LETTER TO THE EDITOR

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

Melissa J. Nirenberg

Department of Neurology and Neuroscience, Weill Cornell Medical College, New York, NY, USA

Correspondence to: Melissa J. Nirenberg,
Department of Neurology and Neuroscience,
Weill Cornell Medical College,
428 East 72nd Street, Suite 400,
New York, NY 10021,
USA
E-mail: mjnirenb@med.cornell.edu

Sir, I read with interest the manuscript by Dr Thobois and colleagues (Thobois et al., 2010), in which the authors report the occurrence of depression and apathy after deep brain stimulation surgery for Parkinson's disease and correlate these symptoms with mesolimbic dopaminergic denervation on neuroimaging studies. I agree with the authors' interpretation of post-surgical apathy as a drug withdrawal state precipitated by the rapid tapering of dopaminergic medications (Rabinak and Nirenberg, 2010). My strong suspicion, however, is that severe non-motor symptoms that occur after deep brain stimulation are largely attributable to dopamine agonist withdrawal syndrome (DAWS) rather than a non-specific dopamine withdrawal state (Rabinak and Nirenberg, 2010). Furthermore, I have significant safety concerns about the use of piribedil as a treatment for these withdrawal symptoms.

Recognition of DAWS is critical because it: (i) exclusively occurs in patients with baseline dopamine agonist-related impulse control disorders; (ii) responds only to dopamine agonist repletion and not to levodopa or other Parkinson's disease medications; and (iii) includes not only apathy and depression, but also a broad array of other disabling non-motor symptoms (Rabinak and Nirenberg, 2010). DAWS can also precipitate suicidal ideation (M. J. Nirenberg, unpublished observations), and thus may underlie post-deep brain stimulation suicidality (Rabinak and Nirenberg, 2010)—a possibility supported by the authors' prior work showing a close correlation between attempted suicide after deep brain stimulation and the presence of baseline impulse control disorders or compulsive medication usage (Voon et al., 2008). The distinction between DAWS and a non-specific dopamine withdrawal state may explain the previously reported lack of correlation between apathy and overall dopaminergic medication reduction. Moreover, the relative selectivity of dopamine agonists for D3 dopamine receptors—which are disproportionately expressed in limbic pathways (Murray et al., 1994)—supports the hypothesis that post-deep brain stimulation apathy and depression are manifestations of mesolimbic dopamine deficiency.

The symptoms of DAWS are usually immediate in onset, but most (e.g. anxiety, panic, agoraphobia, dysphoria, fatigue, orthostatic hypotension, diaphoresis and pain) were not the focus of the study by Thobois et al. (2010), and such common, non-specific symptoms might easily be unrecognized in the post-operative period. In contrast, the delayed onset, more chronic symptoms of apathy and marked depression may represent a protracted abstinence syndrome and/or the unmasking of underlying mesocorticolimbic dopamine deficiency that had previously been controlled by dopamine agonists.

Patients who undergo deep brain stimulation are generally at high risk for impulse control disorders and DAWS—they tend to be relatively young and/or have young onset of Parkinson's disease, are frequently treated with dopamine agonists, often have severe motor complications and are by definition less risk averse than other patients with Parkinson's disease in that they have chosen to pursue a neurosurgical procedure (Weintraub et al., 2008; Evans et al., 2009; Weintraub, 2009). Subjects in the study by Thobois et al. (2010) certainly fit this description, including baseline dopamine agonist use in most (59/63 = 93.7%), and identified impulse control disorders or compulsive medication in one-third (21/63 = 33.3%) of study subjects. Rapid discontinuation of dopamine agonists in this high-risk population would be expected to precipitate DAWS in a subset of patients.

Patients with a history of impulse control disorders and DAWS appear to be sensitized to dopamine agonists, and are at extremely high risk for recurrent impulse control disorders when dopamine...
agonist treatment is resumed, even at very low dosages (Rabinak and Nirenberg, 2010). This raises serious safety concerns about the use of piribedil as a treatment for post-deep brain stimulation apathy. Piribedil is a dopamine agonist with moderate to high affinity for D3 dopamine receptors (Cagnotto et al., 1996), which has been associated with impulse control disorders (Fan et al., 2009; Tschopp et al., 2010). Thus, piribedil would be expected to precipitate recurrent impulse control disorders in sensitized subjects, with potentially devastating financial, medical and psychosocial consequences. Although impulse control disorders and compulsive medication usage had reportedly ‘disappeared’ in all subjects at the endpoint of the Thobois et al. (2010) study, the recurrence of hyperdopaminergic behaviours is extremely likely in this cohort, given ongoing dopamine agonist usage in a large percentage of patients (23/63 = 36.5%) and the addition of piribedil (another dopamine agonist) to the medication regimen of these high-risk, sensitized subjects. Longitudinal follow-up of this cohort is therefore strongly indicated to exclude the recurrence of these behaviours; outside informants should be involved in these assessments to minimize underreporting.

While it is often necessary to restart very low-dose dopamine agonists to mitigate DAWS symptoms, patients frequently recover from DAWS if exposure to dopamine agonists is curtailed. For this reason, my recommendation is to avoid rapid discontinuation of dopamine agonists, monitor patients closely for symptoms of DAWS as dopamine agonists are tapered and avoid the use of piribedil and other dopamine agonists in the treatment of isolated post-deep brain stimulation apathy. If the severity of DAWS is such that dopamine agonists must be restarted, then the lowest effective dosage should be used, and patients should be closely monitored for recurrent impulse control disorders (Nirenberg and Rabinak, 2010). These changes may help to reduce the risk of post-operative suicidality and other debilitating symptoms of DAWS, while minimizing the prevalence and long-term negative consequences of chronic impulse control disorders.

References