

1 **Spencer CM**, Wilde MI. Milnacipran. A review of its use in depression. *Drugs* 1998;**56**:405–27.
2 **Caley CF**. Extrapyramidal reactions and the selective serotonin-reuptake inhibitors. *Ann Pharmacother* 1997;**31**:1481–9.
3 **Di Rocco A**, Brannan T, Prikhojan A, *et al*. Sertraline induced parkinsonism. A case report and an in-vivo study of the effect of sertraline on dopamine metabolism. *J Neural Transm* 1998;**105**:247–51.
4 **Frechilla D**, Cobreros A, Saldise L, *et al*. Serotonin 5-$HT_{1A}$ receptor expression is selectively enhanced in the striosomal compartment of chronic parkinsonian monkeys. *Synapse* 2001;**39**:288–96.
5 **Rogóz Z**, Margas W, Dlaboga D, *et al*. Effect of repeated treatment with milnacipran on the central dopaminergic system. *Pol J Pharmacol* 2000;**52**:83–92.

# The relation between daytime sleepiness, fatigue, and reduced motivation in patients with adult onset myotonic dystrophy

Daytime sleepiness, apathy, and lack of motivation are established clinical manifestations of myotonic dystrophy.[1 2] A recent study showed that modafinil reduced daytime sleepiness and average sleep latency in a group of nine patients with myotonic dystrophy.[3] This finding suggests that daytime sleepiness in patients with myotonic dystrophy and without obstructive sleep apnoea might be central in origin. A magnetic resonance imaging study indeed found evidence for a possible association between cerebral abnormalities in myotonic dystrophy and excessive daytime sleepiness.[4] Although several studies have measured levels of fatigue with validated questionnaires in different neurological patient populations,[5 6] fatigue questionnaires have not yet been related to the symptoms of daytime sleepiness in myotonic dystrophy. With the results of the modafinil study mentioned above in mind, our goal was to test the relations between excessive daytime sleepiness, experienced fatigue, and reduced motivation.

## Methods

### Patients

The study was conducted at the outpatient clinic of the Neuromuscular Centre Nijmegen, based at the Institute of Neurology of the University Medical Centre Nijmegen in the Netherlands. Consecutive ambulant patients with a genetically confirmed diagnosis of (adult onset) myotonic dystrophy and an expanded CTG repeat on chromosome 19q13.3 (DM1) were invited to take part. Fatigue was not a criterion for inclusion, and the patients came to the hospital for their regular visits. Those willing to participate were asked to complete the questionnaires at home and then send them back to the hospital.

Data were collected on 32 patients (16 female/16 male), mean age 43.8 years (range 22 to 73), and mean complaint duration 10.1 years (range 1 to 35). Myotonia and muscle weakness were rated using the five point muscular disability rating scale (MDRS).[7] The scores in this group ranged from 0 (absent myotonia and muscle weakness) to 4 (severe proximal muscle weakness and wheelchair dependence), and the mean (SD) MDRS score for the group was 2.3 (1.1) (range 0 to 4).

### Measurements

#### Daytime sleepiness

Three items (Nos 2, 5, and 7) of the subscale sleep/rest of the sickness impact profile refer specifically to increased daytime sleepiness.[8] These three items ("I feel continuously like dozing off"; "I am often hanging around half asleep"; "I sleep more during the day") were summed, and a score $> 0$ was taken as an indication of increased sleepiness.

#### Fatigue severity

The subscale "fatigue severity" of the checklist individual strength (CIS) measures the experience of fatigue associated problems during the previous two weeks. The CIS-fatigue severity scale contains eight items that can be scored on a seven point Likert scale. Scores can range between 8 and 56; higher scores indicate higher levels of fatigue, and scores exceeding 40 points are considered to indicate severe fatigue.[5 6 9]

#### Reduced motivation

The CIS subscale "reduced motivation" contains four items that are also scored on a seven point Likert scale (score range 4 to 28). Higher scores (range 4 to 28) are indicative of taking less initiative and of decreased motivation.[9]

#### Statistics

Independent *t* tests were used to compare the groups of patients with and without sleepiness symptoms with respect to their mean CIS-fatigue, CIS-lack of motivation, and MDRS scores. Significance testing was two sided, with $\alpha$ set at 0.05.

## Results

Ten (31%) of the 32 patients answered positively on one or more of the three sleepiness items. The patients were then divided into a group which reported at least one of the three sleepiness symptoms (sleepiness; $n = 10$) and a group which reported no sleepiness symptoms (non-sleepiness; $n = 22$). Independent *t* test showed no significant differences between the mean CIS-fatigue scores of the two groups (sleepiness, 44.6 (7.5); non-sleepiness, 41.0 (10.2); $t = 0.98$, $p = 0.33$), but there was a significant difference for the CIS-reduced motivation score. The sleepiness group reported a significantly greater reduction in motivation than the non-sleepiness group (sleepiness, 22.5 (3.5); non-sleepiness, 15.1 (4.8); $t = 4.35$, $p < 0.001$). The groups did not differ with respect to their MDRS scores (mean MDRS in the sleepiness group, 2.2 (1.5); in the non-sleepiness group, 2.4 (1.0); $t = -0.4$, $p = 0.69$). The MDRS score was also not significantly correlated with the CIS-fatigue score (Spearman $\rho = 0.19$, $p = 0.32$).

