

## Article

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Abbott, Janice and Bilton, Diana

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**EDITORIAL**  
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**Adherence to Ivacaftor is suboptimal**

**Janice Abbott<sup>1</sup>, Diana Bilton<sup>2</sup>**

<sup>1</sup>School of Psychology, University of Central Lancashire, Preston, PR1 2HE, UK

<sup>2</sup> Faculty of Medicine, Imperial College, London, SW7 2AZ, UK

**Corresponding Author**

Professor Janice Abbott

E-mail [jabbott@uclan.ac.uk](mailto:jabbott@uclan.ac.uk)

Phone +44 (0)1772 893790

Ivacaftor, the first cystic fibrosis (CF) transmembrane conductance regulator (CFTR) potentiator provides a remarkable example of personalised medicine that has the capacity to transform lives and patient care. For those with a CFTR-G551D mutation, two phase three trials (adult and paediatric age 6+ years) and a follow-up open label trial have demonstrated remarkable and sustained improvements in CFTR function, FEV<sub>1</sub> (approximately 10% points) and a reduction in pulmonary exacerbations with Ivacaftor 150mg every 12-hours [1-3].

From a clinical perspective it is reasonable to assume that a life-changing, life-saving oral medication with a simple dosing schedule would be taken as prescribed. In this issue of the Journal Siracusa and colleagues report important preliminary work [4] highlighting the fact that 'non-adherence to Ivacaftor is a significant issue'. Their sample size was small (n=12) but the work has merit in having repeated assessments over three-four months. As recommended [5] adherence rates were obtained using multiple methods: self-report (100%), pharmacy refill data (medication possession ratio – 84%) and using the gold-standard of electronic monitoring, adherence to Ivacaftor was 61%. This appears to be a reasonable estimate as it is consistent with the vast literature on adherence rates. While self-report is known to generate higher adherence rates, 100% adherence is rare and potentially reflects the high expectation shouldered by patients concerning this new class of drugs. Also consistent with the literature, Siracusa *et al.* observed a decrease in the rate of adherence and an increase in the time between doses over time [4]. The development of this new, truly disease modifying oral medication provided the hope that better adherence would be a natural consequence. With an adherence rate of only 61% of recommended dosing, unfortunately, this is not the case. This has important implications in terms of clinical and patient outcomes and cost implications for commissioners / funders and cost-effectiveness analysis.

From a behavioural science perspective these data are not surprising. For over 20 years adherence rates in CF have been shown to be variable and treatment-specific with many idiosyncratic barriers to therapies identified [6]. From follow-up phone conversations with patients, Siracusa *et al.* [4] recognised the effort required to engage patients in an 'adherence dialogue' and ascertained some patient-reported barriers ('I forgot to take it'; 'I do not like how the medication makes me feel'). Further work is essential to elicit the reasons why patients are unable to adhere. In the adult trial, an improvement of over 10 percentage points

in the percent of predicted FEV<sub>1</sub> was only accompanied by a small improvement in patient-reported respiratory symptoms (approximately 6 points). The wide confidence intervals indicate that whilst some patients report moderate / large improvements, others report little improvement [1]. This requires unravelling. Do these patients have more respiratory / general side effects? This is likely to impact on adherence and may, in part, explain why this patient-reported outcome was less impressive than might be expected from longitudinal modelling [7]. Indeed, in the paediatric trial, patient/parent reported respiratory symptoms of those in the ivacaftor group were no better than placebo at some time points over the study period [2].

The efficacy and cost-effectiveness analyses of ivacaftor were calculated using an adherence rate of 91% [6] (returned 'pill counts' during the trials). This is very high and may be inflated given the measurement method although participation in a trial does increase adherence to both trial-related and nontrial-related treatment [8]. Consequently, in clinical practice, patients may be unlikely to attain the remarkable benefits seen in closely monitored trials. The NHS England estimate of the increased cost for the first year of prescribing ivacaftor to 271 eligible patients was £43M million (61M Euro; 67M USD). The annual cost of caring for all 7329 individuals was estimated at £150 million (214M Euro; 234M USD). Based on three scenarios for the longer-term effect of ivacaftor, the incremental cost-effectiveness ratio ranged from £335,000 to £1,274,111 (476K-1.8M Euro; 522K-2.0M USD) - for each quality-adjusted life-year gained. The total additional lifetime costs ranged from £438 million to £479 million (623M-681MEuro; 683M-747M USD) – the lifetime cost for standard care being £72 million (102M Euro; 112M USD) [9]. These cost-effectiveness models provide good estimates based on the available data (which included the 91% adherence rate). If adherence is much lower the consequences of decreased clinical benefit and increased direct health costs may substantially alter these estimates.

Access to life-transforming personalized medicines are welcome developments but insufficient in themselves for the successful treatment of CF disease. This new class of drugs has brought the adherence issue to the fore. Suboptimal health outcomes have been tolerated for many years with the 'adherence issue' put on 'the back burner'. There has always been 'bigger fish to fry' with more prestigious clinical studies to engage in. With the developments

of Ivacaftor and Lumacaftor *Moby-Dick* has landed! It is time to address 'adherence' - a principal cause of treatment failure [10].

It is notable that the National Institute for Health Research (NIHR) in the UK has recently awarded £2 million to Wildman and colleagues to test the hypothesis, in a randomised trial, that novel motivational interventions will improve adherence to chronic therapies and thus outcomes in CF (<http://www.sheffield.ac.uk/scharr/sections/hsr/mcru/actif>). Previous interventions have been disappointing [10] but it is certainly high time for the CF community to put their weight behind such well designed randomised studies examining new interventions.

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