Medication adherence – key considerations for clinical pharmacologists

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For all the advances in pharmacology and the armamentarium of treatments available to alleviate, manage and cure diseases, medicines can only be effective if taken appropriately. Human behaviour plays a large part in the effectiveness of medicines. Whether or not patients are adherent may depend, amongst other factors, on their cognition, their beliefs, their medical and social contexts, and their healthcare settings. Concerns about medicines and difficulties in taking them regularly, whether intentional or unintentional, are common. Most patients are non-adherent most of the time. But what do we mean by 'adherence'? Vrijens et al [1] provided a conceptual definition which considers three components: initiation, implementation and discontinuation. Initiation occurs when the patient takes the first dose of a prescribed medication; discontinuation occurs when the patient stops taking the prescribed medication; and implementation is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until discontinuation. Clarity around these terms is essential in the context of medication adherence: How otherwise can "50% adherence" be interpreted?

Medication adherence research is challenging from many perspectives. It transects many disciplines, from health psychology to pharmaceutics, pharmacometrics to clinical pharmacology. Added to which there are innumerable difficulties in identifying and measuring adherence, predicting patients susceptible to poor adherence and developing interventions to improve health outcomes. The Hawthorne effect, for example, which describes the extent to which behaviour is influenced by its measurement, is known to result in 'white coat' effects where patients take their medicines immediately prior to clinic assessments. The use of questionnaires to identify and measure non-adherent behaviours are plagued by recall and responder bias. Alternative approaches include measurements of drug and metabolite concentrations in the blood, but these only inform recent dose-taking histories. 'Big data' in the form of prescription (or dispensing) records are collected routinely at low cost but have low granularity and require a strong assumption that medication possession implies consumption. Conversely, electronic devices provide detailed longitudinal data [2]; some (e.g. Proteus Discover®) even confirm ingestion but such technologies can be expensive and difficult to implement in practice.

This virtual issue brings together a collection of articles published in the British Journal of Clinical Pharmacology that consider these challenges, and offer insights into the complex behaviour that is adherence, and its effects on pharmacotherapy.

Treatment initiation can be problematic for a number of reasons, including cost, lack of perceived need, healthcare provider communication and other health system related factors, as well as medical and social barriers. In the management of hypertension, the prevalence of non-initiation in a Spanish cohort of patients in the first month following prescription was 18% [3]. This, together with undisclosed sub-optimal implementation or complete discontinuation, is recognised increasingly as contributing to apparent resistance to antihypertensive treatment. Using liquid chromatography

tandem mass spectrometry to quantify a wide panel of antihypertensive drugs in plasma, Avataneo et al [4] found that 18% of seemingly treatment-resistant patients had undetectable concentrations of all their prescribed drugs. A similar proportion was reported by de Jager et al [5] who found 16% of patients to be completely non-adherent, with a further 52% of patients implementing sub-optimally.

An important consideration when assessing adherence using questionnaires, is to understand what exactly they measure [6]. Very few are count-based measures. The majority combine items that relate to patients' recall of their dosing history with questions about their beliefs and concerns about their prescribed medicines. The often used Medication Adherence Rating Scale (MARS) questionnaire, for example, includes a question which asks whether patients consider it unnatural to be controlled by medication. There is little surprise, therefore, that questionnaire-based assessments correlate poorly with quantitative measures of dose administrations, such as tablet counts or electronic records. This has implications when selecting outcome measures for clinical trials. An increased score on the MARS may reflect a better understanding of medicines and how they work (e.g. following an educational intervention) without any corresponding improvement in dose-taking.

From a clinical pharmacologist's perspective, one area of particular relevance, is the concept of drug forgiveness – the ability of a drug to maintain therapeutic effect in spite of the occasional missed or delayed dose. Patients with problems remembering to implement punctually may experience greater benefits from a forgiving drug than a more effective, but less forgiving alternative. Notwithstanding large inter- and intra-individual variations in its effects, warfarin is an example that illustrates this point. With a mean plasma half-life of 40 hours and an indirect mechanism of action, its offset of effect is 2-4 days, far exceeding the dosing interval. Contrast with rivaroxaban and edoxaban, which are also dosed once daily, but with shorter elimination half-lives in the range of 5–13 (depending on age) and 10–14 hours, respectively. Their rapid offset of effect (~1 day) is due to direct and reversible inhibition of factor Xa being closely correlated with their plasma concentrations. These are far less forgiving, and more likely to result in under anticoagulation and the associated risk of thrombosis in patients who poorly implement their dosing. Health outcome data from observational studies seem to corroborate these pharmacokinetic – pharmacodynamic relationships in the context of sub-optimal adherence [7,8]. Consideration of forgiveness in drug design, formulation and posology could therefore help mitigate the effects of dose-taking errors, which can happen with the best of intentions.

Attempts at designing effective methods for improving medication adherence have not generally yielded great success. A Cochrane review of the related evidence concluded that study findings were inconsistent, with only a minority of robust randomised controlled trials showing improvements in both adherence and clinical outcomes [9]. One explanation is a lack of appreciation of the multifactorial determinants of non-adherence. Patients who do not initiate because of their prior beliefs, or who discontinue because of intolerability will not become adherent in response to reminders; and communicating the potential benefits of treatment is unlikely to improve implementation in patients who forget their evening doses. Tailored interventions are therefore necessary, as one size does not fit all. This area is ripe for research to develop personalised medicine approaches.

In order to improve the transparency and to standardise reporting, authors of medication adherence research are encourage to follow the EMERGE guideline [10]. Developed by the International Society for Medication Adherence, this is designed to complement existing guidelines (such as CONSORT and STROBE), and is structured around four minimum reporting criteria and 17 items that reflect best practices for reporting. The routine use of EMERGE will help progress the field.

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