The autoimmune hypothesis of narcolepsy and its unexplored clinical features

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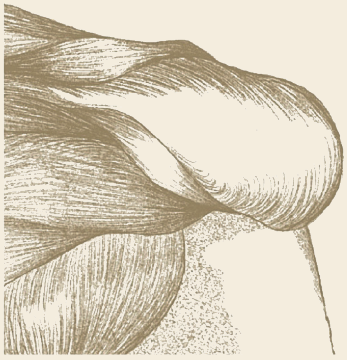

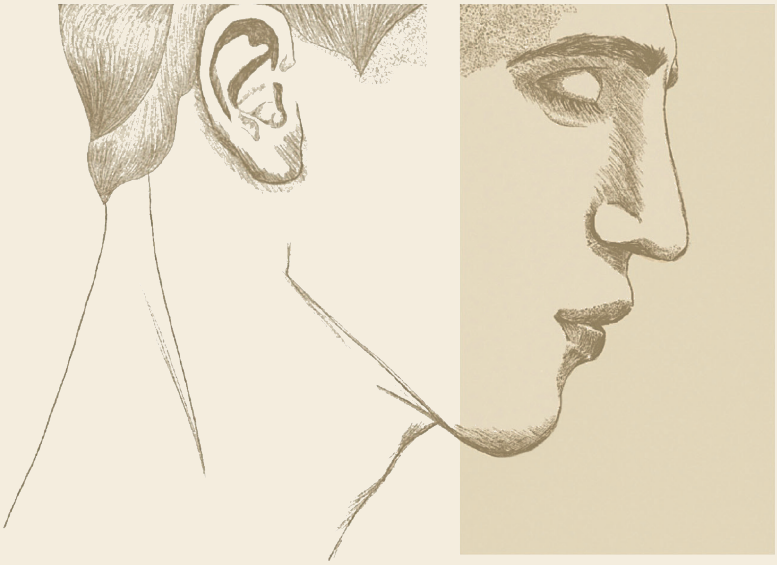

Chapter 5

Decreased body mass index during treatment with sodium oxybate in narcolepsy type 1

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Abstract

Narcolepsy type 1 patients is characterized by an increase in body weight after disease onset, frequently leading to obesity. It was suggested that this weight gain may be counteracted by treatment with sodium oxybate (SXB). We here provide longitudinal BMI data of patients with narcolepsy type 1 after starting treatment with SXB, compared to patients in whom treatment with modafinil was initiated. 81 individuals with narcolepsy type 1 fulfilled the entry criteria for this retrospective study: 59 had newly started treatment with SXB, and 22 had newly started modafinil. Gender-specific differences between both treatment groups were compared using Student's t-tests and mixed effect modeling. Patients using SXB lost weight with a mean BMI decrease of 2.56 kg/m^2 between the first and last measurement (women; p=0.001) and 0.84 kg/m^2 (men; p=0.006). Patients using modafinil, however, gained weight with a mean BMI increase of 0.57 kg/m^2 (women; p = 0.033) and 0.67 kg/m^2 (men; p=0.122). Medication (p=0.006) and baseline BMI (p=0.032) were predictors for BMI decrease. In conclusion, treatment with SXB is associated with a BMI reduction in narcolepsy type 1, while modafinil treatment is not. This effect is most pronounced in those who already have a higher baseline BMI.

Introduction

Narcolepsy type 1 (NT1) is a chronic neurological disorder characterised by excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations and disturbed nocturnal sleep (Black et al., 2017). In addition to the classical symptoms, other symptoms have been reported. These include autonomic abnormalities and obesity (Fronczek et al., 2008). Narcolepsy type 1 is caused by a loss of hypothalamic hypocretin (orexin)-producing neurons (Nishino et al., 2001). Hypocretin neurons project throughout the central nervous system to areas known to be important in the control of sleep-wakefulness, but also to areas important in neuroendocrine homeostasis, autonomic regulation and the control of feeding (Willie et al., 2001).

