

## Pharmacotherapy in Down's syndrome: which way forward?

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Down's syndrome has come to the forefront of medical science as an intellectual disability with the potential for treatment. In *The Lancet Neurology*, Rafael de la Torre and colleagues<sup>1</sup> report the results of a randomised, double-blind, phase 2 trial designed to assess the cognitive benefits of epigallocatechin-3-gallate (EGCG) in this population. 43 young adults with Down's syndrome were given a decaffeinated green tea supplement containing 45% EGCG for 12 months and participated in weekly sessions of online cognitive training. 41 individuals from the same recruitment pool participated in the same training exercises while taking a placebo. EGCG antagonises DYRK1A, a kinase encoded by a gene located on a region of chromosome 21 thought to contribute to intellectual disability.<sup>2</sup> Dierssen and colleagues previously found that EGCG improved spatial memory in a Down's syndrome mouse model, and that the improvement was affected by environmental enrichment.<sup>3,4</sup>

To assess the efficacy of EGCG and cognitive training, de la Torre and colleagues<sup>1</sup> used the TESAD battery, a 90 min neuropsychological assessment comprised of 15 outcome measures for an array of functional domains.<sup>5</sup> Carer reports on the Adaptive Behavior Assessment System (ABAS-II), a readout of nine adaptive skills, were also assessed. All outcomes were assessed at baseline, at 3 months, 6 months, and 12 months into the treatment schedule, and 6 months after washout.

As expected, most participants with Down's syndrome tolerated the green tea extract; only mild adverse effects were noted. With regards to efficacy, EGCG and cognitive training did not produce significant effects on 13 of 15 measures tested by TESAD or on eight of nine adaptive skills in the ABAS-II. However, relative to placebo and cognitive training, participants given EGCG and cognitive training scored significantly better on pattern recognition memory (6.23 points higher on a 100 point scale during the 12 month evaluation point) and on the immediate, but not delayed, free-verbal recall portion of the cued recall test (1.98 points higher on a 36 point scale at the 6 month follow-up). These differences were not observed at the earlier 6 month assessment. At each timepoint tested, including the 6 month follow-up, participants receiving EGCG also had better

behavioural inhibition on the Cats and Dogs task (0.48–0.51 point improvements in the range near ceiling on a 16 point scale) and significantly higher ratings on the functional academics division of the ABAS-II.

Where noted, the improvements linked to EGCG and cognitive training were considered below the threshold for clinically significant change. In the case of the cued recall and behavioural inhibition tasks, the improvements cannot be put into perspective because those assessments were designed for individuals with intellectual disability and cannot be compared with normative data.<sup>6,7</sup> However, two secondary outcomes of this clinical trial are worth considering. In a subgroup of participants with Down's syndrome given EGCG and cognitive training, biomarkers associated with better functional brain connectivity were observed over the placebo group. Treated individuals had significant increases in regional frontal connectivity based on resting-state functional MRI activity and normalisation of cortical excitation based on transcranial magnetic stimulation. Both findings were observed during the evaluation window and similar effects have been previously reported.<sup>8</sup>

The limitations of the TESAD trial relate to the difficulties in establishing neuropsychological measures for cognitive rehabilitation in Down's syndrome. In the absence of a gold standard method, which would couch the therapeutic effects of an intervention on cognition within a short examination, researchers are pushed to test for efficacy in a variety of domains using an assortment of assessments. This shotgun approach inevitably requires prolonged assessment times in individuals with Down's syndrome, who have well-documented problems with motivation and attention.

Therefore, it is becoming increasingly difficult to ignore the fatigue effects shown by individuals with Down's syndrome in pharmacointervention efforts attempting to translate significant findings from Down's syndrome mouse models. Here, the length of the TESAD battery might have prevented seeing more substantial effects of EGCG on pattern recognition. Much of the treatment response in the EGCG and cognitive training group reflected a higher preservation of memory through the observation period

compared with the placebo group, which saw declines in performance over repeat testing.

A similar situation is likely to have affected a trial evaluating the cognitive benefits of memantine in a US cohort of participants with Down's syndrome (trial registration number NCT01112683). In that trial, Boada and colleagues<sup>9</sup> reported a negative change in scores on pattern recognition and on several measures of verbal fluency and language in control participants with Down's syndrome who were tested at the end of a 4 month period relative to baseline. The test battery in Boada and colleagues' study took 2 h to administer and, of the many measures tested, only one showed a significant effect of memantine. The combination of the results from de la Torre and colleagues<sup>1</sup> and Boada and colleagues<sup>9</sup> lead us to conclude that we are putting the cart before the horse in clinical trials of Down's syndrome. If we are to continue attempts at pharmacological intervention in this group, we must invest in measures of validation that reduce the guesswork and maximise the efficiency of outcome assessments. In doing so, future trials will be less likely to produce equivocal results.

Furthermore, because of funding and recruitment difficulties, clinical trials have been underpowered, with limited means to explore how individual differences affect treatment responses. Down's syndrome is not a homogeneous condition, but is characterised by a diffuse developmental heterogeneity reflecting variation in medical, genetic, and environmental background factors.<sup>10,11</sup> No clinical trial has adequately addressed this variation. For instance, individual differences in sleep among people with Down's syndrome, including diagnosed obstructive sleep apnoea (present in about 50%), significantly correlate with variation in executive functions, the cognitive domain most likely affected by EGCG.<sup>12</sup>

Overall, the TESDAD trial represents an ambitious undertaking that might redefine how we evaluate cognitive improvement in Down's syndrome. However, in building the future, we should take time to think through the crucial next steps. Down's syndrome is a multifaceted condition that requires care in devising new assessment strategies allowing for repeated testing in clinical trials across the lifespan. This work is far from complete. Likewise, we can no longer afford to

view someone with Down's syndrome solely through the lens of trisomy 21, but must seek to understand each individual in light of their larger genetic and environmental background, including comorbidities and their access to educational opportunities.

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JOE reports grants from the LuMind Research Down Syndrome Foundation, grants and personal fees from Hoffman La Roche Ltd, personal fees from Novartis, grants from the Lejeune Foundation, grants from the Bill & Melinda Gates Foundation, and grants from the National Institutes of Health, outside the submitted work; JOE has a patent (US patent 20 150 379 877), System and Methods for Neuropsychological Assessment pending to the University of Arizona. FF has a patent (US patent 8 729 067, 2014), Pharmacological Treatment of Cognitive Impairment, issued; this patent, of which he is an inventor, has been licensed by Stanford University to Balance Therapeutics and as part of the licensing agreement, Stanford University transferred a small share of Balance Therapeutics stock to him in 2010–11.

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