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► To cite this version:

Stéphane Thobois, Emmanuelle Broussolle, Magaly Aya Kombo, Pierre Pollak, Paul Krack. Reply : Dopamine agonist withdrawal syndrome and non-motor symptoms after Parkinson's disease surgery. *Brain - A Journal of Neurology* , 2010, 133, pp.1-4. inserm-00667436

HAL Id: inserm-00667436

<https://inserm.hal.science/inserm-00667436>

Submitted on 7 Feb 2012

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LETTER TO THE EDITOR

Reply: Dopamine agonist withdrawal syndrome and non-motor symptoms after Parkinson's disease surgery

Stephane Thobois,^{1,2} Emmanuel Broussolle,^{1,2} Magaly Aya Kombo,^{3,4} Pierre Pollak^{3,4} and Paul Krack^{3,4}

1 Université Lyon I; Hospices Civils de Lyon, Hôpital Neurologique Pierre Wertheimer, Service de Neurologie C, Lyon, France

2 CNRS, UMR 5229, Centre de Neurosciences Cognitives, Lyon, France

3 Movement Disorder Unit, Department of Psychiatry and Neurology, CHU de Grenoble, Joseph Fourier University, Grenoble, France

4 INSERM, Unite 836, Grenoble Institut des Neurosciences, Grenoble, France

Correspondence to: Paul Krack,
Department of Neurology,
University of Grenoble,
BP217,
Grenoble 38043, France
E-mail: paul.krack@ujf-grenoble.fr

We would like to thank Dr Nirenberg for her thoughtful comments on our prospective study reporting the occurrence of a delayed withdrawal syndrome in patients with Parkinson's disease treated with bilateral subthalamic stimulation. This syndrome, which includes depression, apathy and anxiety, is the consequence of a marked decrease in dopaminergic treatment rendered possible by a major improvement in motor symptoms (Thobois *et al.*, 2010). This study identified preoperative non-motor fluctuations as predictors of post-operative apathy and demonstrated that non-motor psychic symptoms of Parkinson's disease can be explained by mesolimbic dopaminergic denervation. In order to examine and discuss the points raised by Dr Nirenberg (2010), several aspects of our study need to be highlighted and clarified. The fact that Parkinson's disease surgery that preferentially targets the sensorimotor rather than the limbic subthalamic nucleus deep brain stimulation produces better motor than non-motor effects provides an almost experimental model with which to study non-motor psychic symptoms of Parkinson's disease. This study was designed to obtain a better understanding of post-operative non-motor withdrawal symptoms, their time course and mechanisms. In accordance with our study protocol, dopaminergic treatment was reduced drastically, with complete arrest of dopamine agonists at time of surgery and marked reduction of levodopa depending on patients' motor state in the two weeks following surgery, when stimulation parameters were increased. Reduction of dopaminergic treatment after surgery is a normal procedure,

which is necessary for the adjustment of subthalamic stimulation parameters and the establishment of satisfactory control of motor fluctuations and dyskinesias (Krack *et al.*, 2002; Thobois *et al.*, 2003). It is important to note that the management of medication in our study differs from routine practice, where medication is adapted more individually and where low-dosage dopamine agonists are often maintained in order to prevent the delayed appearance of post-operative apathy (Krack *et al.*, 2002). Thus, our experimental protocol should not be mistaken for a recommendation for post-operative drug management and we fully agree with Dr Nirenberg that abrupt discontinuation of dopaminergic treatment should be avoided and patients should be monitored for symptoms of withdrawal as dopaminergic treatment is tapered off. As a precaution we evaluated our patients monthly for early detection of apathy and depression; this approach has proven to be safe. While delayed depression was detected in 25% of the patients during the follow-up, it had disappeared in all patients at the 1 year follow-up evaluation, mainly in response to the reintroduction of a dopamine agonist. Apathy was more frequent than reported previously. This can be explained by both management of drugs in this study and systematic screening using a specific apathy scale. Impulse control disorders were also systematically evaluated before and after surgery. This prospective study showed an almost complete disappearance of preoperative impulse control disorders and may help to restore law and order in a hitherto confusing body of literature in which retrospective

studies—introducing selection bias and using non-standardized evaluation and management—come to opposing conclusions, showing either worsening (Houeto *et al.*, 2002; Smeding *et al.*, 2007; Lim *et al.*, 2009) or improvement (Witjas *et al.*, 2005; Ardouin *et al.*, 2006) of impulse control disorders after subthalamic surgery.