From as early as the 1930s it has been reported that obesity is more prevalent in narcolepsy patients than in healthy controls (Daniels 1934; Wang et al., 2016). Abdominal fat deposition and waist circumference were found to be significantly increased in narcolepsy patients (Kok et al., 2003). who also have a higher prevalence of the metabolic syndrome compared to idiopathic hypersomnia patients (Poli et al., 2009). Also in children NT1 onset was associated with rapid weight gain (Ponziani et al., 2016). Cause for the observed obesity in NT1 has not been elucidated. It is probably not secondary to inactivity or to medication use (Black et al., 2017). Studies of eating habits showed conflicting results regarding caloric intake, the prevalence of eating disorders in NT1 (Fortuyn et al., 2008) and basal metabolic rate. A recent study in children with NT1 showed a lower basal metabolic rate (BMR) closely after disease onset, which restored to normal levels in the following months (Wang et al., 2016). Therefore, it is hypothesized that NT1 induces a change in the individual body mass index (BMI) set point (Dahmen et al., 2009), but the exact mechanism causing this hypothesized change in NT1 patients remains unclear. Management of BMI in NT1 is important, as a higher BMI seems a risk factor for diseases, such as diabetes type 2 and cardiovascular disease (Kok et al., 2003) and predisposes to psychosocial and professional disability (World Health Organization, 2000; Narbro et al., 1996).

Recent observations suggest that pediatric and adult narcolepsy patients lose weight when using sodium oxybate (SXB; Boscolo-Berto et al., 2012; Ponziani et al., 2016). Weight loss in narcolepsy patients with (mean loss of 5.1kg) and without cataplexy (mean loss of 2kg) treated with SXB has been reported (Husain

et al., 2009), while another study showed a 5.2kg weight loss after 3 months of SXB treatment (Donjacour et al., 2014). This has not yet been confirmed and long-term follow-up data is not available. We here provide longitudinal BMI data of NT1 patients after starting treatment with SXB, compared to patients in whom treatment with modafinil was initiated. Our hypothesis is that BMI decreases upon introduction of SXB, while use of modafinil will not affect BMI.

Methods

Subjects

Medical records of consecutive individuals diagnosed with NT1 attending the outpatient clinic of the Sleep-Wake Center Stichting Epilepsie Instellingen Nederland (SEIN) and the outpatient clinic of the Leiden University Medical Centre between 2009 and 2017 were reviewed retrospectively. All individuals included (n=81) fulfilled the criteria for NT1 as formulated in the third edition of the International Classification of Sleep Disorders (ICSD-3, 2014). Only those who initiated treatment with either SXB or modafinil and used it for at least three months were included. Those who had already used one of the medications were excluded. Patients were also excluded if there were no measurements recorded, if they suffered from another disorder that is associated with obesity (e.g. hypothyroid disease) or if they were under the age of 18 years. The follow up period ended prematurely if the SXB or modafinil treatment was discontinued, or when additional medication was started. Relevant co-medication use (antidepressants, methylphenidate, dexamphetamine) was extracted from the records. The decision to prescribe either modafinil or SXB was a clinical decision based on the presence and severity of the various NT1 symptoms. Weight at treatment start did not play a role in this decision.

Study design

This is a retrospective follow-up study in which the above described individuals were followed up to July 31st 2017. Weight, length and medication, assessed at the beginning of each visit to the outpatient clinic were extracted from the records. BMI was calculated by dividing the weight (kg) by the squared length (m^2) for each visit.

Statistical analysis

Differences at baseline in participant characteristics between the SXB and modafinil group were calculated with Mann-Whitney U (age), chi-square (gender, co-medication), and Student's t-tests (baseline BMI, treatment duration). To estimate if the BMI of the study cohort was significantly higher than that of the general Dutch population, data from Statistics Netherlands (Centraal Bureau voor de Statistiek, 2016) were used.

