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Why Does the *Goalkeeper* Eschew Medication: The Challenge of New Treatments for Tourette Syndrome

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Four years ago, the [then] U.S. Tourette Syndrome Association [now the Tourette Association of America] described Tim Howard, the former goalkeeper of the English Premier League football teams Manchester United and Everton and of the U.S. national soccer team, as ‘the most notable person in the world with the condition’ and conferred on him their Champion of Hope Award. Yet Howard does not take or advocate medication. Why? In his autobiography *The Keeper* and associated media interviews he refers to such treatment as ‘a concoction of drugs for other ailments’ and opinion that they ‘make you drowsy, make you zombie-like’.

Recent reviews on Gilles de la Tourette syndrome juxtapose the complexities of this disorder in terms of epidemiology, phenomenology, assessment and dysfunction with the yet more challenging domains of comorbitidies/coexistent psychopathologies, developmental pathobiology and management. It is in relation to drug treatment that Howard articulates particular concerns. Among a wide range of non-pharmacological and pharmacological interventions investigated over recent decades, having often modest efficacies and problematic adverse effects, the evidence base as to efficacy is strongest for the use of first- and subsequently second-generation antipsychotic drugs, all of which either antagonise D2-like (primarily D2) dopamine receptors or exert partial agonist activity to attenuate transmission through D2 receptors. However, the efficacy of such agents must be set against their often challenging adverse effect profiles, even for second-generation agents and especially on considering their long-term use in children. This evidence base for therapeutic efficacy via attenuation of activity through D2 receptors is complemented by increasing positron emission tomography (PET) and single photon emission computed tomography (SPECT) evidence for dopaminergic hyperfunction in the caudate and/or putamen in Tourette syndrome, which may involve increases in both tonic and phasic
dopaminergic function through D2 receptors, possibly due to dopaminergic hyperinnervation\(^6\).

Clearly, D1-like (primarily D1) dopamine receptors have been ascribed little import in this regard. Indeed, though D1 and D2 receptors were co-identified, the D1 receptor remained very much a ‘Cinderella’ site until the identification of the first selective D1 antagonists and initial evidence that D1 receptors were not only behaviorally relevant but also participated in important functional interactions with D2 receptors\(^7,8\). Initial clinical studies with the selective D1 antagonist ecopipam (SCH 39166) indicated it and another selective D1 antagonist NNC 01-0687 to be without material antipsychotic activity or major adverse effects\(^9\). Subsequent clinical studies with ecopipam have focussed variably on cocaine abuse, obesity, gambling disorder and, most recently, Tourette syndrome. The logic for studying this latter indication derived from what was then current understanding of the functional roles of dopamine within cortical-striatal-pallidal-thalamo-cortical circuitry to facilitate movement via D1 receptors on direct-pathway spiny projection neurons in the basal ganglia and reduce movement via D2 receptors on indirect-pathway spiny projection neurons\(^10\). This would not only account for the established efficacy of D2 antagonists\(^5\) but also predict efficacy for D1 antagonists, an effect augered in an intial open-label study of ecopipam in 15 adults with Tourette syndrome\(^11\).

Thus, the double-blind, placebo-controlled crossover study by Gilbert and colleagues in the current issue of *Movement Disorders*\(^12\) is a welcome elaboration of this premise. Relative to placebo, the authors report ecopipam to significantly reduce YGTSS total tic score at 16 and 30 days of treatment in 40 children and adolescents, without effects on the comorbidities/coexistent psychopathologies of ADHD, OCD and depression; treatment with ecopipam was generally well tolerated, there being no
other motoric effects, weight gain or abnormalities in vital signs, EEG and laboratory tests.

However, some aspects of the study are worthy of further consideration. Within the overall study, which sought to apply commendably rigorous statistical approaches to the known methodological challenges (and advantages) of crossover designs, reduction in YGTSS total tic score at day 30 for ecopipam relative to placebo was modest at -3.2 (-17% on ecopipam, -10% on placebo); these reductions appear somewhat smaller than those generally reported in several studies involving D2 antagonists\(^5\), though with fewer adverse effects. In Fig. 2 of the article by Gilbert and colleagues\(^12\), display using a non-truncated rather than truncated ordinate could have left a rather different impression of clinical impact, as distinct from statistical significance. Furthermore, as noted by the authors, the magnitude of reduction in YGTSS total tic score appeared greater in subjects who received ecopipam in the second period relative to those who received it in the first period of the crossover design. It would have been interesting to see the results of statistical analysis for any significant interaction between treatment and period that might prompt review of previous crossover studies with D2 antagonists for any similar or distinct sequence effects revelatory of methodological issues and/or underlying pathobiological processes.

Gilbert and colleagues\(^12\) correctly position and interpret their study in accordance with understanding of basal ganglia physiology and pathophysiology within the time frame between its initiation and completion\(^10\). However, very recent advances indicate greater complexity whereby both the spatiotemporal clustering and rates of activity through D1 receptors on direct-pathway spiny projection neurons and D2 receptors on indirect-pathway spiny projection neurons appear crucial for normal and abnormal
striatal function\textsuperscript{13}; these pathways might regulate not movement initiation but, rather, the dynamic shaping of movement patterns\textsuperscript{10}.

Irrespective of these considerations, the study of Gilbert and colleagues\textsuperscript{12} presents novel findings that extend our understanding of dopaminergic mechanisms in the pathobiology of movement disorders and indicate a novel approach to the treatment of Tourette syndrome. Future studies may help to clarify the extent to which this approach might be developed into a yet more clinically impactful treatment in the context of new insights into the increasingly complex roles of D1 and D2 receptor-mediated processes in basal ganglia function in general and in Tourette syndrome in particular. It may repay the \textit{goalkeeper} to extend his career a little longer should he wish to re-consider his decision.

REFERENCES