Eradication of impulse control disorders is, however, a double-edged sword, given the risk of the occurrence of apathy, depression and anxiety. There is indeed a thin line between hypo- and hyperdopaminergic behaviours, especially in patients who have already developed behavioural sensitization (Evans *et al.*, 2006) manifesting as non-motor fluctuations (Thobois *et al.*, 2010), addiction to dopaminergic drugs (Lawrence *et al.*, 2003) and impulse control disorders (Weintraub, 2008). Epidemiological studies have shown that impulse control disorders are more frequent in patients treated with dopamine agonists in association with levodopa compared with patients on levodopa monotherapy (Voon *et al.*, 2006). This does not mean that impulse control disorders do not occur with levodopa as a monotherapy. This is nothing new, and the levodopa-induced beneficial and deleterious behavioural effects have been described since the first studies dealing with long-term treatment of the drug (Barbeau, 1969; Yahr *et al.*, 1969; Sacks, 1982). Impulse control disorders have become the focus of interest in recent years, and publications on this topic have grown considerably. An increase in the frequency of impulse control disorders may be partly explained by prevailing treatment recommendation of the last decade (Olanow *et al.*, 2001), resulting in the use of high-dose dopamine agonist treatment in young patients based on studies showing that dopamine agonists induce less dyskinesia (Montastruc *et al.*, 1994). Endogenous dopamine, treatment with its precursor levodopa or with its agonist apomorphine, all have a similar profile, stimulating both D1 and D2 receptors, and are more effective on motor symptoms. All other commercially available non-ergot dopamine agonists for use in humans have preferential affinity to D2 and D3 receptors. Preferential binding to the mesolimbic D3 receptor (Murray *et al.*, 1994) is generally put forward as the main explanation of the greater non-motor benefits and side effects of dopamine agonists compared with levodopa (Weintraub, 2008). Presynaptic sensitization of the dopaminergic system in the ventral striatum has been shown during a levodopa test in patients with dopamine addiction and impulse control disorders (Evans *et al.*, 2006). The sensitized ventral striatal dopamine neurotransmission produced by levodopa in these individuals correlated with self-reported drug 'wanting' and was related to heightened psychomotor activation. Furthermore, pulsatile stimulation of the D1 receptor family in Parkinsonism leads to post-synaptic mesolimbic sensitization with an up-regulation of D3 receptor expression (Guillin *et al.*, 2001), arguing for the important role of levodopa or subcutaneous apomorphine injections in the pathophysiology of impulse control disorders, especially in association with selective D3 receptor stimulation using dopamine agonists.

Apathy, anxiety and depression are also frequent symptoms in the non-surgical Parkinson's disease population, and these symptoms do respond to levodopa (Barbeau, 1969; Yahr *et al.*, 1969; Maricle *et al.*, 1995) and dopamine agonists (Barone *et al.*, 2010). Rabinak and Nirenberg (2010) have drawn attention to an acute

withdrawal state syndrome following abrupt reduction of dopamine agonists in patients who have developed an addiction to their dopaminergic treatment. This withdrawal syndrome manifests with anxiety, panic attacks, agoraphobia, depression, dysphoria, diaphoresis, fatigue, pain, orthostatic hypotension and drug craving (Rabinak and Nirenberg, 2010). While akinetic crisis is a well-known complication of acute levodopa withdrawal, generally accompanied by depression and vegetative signs as in neuroleptic malignant syndrome (Friedman *et al.*, 1985), selective dopamine agonist withdrawal provides another model for a more selective study of the non-motor autonomic, sensory, affective and psychic symptoms well known in non-motor off-periods in Parkinson's disease (Raudino, 2001; Witjas *et al.*, 2002; Evans *et al.*, 2010). The retrospective cohort study of dopamine agonist withdrawal in a non-surgical population (Rabinak and Nirenberg, 2010), describing the development of acute dopamine agonist withdrawal state in 5 out of 26 patients following dopamine agonist reduction, is complementary to our prospective study on dopamine agonist withdrawal in 63 patients with Parkinson's disease treated by subthalamic nucleus deep brain stimulation in which half of the patients developed delayed apathy and half of the latter group also developed depression (Thobois *et al.*, 2010). There are notable differences in study design, patient population and management, which may largely explain apparent differences in the clinical syndromes described and in the time course of appearance. Most importantly, subthalamic nucleus deep brain stimulation has positive psychotropic effects very similar to those of levodopa and therefore largely compensates for drug withdrawal (Funkiewiez *et al.*, 2003). The longer delay in occurrence of apathy and depression in our study thus reflects the unmasking of long-term effects in dopaminergic treatment (Fahn *et al.*, 2004), acute withdrawal syndromes having been managed with subthalamic nucleus deep brain stimulation and levodopa. We observed no cases of new appearance of hypotension or diaphoresis. The absence of diaphoresis, which is part of the spectrum of non-motor fluctuations (Raudino, 2001; Witjas *et al.*, 2002), may be explained by the fact that chronic subthalamic nucleus deep brain stimulation improves the non-motor off symptoms (Witjas *et al.*, 2005; Ardouin *et al.*, 2006), including drenching sweats (Krack *et al.*, 2002). In our study, discontinuation of dopamine agonists proved impossible in 4 patients due to ensuing acute and severe restless legs syndrome. Others from our total cohort of 63 patients experienced acute mild withdrawal symptoms during the first two post-operative weeks, but these were managed by increasing stimulation intensity and/or re-increasing levodopa. Pain, fatigue, dysphoria and anxiety were frequently observed symptoms that developed on a parallel time course with those of apathy.