To assess whether statistically significant BMI changes occurred during follow-up, a paired sample Student´s test was performed to compare BMI at baseline with BMI at the last visit for four separate groups (based on gender and treatment). Since this comparison is still subject to factors influencing BMI and there was a single outcome parameter, a linear mixed model with a random slope and a random intercept for each individual was fitted. The outcome was the difference in BMI with respect to baseline. As fixed effects we added medication, gender, baseline BMI and follow-up duration, and also the interactions of medication, gender and baseline BMI with follow-up duration. Normality of the fitted mixed model was subsequently assessed using scatter plots and quantile-quantile plots of the model's residuals. Correlations between medication dose and BMI change for individual patients were assessed using Spearman's rank-order correlation tests. P-values below 0.05 were deemed significant. Bonferroni corrections were executed when needed. All analyses were conducted using the IBM SPSS Statistics 23 software package.

Results

Patient characteristics

59 individuals started treatment with SXB and 22 with modafinil (Table 5.1). Follow-up frequency and duration varied considerably among patients (range 0.14-6.94 years). There were no significant differences found in age and baseline BMI between groups. More males were in the SXB group. Mean duration of treatment for the SXB group was longer than that of the modafinil group.

Table 5.1. Characteristics of narcolepsy type 1 patients. Data indicate mean ± standard deviation.

	SXB	Modafinil	p-value
N	59	22	
Age (years)	34.5 ± 13.4	39.0 ± 19.7	0.332
Males (%)	38 (64%)	6 (27%)	0.005
Baseline BMI (kg/m^2)	28.6 ± 4.3	26.5 ± 5.5	0.070
Follow-up (years)	2.0 ± 1.7	1.2 ± 1.2	0.054*
Male	1.9 ± 1.5	0.9 ± 0.7	0.152*
Female	2.2 ± 1.9	1.3 ± 1.4	0.134*
HLA-DQB1*06:02 +	56/57	18/19	0.408
Hypocretin < 110pg/mL	32/35	6/7	0.638

BMI = body mass index; SXB = sodium oxybate. P-values result from Student's t-tests for the difference between treatment groups. * To adjust for multiple testing, p-value <0.05/4 was considered to be significant.

Co-medication

There were no significant differences between the percentages of patients in the SXB and the modafinil group who received no additional medication (p = 0.209) and patients who used antidepressants (p = 0.094). The amount of patients using methylphenidate or dexamphetamine was higher in the SXB group (p = 0.007; Table 5.2).

Table 5.2. Co-medication of narcolepsy type 1 patients. Data indicate number of patients (%). Antidepressants (N SXB-group/N modafinil-group): clomipramine (7/6), venlafaxine (3/0), imipramine (2/1), citalopram (0/1). Median treatment 0.96 years (range 0.25-19 years). P-values result from Student's t-tests for the difference between treatment groups. SXB = sodium oxybate.

	SXB (N = 59)	Modafinil (N = 22)	p-value
None	23 (39.0)	12 (54.5)	0.209
Antidepressant	12 (20.3)	8 (36.4)	0.167
Methylphenidate/dexamphetamine	24 (40.7)	2 (9.1)	0.007

BMI in NT1 patients is higher than mean BMI in Dutch people above 18 years old

The mean BMI of the patient cohort differed significantly from that of a representative sample of Dutch people above 18 years old. In men, the mean BMI of our study population was significantly higher than the mean BMI of Dutch males above 18 years old (mean ± standard error of the mean (SEM) 27.9 ± 0.58 kg/m^2 vs 25.3 kg/m^2; p < 0.001). Likewise, women in our patient groups had a significantly higher BMI than the average for Dutch women above 18 years old (mean ± SEM 28.2 ± 0.93 kg/m^2 vs 25.8 kg/m^2; p < 0.001).

BMI decreases in patient groups between first and last measurement

Four separate groups were constructed based on treatment and gender. Those treated with SXB lost weight during follow-up (-1.58 kg/m^2, SD 2.12 kg/m^2; p < 0.001; Figure 5.1 and Figure 5.2). Women using SXB lost weight with a mean BMI decrease of 2.56 kg/m^2 (SD 2.20 kg/m^2; p = 0.001) which corresponds to an average weight loss of 7.1 kg; men with a mean BMI decrease of 0.84 kg/m^2 (SD 1.71 kg/m^2; p = 0.006) which corresponds to 2.8 kg. Patients using modafinil, however, gained weight (0.60 kg/m^2, SD 0.91 kg/m^2; p = 0.005). A mean BMI increase of 0.57 kg/m^2 (SD 0.96 kg/m^2; 1.6 kg) was found in women (p = 0.033), while a mean BMI increase of 0.67 (SD 0.88 kg/m^2; 2.3 kg) was observed in men (p = 0.122). After adjustment for multiple testing BMI decrease in women using modafinil failed to reach statistical significance.

