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Roger M Pinder

York, UK

Pathological gambling and dopamine agonists: A phenotype?

Therapeutic dopamine agonists have been around a long time ever since the deficit of brain dopamine in Parkinson's disease (PD) was first reported in 1960 (Ehringer and Hornykiewicz 1960) swiftly followed by the first clinical trial of levodopa administration in Parkinsonian patients (Birkmayer and Hornykiewicz 1961). Design of new dopamine agonists was also a first love of the Editor of *Neuropsychiatric Disease and Treatment* (Pinder 1970; Miller et al 1974). In those first heady years efficacy in a previously untreatable but rather common neurological disorder seemed more important than side effects, especially as more selective agonists of dopamine than levodopa came on stream. Indeed, in addition to the many variations on levodopa, such as different pharmaceutical formulations and various combinations with enzyme inhibitors, there is now an armamentarium of such drugs available including ergoline derivatives like bromocriptine, cabergoline, and pergolide and non-ergolines such as pramipexole, ropinirole, and rotigotine. Dopamine agonists are even being used as monotherapy in early PD before levodopa-containing drugs are considered (Clarke and Guttman 2002).

Cabergoline and pergolide have recently been associated with an increased risk of valvular heart disease in PD patients (Schade et al 2007; Zanettini et al 2007), because of these findings, pergolide was recently withdrawn from the US market by the FDA. Among the many side effects of all dopamine agonists as treatments for PD are impulse control disorders such as pathological gambling (Driver-Dunckley et al 2003; Dodd et al 2005). Although serious, and often financially and socially catastrophic for the individual patient, compulsive gambling is relatively uncommon and the predictive features for determining who is likely to experience impulsive behavior are unknown. However, in this issue, the group of Hubert Fernandez at the McKnight Brain Institute at the University of Florida proposes a possible 'phenotype' based on the four As: anxiety, anger, age, and agonists (Shapiro et al 2007). They have analyzed whether lifestyle or environmental factors are associated with pathological gambling in PD. Although the sample is relatively small, compulsive gamblers appear to be younger and exhibit higher levels of anxiety, anger, and confusion. A Canadian report has also been published in February with a somewhat larger sample, which confirms the younger age of compulsive gamblers and the use of dopamine agonists, together with a history of medication-induced hypomania or mania, higher novelty seeking, and a personal or immediate family history of alcohol use disorders (Voon et al 2007). If these vulnerabilities can be confirmed in larger and longer-term studies, particularly in other PD populations across the globe, then we may be able to talk about a true phenotype. Identification of PD patients potentially at risk for developing compulsive gambling behavior would be particularly useful to clinicians prescribing dopamine agonists enabling them to be extra vigilant when dealing with this particular sub-population.

Dopamine agonists are also used in another chronic neurological disorder, restless legs syndrome (RLS), despite the lack of a precise dopaminergic pathophysiology for the disorder (Happe and Trenkwalder 2004; Trenkwalder et al 2005). The last issue of *Neuropsychiatric Disease and Treatment* was largely devoted to RLS, and included major reviews on RLS-associated disturbances of sleep (Bogan 2006) and mood (Becker 2006), evaluations of pramipexole (Benbir and Guilleminault 2006),

ropinirole (Kushida 2006) and rotigotine (Bunten and Happe 2006), and an accompanying editorial (Pinder 2006). Now the first cases of pathological gambling in 3 patients with RLS under treatment with dopamine agonists mainly pramipexole have been reported (Tippmann-Peikert et al 2007). Except for age and medication, it is not clear whether the RLS patients fit into the Fernandez phenotype being proposed for PD. It is likely that the triggers for pathological gambling associated with dopamine agonist therapy are similar in RLS and PD, and that ultimately there may be some degree of commonality in the pathophysiology of the two disorders.

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