Dr Nirenberg draws a distinction between withdrawal states after arrest of dopamine agonists and a 'non-specific' dopamine withdrawal state related to decrease in levodopa (Nirenberg, 2010). Despite the apparent differences mentioned above, we consider this distinction to be less categorical, as there appear to be more similarities than dissimilarities. The delayed occurrence of apathy after surgery, for instance, is not specific to withdrawal of dopamine agonists. We have observed severe isolated apathy in patients on levodopa monotherapy with preoperative dopamine addiction and impulse control disorders (Funkiewiez *et al.*, 2004).

Dissociation between mood and motor effects has also been reported on L-dopa therapy (Maricle *et al.*, 1995). In our experience, hypodopaminergic behaviour responds not only to dopamine agonists, but also to levodopa or amphetamines. It is important, however, to be aware of the fact that while equivalent doses of dopamine agonists and levodopa express equivalence of motor effectiveness, they can by no means be considered as equivalents regarding their respective psychotropic effects. Positive mood effects are induced not only with dopamine agonists (Barone *et al.*, 2010; Thobois *et al.*, 2010), but also with levodopa (Barbeau, 1969; Yahr *et al.*, 1969; Maricle *et al.*, 1995). The difference is that beneficial mood effects of dopamine agonists can be obtained with doses that induce less dyskinesia than levodopa, which is more effective on the motor symptoms (Montastruc *et al.*, 1994). Thus, the underlying mesolimbic denervation seems to be the main explanation of a non-motor withdrawal syndrome that can be related to reduction of dopamine agonists and/or levodopa.

The outcome of surgery critically depends not only on patient selection and surgical skills, but also on post-operative management of stimulation parameters and dopaminergic medication. So far, the literature on post-operative behaviour is full of contradictions, and this has discredited a surgical technique with the potential to alleviate both motor and non-motor fluctuations considerably, with a subsequent improvement in patients' quality of life. As long as the mechanisms of changes in post-operative behaviour are not understood, their management will remain sub-optimal. Prospective studies addressing the management of post-operative dopaminergic treatment are needed and are under way. Dr Nirenberg expresses her concerns about the safety of our approach to the treatment of post-operative apathy using dopamine agonists (Nirenberg, 2010). We strongly disagree that in the context of isolated post-operative apathy, dopamine agonists should be avoided. In this context, dopamine agonists are highly effective in the treatment of apathy (Czernecki *et al.*, 2008). Post-operative depression can also respond to treatment by dopamine agonists (Funkiewiez *et al.*, 2004; Thobois *et al.*, 2010), even when the depression has proven resistant to antidepressants (Funkiewiez *et al.*, 2004). Provided behaviour is monitored, dopamine agonists are relatively safe, as the behavioural side effects are dose dependent. On the other hand, untreated isolated apathy can evolve into full-blown hypodopaminergic syndrome with apathy, depression and panic attacks. Failure to introduce a dopamine agonist would expose the patient to the risk of depression and suicide. Post-operative suicide is a frequent complication, and impulse control disorder is known as a preoperative risk factor (Voon *et al.*, 2008). Our study argues in favour of dopamine withdrawal as another major contributing factor to post-operative suicide (Thobois *et al.*, 2010). Increasing doses of levodopa could also be beneficial but would expose patients with disabling preoperative levodopa-induced dyskinesias, as is the case in our study group of relatively young sufferers of Parkinson's disease, to the risk for further debilitating dyskinesias.

Adapting dopaminergic treatment in a patient with dopamine dysregulation syndrome (Lawrence *et al.*, 2003) is like walking a tightrope. The neurologist is used to evaluating dyskinesia and akinesia, and strategies for addressing motor complications are

well known. However, non-motor complications of dopaminergic treatment have been neglected in the past. Better management requires knowledge of the clinical syndromes of hyper- and hypodopaminergic behaviours and non-motor fluctuations, development of evaluation tools and understanding of underlying mechanisms. The neurologist who strives to gain mastery of dopaminergic treatment needs to fine-tune the dosage of levodopa and dopamine agonists on an individual basis, depending on the presence of motor and non-motor signs, respectively.

Funding

Programme Hospitalier de Recherche Clinique Interrégional and Euthérapie Pharmaceutical Company for research in the field of parkinsonian apathy; Medtronic for research purpose in the field of deep brain stimulation (P.P. and P.K.); P.P., P.K. and S.T., E.B. received reimbursement of travel costs to scientific meetings by Medtronic and Euthérapie.

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