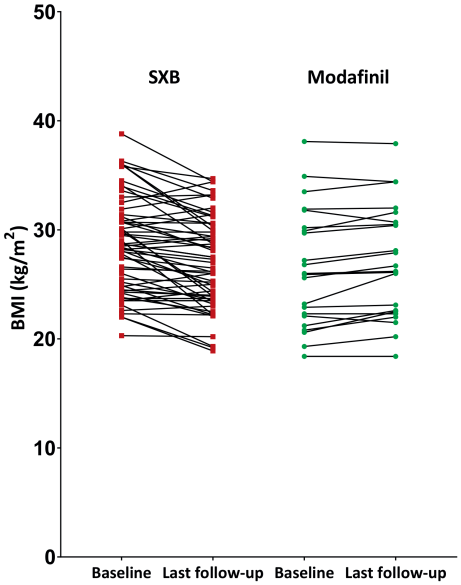

Figure 5.1. Body mass index (BMI) values at baseline and at last follow-up of patients in whom treatment with sodium oxybate (SXB; red, N = 59) and patients in whom treatment with modafinil (green, N = 22) was newly started. Each data point represents one patient at either baseline or follow-up. Individual values per patient are linked.

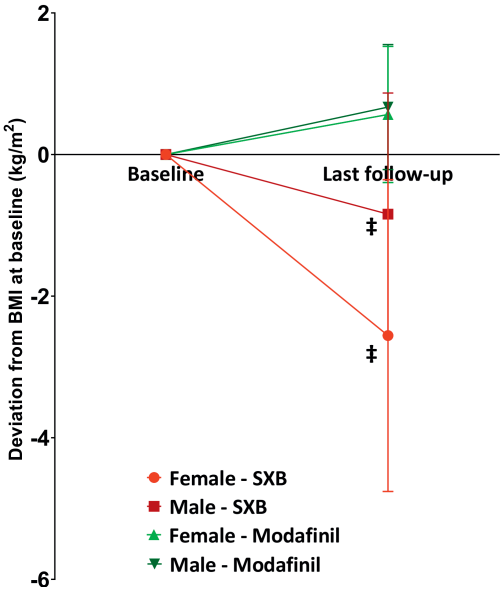

Figure 5.2. Patients treated with sodium oxybate (SXB) showed a decrease in body mass index (BMI) during follow-up while patients treated with modafinil did not. P-values are derived from Student's paired t-tests comparing normalized BMI values at baseline and at last follow-up. Mean follow-up for SXB and modafinil was 2.0 ± 1.7 vs 1.2 ± 1.2 ($p = 0.054$).

⋆ $p < 0.05$ † $p < 0.01$ ‡ $p < 0.001$

BMI at baseline and medication type influence BMI difference over time

Patients using SXB showed a decrease in BMI that was larger than the BMI deviation of modafinil users ($F(1,69.396) = 8.180$, $p = 0.006$). A higher baseline BMI was found to predict a more pronounced BMI decrease ($F(1,26.040) = 5.137$, $p = 0.032$). The effect gender had on BMI deviations was found not to be significant ($F(1,72.923) = 3.464$, $p = 0.067$). An overview of these and all other main and interaction effects can be found in Table 5.3. Mean values of BMI differences from baseline for four groups based on gender and medication type are depicted in Figure 5.3.

