STUDY PARTICIPATION BUT NOT THE ANTIDEPRESSANT BUPROPION REDUCES APATHY IN HUNTINGTON’S DISEASE

Background Apathy is the most common neuropsychiatric syndrome in HD and contributes significantly to the burden of disease. This is in contrast to the prevailing therapeutic nihilism, as no effective treatment is at hand. Several single case reports and case series suggested the effectiveness of the antidepressant bupropion for the treatment of apathy in HD and other neurodegenerative diseases.

Aim To evaluate the efficacy and safety of bupropion in the treatment of apathy in HD.

Methods In this phase 2b multi-centre, double-blind, placebo-controlled crossover trial, individuals with HD and clinical signs of apathy according to the Structured Clinical Interview for Apathy–Dementia (SCIA-D), but not depression (n = 40) were randomised to receive either bupropion 150/300 mg or placebo daily for 10 weeks.

Results At baseline, there were no significant treatment group differences in the clinical primary and secondary outcome parameters. At endpoint, there was a statistically significant difference between treatment groups for all clinical primary and secondary outcome variables. Study participation, irrespective of the intervention, lessened symptoms of apathy. Further studies involving a larger number of patients are warranted.

Conclusion Study participation, but not the antidepressant bupropion alleviates apathy in HD. Our observations document the need for carefully controlled trials when investigating therapeutic interventions for the neuropsychiatric symptoms of HD.

M4 SAFETY AND TOLERABILITY OF BN82451B IN HUNTINGTON’S DISEASE

Background BN82451B is a small, orally active molecule with good CNS penetration. Preclinical studies in tgHD R6/2 mice suggested improved motor function and prolonged survival. In addition antidysskinetic activity was observed in other models. The proposed mechanisms of action (MOA) are (1) antioxidative due to a sodium channel blocking potential, (2) antioxidant, (3) anti-inflammatory due to a cyclooxygenase (COX) inhibitory potential and (4) mitochondrial protective.

Aims The primary objective of this phase 2a study (NCT02231580) is to investigate the safety and tolerability of BN82451B bid versus placebo for 28 days in male HD subjects. Secondary objectives include assessment of pharmacokinetics and pharmacodynamics via the effects on quantitative motor (Q-Motor) measures. UHDRS subscales are implemented as exploratory measures.

Methods Subjects: We intend to recruit 30 male HD subjects. 24 receive BN82451B and 6 placebo. The study is conducted in an inpatient setting at a single phase I unit in Germany.

Design A sequential design was chosen to enable dose escalation starting with 40 mg bid with a potential maximum dose of 80 mg bid. Three subsequent cohorts of 10 patients each are randomised with different starting doses. Subjects in group one are treated with 40 mg bid for 14 days and may be increased to 60 mg bid the subsequent 14 days. In group 2, subjects may first receive 60 mg bid with possible increase to 80 mg bid. Group 3 subjects may receive 80 mg bid for 28 days. Dose increases in the consecutive groups are subject to approval by a Data Review Committee (DRC). The decision to increase the dose in individual patient will be based on the investigator’s judgement.

Results Results of the study are expected for Q4/2016.
Conclusions Recruitment in this trial is difficult as in-patient periods of nearly one month are logistically challenging. Safety data will be available soon and pharmacodynamics readouts such as Q-motor measures may help to guide decisions on the further path of development of BN82451B.

NEURAL NETWORKS LINKED TO EMOTION PROCESSING MODULATED BY INTRanasAL OXYToCIN IN HUNTINGTON’S DISEASE GENE-CARRIERS

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Background Oxytocin (OXT) has shown to play an important role in modulating responses to emotional cues in healthy and clinical populations. Huntington’s disease (HD) is associated with deficits in facial expressions of emotion, particular of disgust, and which have been linked to abnormal neural networks. HD is also associated with a 45% reduction in OXT-expressing neurons in the hypothesalamus, the region where OXT is produced.

Aims We therefore examined whether administration of OXT intranasally to gene-carriers of HD would have beneficial effects on neural networks involved in emotion processing.

