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Suboptimal medication adherence has been recognised since antiquity as a major determinant of poor health outcomes. Hippocrates warned physicians that patients might "lie about the taking of things prescribed" and "…through not taking disagreeable drinks, purgative or other, they sometimes die".[1] More recently, there is increased recognition of the importance of designing specific strategies in clinical practice to enhance medication adherence through education-based, behavioural and/or technological interventions. In a 2002 Cochrane review, Haynes et al. declared that, "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments".[2] Finally, the World Health Organization has declared medication adherence an issue of global importance and has rallied policy makers and health managers to improve public health through effective adherence support.[3]

Despite the critical importance of medication adherence to public health, research in this area was surprisingly scant prior to the 1970's. A cursory look at Medline (OVID, 1946-Jan 20th 2023, accessed January 24th 2023, Figure 1) suggests an expanding research base in recent years and a steady growth in the number of publications from <20 in the early 1970's to > 10,000 a year since 2010. There is now an international community of adherence researchers, a scholarly society (The International Society for Medication Adherence, ESPACOMP https://www.espacomp.eu/), and an annual conference. ESPACOMP leads many global initiatives including calls for the consistent use of terminology about adherence [the Ascertaining Barriers for Compliance (ABC) taxonomy[4]], the development of guidelines for reporting adherence research [the ESPACOMP Medication Adherence Reporting Guideline (EMERGE[5])] and guidance for operational definitions in the measurement of adherence [the Timelines-Events-Objectives-Sources (TEOS[6]) framework].

The recent growth of adherence research can be traced to the seminal work of Haynes, Taylor and Sacket, beginning with a conference in 1974[7] and another in 1977[1]. The research agendas proposed at these meetings provided a catalyst for much of the published work in recent decades. We propose that most studies fall into one of four major study types (Figure 2);

1. Studies that explore the causes of nonadherence, often in specific populations of patients. This may include research designed to assess the influence of patient-related factors (e.g. behaviours, beliefs, self-efficacy, illness perceptions); therapy-related

factors (e.g. dosage forms prescribed or dosing frequency); medical condition-related factors; healthcare system related factors (e.g. access to memory aids or self-monitoring of drug response/ disease progress) and social and economic factors.[8]

2. Studies designed to understand the consequences of suboptimal adherence including, the impact on disease management, morbidity, mortality, cost, burden of illness and medicines waste.
3. Studies that propose mitigation strategies to improve adherence. These may include research to develop and evaluate targeted adherence interventions or services in clinical practice at the level of the individual or populations.
4. Research aimed to strengthen the methodological aspects of adherence research including study design, definitions of outcomes, adherence measures and metrics and identifying and mitigating sources of bias.

The magnitude of suboptimal adherence in different patient populations has been well-studied and extensively presented in the literature. While it is often stated that, on average, only about 50% of people are adherent to their prescribed regimen[3], this value does not account for the large variability across patient populations and contexts[9]. In addition, it is not clear how blanket statements about medication taking will relate to the phases of adherence established as part of the ABC taxonomy, nor how this might translate to targeted interventions and services. We suggest that the 'coming of age' of adherence research is partly about researchers addressing the challenges of generating a reliable and accurate evidence base for measuring and managing adherence. Important progress to this end is presented in this themed issue with the contribution from Dima et al.[10] The paper stems from a working party within ESPACOMP involving experts in adherence measurement. The authors use the TEOS operational guideline[6] as a framework and propose three key measurement requirements : 1) data must be available for both the recommended and actual medication taking; 2) measurement must focus on the same medication; and 3) prescribing changes, such as dose escalation, must be taken into account. The authors note that global statements about average adherence rates (e.g. 50% as above) are no longer compatible with our understanding about complex medication taking behaviours. The recommendations proposed by the authors provide useful guidance to inform future study designs.

Pasquier et al.[11] also address the methodological challenges around adherence measurement. The authors note that the analysis of data from electronic monitoring systems, while perhaps seen as the Gold Standard because of the granular data on medication taking, can be challenging from a methodological perspective. In particular, the statistical approaches used to model the data require suitable expertise. A particular challenge highlighted by the authors concerns data censoring. Censored data in this context can be related to patient behaviour (i.e. lost to follow-up etc.) or because of changes in therapy driven by the prescriber (e.g. withholding cancer treatments due to adverse effects etc.). The authors provide a useful theoretical framework for analysing electronic monitoring data and present a novel approach for handling censored data to achieved unbiased estimates of medication adherence.

