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Bodyweight gain under pregabalin therapy in epilepsy: Mitigation by counseling patients?

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Summary

Objective: To evaluate bodyweight gain during pregabalin therapy for epilepsy and the utility of a short counseling program to prevent this side effect.
Methods: Randomized controlled trial on the effects of extended versus standard patient counseling on the risk of bodyweight gain with 3- and 6-month follow-up including a consecutive sample of adult outpatients with epilepsy eligible for pregabalin add-on treatment ($N = 98$).
Results: The seizure response rate was about 30%, the seizure freedom rate was 5% at the 6-month follow-up (intent-to-treat sample, $N = 98$). The median bodyweight gain for the according-to-protocol sample ($N = 62$) was 4.0 kg with no effect of extended counseling. Bodyweight gain was correlated with number of anticonvulsant drugs ($r = .32$, $p < .05$).
Conclusions: Pregabalin treatment is associated with a high risk for bodyweight gain which in part depends on total anticonvulsant drug load. This side effect cannot be prevented by extended patient counseling within a standard clinical setting.

Bodyweight gain is a frequent adverse effect during anticonvulsant (e.g., valproate, carbamazepine and vigabatrine) and other neuropharmacological therapies (e.g., atypical antipsychotics).[1,2] Other anticonvulsants may induce weight loss (e.g., zonisamide and topiramate) or may be weight-neutral (e.g., levetiracetam).[3] Weight gain is a serious side effect because it may lead to non-compliance or premature termination of the treatment. Furthermore, it has been implicated to have a negative impact on glucose control, blood pressure, and lipid profile and thus, it may increase the risk for diabetes mellitus, heart disease or stroke.[2]

Pregabalin is a newly approved add-on treatment for partial epilepsy in adult patients.[4] The pharmacologically active S-enantiomer of

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3-aminomethyl-5-methyl-hexanoic acid binds with high affinity and specificity to the alpha(2)-delta subunit protein of voltage-gated calcium channels in CNS tissues and acts as a presynaptic modulator of excitatory neurotransmitter release by inhibiting calcium influx.[5] Although it is a structural analogue of GABA, it does not act on GABA receptors or GABA uptake.[6] Four multi-centre, prospective randomized double-blind placebo-controlled trials confirmed anticonvulsant efficacy against partial-onset seizures in a total of 1396 patients.[7] The responder rate (i.e., percentage of patients with 50% or more reduction in seizure frequency vs. baseline) in these studies ranged from 14% to 51% of the enrolled patients. In addition to somnolence, dizziness, and ataxia, an increase in bodyweight of 7% or more of the baseline body weight was reported as an adverse effect in about 14% of the patients at a dose of 600 mg/day.[4]

In Germany, pregabalin was available for add-on treatment of epilepsy in adult patients since September 2004. We wanted to assess the therapeutic and side effects right from the start of marketing. Furthermore, being aware of the bodyweight gain issue and its negative implications, we embedded a randomized controlled trial to test the hypothesis that more extended counseling of the patients may help to prevent this adverse effect. This counseling addressed the need for a weekly bodyweight control as well as appropriate behavioral counter-measures in case of bodyweight gain such as diet control (less energy up-take) and physical exercise (more energy expenditure).

Methods

Randomized controlled trial

We defined two groups of patients. In one group patients received extended counseling on the risk of bodyweight gain during pregabalin add-on therapy before titration. Extended counseling comprised a comprehensive description of this risk factor and a discussion of possible behavioral interventions that may allow the patient to prevent weight gain. In particular, the patients were asked to check their bodyweight once a week and to react in case of substantial bodyweight gain by reducing ingestion and by increasing energy consumption (e.g., physical exercise). Patients received a written handout with the essentials of these explanations (see Appendix A). The study design did not allow controlling patient compliance. In the other experimental group patients were generally informed about all possible risks of pregabalin treatment including bodyweight gain according to the clinical standards. However, no particular emphasis was placed on bodyweight gain and no suggestions to check bodyweight or to react in case of bodyweight gain were given by the physician. The patients in the second group did not receive the handout. Patients were randomly allocated to either group. The follow-up examinations were scheduled for 3 and 6 months.

Baseline medication and pregabalin titration

It was intended that baseline medication generally remains unchanged during the study if possible, but clinically reasonable adaptations were permitted within the protocol. Pregabalin was slowly titrated with a daily dosage increment of 75 mg/week (0-0-1, 1-0-1, 1-0-2, 2-0-2 and so on) thus reaching the prescribed dosage of 300 or 450 mg/day after 4 or 6 weeks, respectively. Depending on seizure outcome and adverse side effects at the 3-month follow-up the dosage was further up or down-titrated according to the same regimen.

Patients

From September 2004 to May 2005, adult outpatients who appeared to be appropriate candidates for pregabalin add-on treatment were asked to participate in the study. From 140 adult patients receiving pregabalin during this period, 98 patients (70%) gave written informed consent and were enrolled in the study. The general and clinical data of these patients are given in Table 1.

Methods and measures

Bodyweight and body height were determined at baseline in all patients. The body mass index (BMI) was calculated (BMI (kg/cm^2) = body weight (kg)/body height $(m)^2$). Body weight classes were assigned according to the WHO International Classification of Diseases (ICD-10): low weight ($18.5 \leq BMI < 20$), regular weight ($20 \leq BMI < 25$), overweight ($25 \leq BMI < 30$), obesity grade I ($30 \leq BMI < 40$). Bodyweight was monitored at each follow-up.

All patients were asked to fill-out the *Adverse Event Profile* questionnaire.[8] This questionnaire comprises 19 frequent adverse events including bodyweight gain (item #14). Seizure frequency per month was calculated from the patients' seizure diaries based on the last 3 months at baseline (retrospectively), 3- and 6-month follow-up. Simple partial seizures (SPS), complex partial seizures (CPS), generalized tonic-clonic seizures (GTCS) and drop attacks were counted separately.