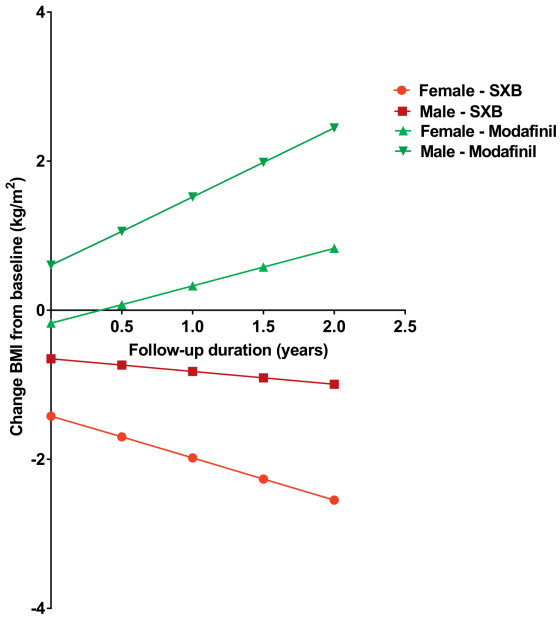

Figure 5.3. Mixed model estimations of the averaged subject in four groups based on gender and medication type. Body mass index (BMI) at baseline is set at 28.0 kg/m^2, the grand mean of our study population. Values for different groups at Follow-up duration = 0 depicts the average baseline BMI value of all patients in that particular group. SXB = sodium oxybate.

BMI change in patients is not correlated with either modafinil or SXB dose

A higher dose of either modafinil or SXB was not correlated with BMI change in our patient cohort. Spearman's rho was 0.188 in modafinil-treated patients ($p = 0.402$) and 0.153 in SXB-treated patients ($p = 0.294$).

BMI decrease in SXB group not explained by methylphenidate or dexamphetamine use

Given the fact that stimulant use is significantly higher in the patient group in which SXB treatment was initiated, a mixed model was fitted on the dataset in which patients using methylphenidate or dexamphetamine were excluded (n = 24 in SXB group, n = 2 in modafinil group; data not shown). Also in this fitted model there was a significant main effect of SXB on BMI ($F(1,40.073) = 16.003$, $p < 0.001$). Additionally, we fitted a mixed model in which dexamphetamine or methylphenidate use was added both as a main effect and as an interaction effect with time (Supplementary Table 5.1). The main effect of dexamphetamine

or methylphenidate use was significant ($F(1,78.787) = 10.215$, $p = 0.002$). However, there still remained a highly significant main effect of SXB on BMI ($F(1,66.799) = 14.916$, $p < 0.001$).

Discussion

Our findings (1) confirm that SXB reduces BMI in NT1 patients and (2) suggest that this is a long lasting effect. Even when accounting for baseline BMI, gender, treatment duration and the interactions between them, the mixed model we fitted statistically significantly demonstrates a BMI decrease in the SXB group, in contrast to a BMI increase in the modafinil group. The BMI decrease in the SXB group is seen in both males and females but is more pronounced in women. Patients using modafinil gain rather than lose weight. Another interesting finding is that a higher BMI at baseline predicts a more pronounced decrease in BMI during medication use over time. This suggests that BMI decrease constitutes an additional beneficial effect of SXB for NT1 patients, especially for those with a higher BMI at baseline. A correlation between medication dose and BMI change is not found in our cohort.
Our findings are in line with a previous report (Husain et al., 2009) on weight loss amongst patients treated with SXB. Patients with NT1 and -2 were assessed, yet without a control group; and data on age, gender or BMI of the smaller cohort were lacking.
Narcolepsy patients have a higher prevalence of obesity than the general population. Indeed, the mean baseline BMI of our cohort was significantly higher than that of a representative sample of Dutch people older than 18 years old.

The exact mechanism by which SXB leads to weight loss is unclear, though several theories exist. It is known (Donjacour et al., 2011) that SXB leads to a consistent increase in nocturnal growth hormone (GH) secretion and that SXB strengthens the temporal relation between GH secretion and slow wave sleep. GH is a potent lipolytic agent and a GH deficiency decreases lean body mass while increasing fat mass. It was suggested that SXB could lead to an increase in lipolysis by restoring GH secretion. This hypothesis was tested in a study showing that SXB stimulates lipolysis in NT1 (Donjacour et al.,