Methods We compared 9 gene-carriers of HD and 10 age-matched controls, who were right-handed males, aged between 18–65 years, not medicated, and non-smokers. Using a randomised double-blind placebo-controlled design, each participant administered acute doses of intranasal OXT (24 IU) and placebo sprays over two visits. Participants completed an fMRI task involving matching emotional faces (disgust, happy, anger, fear, sad, surprise and neutral) or geometric shapes.

Results Under placebo, and compared to controls, HD gene-carriers showed hypo-activity to disgust (middle/superior prefrontal gyrus) and hyper-activity to surprise (inferior/middle temporal gyrus). Significant Group x Drug interactions were found for five of the seven emotions (angry, disgust, fear, happy, and sad). Post-hoc analyses showed significant within-group effects, corrected for multiple comparisons, where OXT significantly increased brain reactivity for happy (middle temporal gyrus) and disgust (precentral/inferior frontal gyrus) in the HD group.

Conclusions We found evidence of hypo- and hyper-reactivity to disgust and surprise emotions respectively in HD gene-carriers. OXT increased brain activity in previously hypo-active regions in HD. We provide initial evidence of ‘normalisation’ effects and a broader physiological role of OXT in HD.

NABILONE IN HUNTINGTON’S DISEASE: A CASE SERIES OF FIVE PATIENTS

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Background and objective There is limited evidence about the efficacy and safety of cannabinoids in the treatment of patients with Huntington’s disease (HD). Five patients with HD were treated with nabilone, a synthetic cannabinoid, in order to alleviate therapy-resistant symptoms.

Methods All patients and caregivers were informed about the off-label use of nabilone and gave written informed consent. A Clinical Global Impression Scale (CGI) and the Unified Huntington’s Disease Rating Scale (UHDRS) were applied prior, after one and four weeks to decide on the continuation of nabilone treatment.

Case reports

Patient 1 is a 20-year-old male who presented with disabling tics, generalised chorea and increased irritability. He developed severe parkinsonism during therapy with amisulpiride and olanzapine. Amisulpiride was stopped and he was treated with nabilone 1 mg/d.

Patient 2 is a 48-year-old female with 10 years history of HD and chronic pain. Multiple treatment trials were ineffective. Nabilone 2 mg/d was introduced.

Patient 3 is a 62-year-old female with disabling chorea and increased irritability. She developed severe akathisia as a side effect of several antidopaminergic therapies. Treatment with nabilone 1.5 mg/d was commenced.

Patient 4 is a 46-year-old female who had parkinsonism and depression under therapy with tetrabenazine. Treatment with nabilone 3 mg/d was introduced as monotherapy.

Patient 5 is a 67-year-old female with disabling chorea and increased irritability. She developed parkinsonism during therapy with tetrabenazine. Medication was changed to 2 mg/d nabilone.

Results Transient mild sedation during titration occurred in patients 3, 4 and 5, mild non-disturbing xerostomia in patient 3. All patients reported improved symptoms as assessed by the CGI, UHDRS and Chorea-scores improved in all patients. A reduction of tics without worsening of parkinsonism with nabilone was seen in patient 1. Patient 2 reported that her pain completely subsided. Irritability substantially improved with nabilone in patients 3, 4 and 5. Moreover, tetrabenazine could be stopped in patients 3, 4 and 5. This resulted in a remission of akathisia in patient 3, in improved parkinsonism in patients 4 and 5 as well as in ameliorated mood in patient 4.

Conclusions These case series suggest that nabilone may be an effective and well tolerated adjunct to the drug treatment of HD. However, larger controlled trials are needed to confirm these preliminary open-label observations.

A PROSPECTIVE TRIAL FOR PALLIDAL DEEP BRAIN STIMULATION IN HUNTINGTON’S DISEASE

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Huntington’s disease (HD) is a hereditary neurodegenerative disorder which is associated with severe disturbances of motor function, especially choreic movements, cognitive decline and psychiatric symptoms. Various brain stimulation methods have been used to study brain function in patients with HD. Moreover, brain stimulation has evolved as an alternative or additive treatment option, besides current symptomatic medical treatment. We intend to better understand the characteristics of cortical excitability and plasticity in HD and give a perspective on the therapeutic role for non-invasive and invasive neuromodulatory brain stimulation methods. We furthermore assessed procedure safety of deep brain stimulation, equality of internal- and external-pallidal stimulation and efficacy followed up for 6 months in...