The challenges, and potential utility, of estimating adherence using urine drug screening data are highlighted by two papers. Jamshidi et al.[12] used paired measurements of plasma and urine buprenorphine and the metabolite norbuprenorphine to test the utility of screening adherence in patients attending an opioid addiction clinic. The urine samples were measured using an ultra-performance liquid chromatography-tandem mass spectrometry as well as a gas chromatography-mass spectrometry screening method. The latter urine screen was noted to only detect the presence or absence of the compounds, but is a less costly method that can be mandated as part of the addiction treatment. It was reported that the gas chromatography-mass spectrometry screening method had a higher rate of false negatives than the more expensive liquid chromatography assay, particularly when the buprenorphine plasma and urine concentrations were in the lower range. This has important implications for the clinical (and legal) decision-making involved in patient management. By contrast, Curneen et al.[13] use urine screens as an objective means of detecting suboptimal adherence in patients taking antihypertensive medications. The authors compared the urine screening result with patient self-reporting in a small group of hypertensive patients. It was reported that, while 75% of the patients self-reported being adherent to their medicines, only 36% were adherent based on the urine screen. The study highlights the challenges of detecting longitudinal medication-taking behaviour from scant cross-sectional clinical data.

The topic of adherence screening was also presented by Smith-Diaz et al.[14] who developed and evaluated a screening tool to detect allopurinol sub-optimal adherence in gout trials. The authors used stochastic simulations from a pharmacometric model for oxypurinol

pharmacokinetics (the active metabolite of allopurinol) to determine the threshold plasma concentration below which suboptimal urate-lowering taking can be concluded. The predictive performance was assessed against external data and the authors conclude that the tool had suitable sensitivity and specificity for screening and to support decision-making in the clinic. As above, the cross-sectional nature of the oxypurinol plasma concentration data will limit the ability to detect longitudinal adherence behaviour and the use of plasma concentrations will be confounded by the 'white coat effect', the tendency of patients to change their medication-taking behaviour prior to a clinic visit.

The critical role of suboptimal adherence in treatment failure and the development of antimicrobial resistance is perhaps nowhere more evident than in the management of tuberculosis. Fox et al.[15] provide insight into the relationship between medication taking patterns, the predictors of suboptimal adherence and treatment outcomes in a cohort of subjects (n=3724) with tuberculosis. It was reported that missing only 4 clustered treatment days in one month increased the risk of treatment failure or relapse by 61%. The paper highlights that, even for a global health priority such as tuberculosis, there remains a fine line between treatment success and failure with adherence as a critical determinant.

The importance of understanding the patient's perspective about medication taking behaviour is highlighted by Spragg et al.[16] The authors interviewed 26 people with gout to understand the facilitators and barriers to allopurinol adherence. While motivation to prevent gout flares was found to be a facilitator for the successful initiation of allopurinol therapy, continued gout flares after starting urate-lowering treatment, a common occurrence during the slow dose escalation recommended for allopurinol, was identified as both a barrier to implementation and a factor in the patients' choice to discontinue therapy. A common theme was the importance of education by health providers in helping people to remember to take allopurinol, to understand gout, and to persevere with treatment.

An insightful commentary from Schneider et al.[17] further emphasises the importance of understanding the patient's perspective. Here the authors argue that adherence is best managed in a partnership between the patient and an interprofessional team of health providers. A new model of care is proposed with the patient taking a central role while the

health care team act as facilitators in the education of the patient about their conditions and medicines.

Adherence research is often rooted in the translation of research outputs to practice. Yet, as Hogervorst et al.[18] note, many targeted adherence interventions and services are not actually implemented in a practice setting. The authors examine the factors that influence the scalability of interventions identified in the research setting that will facilitate their translation to routine use in patient care.

The papers in this themed issue contribute to the 'coming of age' of adherence research. The diversity of the field is on display with papers covering all four of the proposed research themes noted in Figure 2. Similarly, the multi-disciplinary nature of adherence research is evident with contributions from pharmacists, doctors, health psychologists, and statisticians, amongst others. After 50+ years of research, medication adherence is now recognised as a complex, multifactorial phenomenon that encompasses three phases: initiation (when the first dose of a prescribed medication is taken); implementation (how well a patient's actual dosing regimen matches the prescribed regimen); and discontinuation (when the patient stops taking the medication)[4]. Strategies and technologies to improve medication taking in drug development and practice have proliferated to include the use of electronic medicine monitoring, clinical intervention services, reminders on mobiles phones, and point of care testing to encourage patient self-management, for example. Despite these advances, there is now a growing recognition that there is no easy fix to improve adherence behaviour and, despite prolific research outputs in the past 50 years, there are important limitations to the current state of the evidence . As the papers in this themed issue highlight, the upcoming challenges in adherence research will focus on improving how we can effectively measure and report medication adherence, and how we better personalise interventions and design robust studies to test their effectiveness.

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206 **Figure legends**

207 Figure 1. Numbers of papers appearing in MEDLINE related to medication adherence. The
208 figure is indicative only, i.e. it was a cursory search. Mesh Terms: *exp Patient Compliance or*
209 *exp Medication Adherence or exp "Treatment Adherence or compliance"*. Text words: *med**
210 *adj2 persistence*.

211 Figure 2. Proposed major study types focused on medication adherence.