2014). Participants in this study lost on average 5.2 kg in three months of SXB treatment, which supports our results (Husain et al., 2009). If weight loss is mediated through this pathway, gender differences in fat metabolism (Williams et al., 2004) could account for the different trends in BMI change between men and women in our study.
Another hypothesis is that BMI decrease results from the effect of SXB on ghrelin and leptin secretion. A comparison between NT1 patients and healthy controls (Donjacour et al., 2013) did not show any differences in ghrelin and leptin secretion after 3 months of SXB treatment. It was speculated there that the weight loss may also be due to an decrease of food intake and an increase of physical activity leading to a negative energy balance secondary to the sleep-promoting effects of SXB.
In addition to these hypotheses, we propose that the fact that patients who start using SXB are required to cease using alcohol might play an additional role in BMI loss in this patient group. Even though the exact relation between alcohol consumption and weight gain is complex, it can be said that alcohol consumption leads to weight gain (Suter et al., 2005).

The effects of SXB on BMI were compared with modafinil, a commonly prescribed therapy for narcolepsy. The decision to treat an individual with either SXB or modafinil is not always clear-cut. SXB is more often prescribed when cataplexy and disturbed nocturnal sleep are the most invalidating symptoms (Bosch et al., 2012; Boscolo-Berto et al., 2012) while modafinil is prescribed in those suffering most from excessive daytime sleepiness (Guilleminault and Cao, 2011). If cataplexy would have an effect on weight it could therefore lead to a selection bias in our study. There is no data on the relation between cataplexy and BMI. We have also no reason to expect other confounding parameters to be present than the ones we accounted for in our analysis. Earlier studies on the effect of modafinil in NT1 showed no significant BMI changes in those treated with it (Moldofsky et al., 2000; US Modafinil in Narcolepsy Multicenter Study Group, 1998). These studies had a shorter follow up time compared to our study.

Our study has a few limitations. Firstly, due to the retrospective nature we were not able to randomize patients and we were dependent on the methods and data collection which was chosen for the individual. The retrospective design

led to incomplete data about symptom severity at treatment initiation and made correlation between treatment effects on BMI and treatment effects on other symptoms impossible. We were, however, able to review the medical records of all patients with NT1 patients who had treatment started at the outpatient clinic, thereby reducing the risk of selection bias. Our cohort is also larger than those presented in earlier studies on weight loss and SXB (Donjacour et al., 2013; Husain et al., 2009); and we only included NT1 patients as diagnosed based on ICSD-3 guidelines.

Co-medication constituted a concern in our study. The use of methylphenidate or dexamphetamine was found to be significantly different between groups. Methylphenidate, a stimulant often used in narcolepsy, is known to decrease appetite and dietary fat intake in healthy subjects (Goldfield et al., 2007). In NT1 no such effect has been observed (Kok et al., 2003). It remains unclear whether these findings also lead to a BMI decrease. Given that in our study all patients using these two medications were on a stable dose for at least three months before initiating treatment with SXB or modafinil, it was not likely that this influenced our results in a significant way. We assessed the effect of these stimulants in two ways. Removing individuals using methylphenidate or dexamphetamine from the model still shows a highly significant effect of SXB on BMI. In addition, adding use of dexamphetamine or methylphenidate to the model shows that it leads to a BMI reduction, but does not interfere with the BMI decrease that is demonstrated in the SXB group. Besides stimulants, a non-significant difference in antidepressant use was found between both groups. Results on the effect on BMI of the most frequently used antidepressant clomipramine are contradictory: two groups have reported an increase in appetite and weight gain in patients using clomipramine (Paige et al., 2015; Maina et al., 2004). However, this effect was only shown in patients without narcolepsy and for a higher dose than normally prescribed in NT1. Another group found no BMI changes in narcolepsy patients using clomipramine in patients who were already on a stable dose (Kok et al., 2003).

Conclusion

We confirm that treatment with SXB is associated with a decrease in BMI in NT1 patients, while modafinil treatment is not. For the majority of NT1 patients, BMI decrease therefore constitutes an additional beneficial effect of SXB. The weight loss is more pronounced in those with a higher BMI at baseline. Possible weight loss could therefore be another reason to opt for treatment with SXB in NT1, especially in those with a higher BMI. Due to the retrospective nature of this study further prospective and longitudinal studies are needed to confirm our results and further characterize BMI change dynamics.

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