## Discussion

Almost one third of this group of consecutive, ambulatory, adult onset myotonic dystrophy patients reported daytime sleepiness. This proportion is comparable with that in the study by Rubinsztein *et al*, in which 39% of 36 adults with non-congenital myotonic dystrophy were identified as hypersomnolent.[2] Another study also found that patients with myotonic dystrophy or Charcot-Marie-Tooth disease reported more daytime sleepiness than healthy controls, but that the majority of patients with myotonic dystrophy had daytime sleepiness scores below the proposed cut off on the Epworth sleepiness scale.[10] In the two daytime sleepiness studies mentioned in our introduction, only small numbers of patients were studied (9 and 11),[3 4] so comparisons of the incidence of daytime sleepiness are rather difficult. However, the fact that we studied consecutive patients makes a bias towards those with fewer symptoms of daytime sleepiness unlikely.

The mean fatigue scores of both the sleepiness group and the non-sleepiness group exceeded the cut off for abnormal fatigue and thus warrants a more extensive study of possible determinants of abnormal fatigue in this multisystem disorder. The findings that the fatigue scores were increased independently of sleepiness, and the fact that neither symptom was associated with the MDRS, suggests that different pathophysiological mechanisms underlie these clinical manifestations. Further assessment of the relation between these independent symptoms and, for example, the endocrinological and neurological status of the patients is required. Post hoc assessment of 21 of our group of patients showed that none of them suffered from thyroid dysfunction, while the prevalence of abnormal sleepiness (38%) and the mean fatigue score of these 21 patients resembled those of the 11 other patients on whom no thyroid function data were available. These findings suggest that abnormal sleepiness or fatigue may occur in myotonic dystrophy despite normal thyroid function.

In the light of these results we would like to advocate the simultaneous use of both daytime sleepiness and fatigue outcome measures in future treatment and fatigue studies.

**Netherlands Fatigue Research Group, S van der Werf, J Kalkman, G Bleijenberg**

Department of Medical Psychology, University Medical Centre Nijmegen, PO box 9101, 6500 HB Nijmegen, Netherlands

**B van Engelen**

Neuromuscular Centre Nijmegen, Institute of Neurology, University Medical Centre Nijmegen

**M Schillings, M Zwarts**

Department of Clinical Neurophysiology, University Medical Centre Nijmegen

Competing interests: none declared

Correspondence to: Dr S P van der Werf; s.vanderwerf@cukz.umcn.nl

## References

1 **Harper PS**. *Myotonic dystrophy*. London: WB Saunders, 2001.
2 **Rubinsztein JS**, Rubinsztein DC, Goodburn S, *et al*. Apathy and hypersomnia are common features of myotonic dystrophy. *J Neurol Neurosurg Psychiatry* 1994;**64**:510–15.
3 **Damian MS**, Gerlach A, Schmidt F, *et al*. Modafinil for excessive daytime sleepiness in myotonic dystrophy. *Neurology* 2001;**56**:794–6.
4 **Giubilei F**, Antonini G, Bastianello S, *et al*. Excessive daytime sleepiness in myotonic dystrophy. *J Neurol Sci* 1999;**164**:60–3.
5 **van der Werf SP**, Jongen PJ, Lycklama, *et al*. Fatigue in multiple sclerosis: interrelations between fatigue complaints, cerebral MRI abnormalities and neurological disability. *J Neurol Sci* 1998;**160**:164–70.
6 **van der Werf SP**, van den Broek HLP, Anten HWM, *et al*. Experience of severe fatigue long after stroke and its relation to depressive symptoms and disease characteristics. *Eur Neurol* 2000;**45**:28–33.
7 **Mathieu J**, De Braekeleer M, Prevost C, *et al*. Myotonic dystrophy: clinical assessment of muscular disability in an isolated population with presumed homogeneous mutation. *Neurology* 1992;**42**:203–8.
8 **Bergner M**, Bobbit RA, Carter WB, *et al*. The Sickness Impact Scale: development and final revision of a health status measure. *Med Care* 1981;**19**:787–805.
9 **Vercoulen JH**, Swanink CM, Fennis JF, *et al*. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994;**38**:383–92.
10 **Phillips MF**, Steer HM, Soldan JR, *et al*. Daytime somnolence in myotonic dystrophy. *J Neurol* 1999;**246**:275–82.