What We Mean When We Talk About Adherence in Respiratory Medicine

Bernard Vrijens, PhD[a,b], Alexandra L. Dima, PhD[c], Eric Van Ganse, MD, PhD, FRCP[d,e], Job F.M. van Boven, PharmD, PhD[f], Michelle N. Eakin, PhD[g], Juliet M. Foster, PhD[h], Marijn de Bruin, PhD[c,i], Alison Chisholm, MSc[j], and David Price, MD, FRCGP[j,k] *Visé and Liège, Belgium; Amsterdam, The Netherlands; Lyon, France; Groningen, The Netherlands; Baltimore, Md; Sydney, Australia; and Aberdeen and Cambridge, UK*

Adequate medication adherence is key for optimal benefit of pharmacological treatments. A wealth of research has been conducted to understand and identify opportunities to intervene to improve medication adherence, but variations in adherence definitions within prior research have led to ambiguity in study findings. The lack of a standard taxonomy hinders the development of cumulative science in adherence research. This article reviews the newly established Ascertaining Barriers to Compliance (ABC) taxonomy for medication adherence with a particular focus on its relevance and applicability within the context of asthma and chronic obstructive pulmonary disease management. Building on traditional definitions and concepts within medication adherence, the ABC taxonomy considers the temporal sequence of steps a patient must undertake to be defined as "adherent to treatment": (A) initiation, (B) implementation, and (C) persistence. We explain the clinical and research relevance of differentiating between these phases, point to differences in its applicability in observational and experimental research, review strengths and limitations of available measures, and highlight recent findings on specific determinants of these behaviors. Finally, we provide recommendations for research and practice with a view to supporting and sign posting opportunities to improve future respiratory medication adherence and

[a]WestRock Healthcare, Visé, Belgium
[b]Department of Public Health, University of Liège, Liège, Belgium
[c]Amsterdam School of Communication Research ASCoR, University of Amsterdam, Amsterdam, The Netherlands
[d]Pharmaco-Epidemiology Lyon (PEL), HESPER, Claude Bernard University, Lyon, France
[e]Respiratory Medicine, Croix-Rousse University Hospital, Lyon, France
[f]Department of Primary Care, Groningen Research Institute for Asthma and COPD (GRIAC), University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[g]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University, Baltimore, Md
[h]Woolcock Institute of Medical Research, Clinical Management Group, University of Sydney, Sydney, Australia
[i]Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK
[j]Respiratory Effectiveness Group, Cambridge, UK
[k]Centre of Academic Primary Care, University of Aberdeen, Aberdeen, UK

The Respiratory Effectiveness Group (REG; www.effectivenessevaluation.org) supported the Expert Adherence Panel Meeting at which many of the concepts presented in this paper were first discussed. REG also supported the manuscript submission costs. ALD, EvG, and MdB have received funding from the European Community's 7th Framework (FP7/2007-2013) under grant agreement no. 282593. Teva supported the meeting costs at which the concepts in this paper were discussed by the co-authors and the open access publication fee for this article. The authors had full editorial control over the ideas presented.

Conflicts of interest: B. Vrijens is a full-time employee of WestRock healthcare, the company that manufactures and commercializes the Medication Event Monitoring Systems (MEMS™). A. L. Dima has received research support from the Respiratory Effectiveness Group. E. Van Ganse is on the Pfizer board; has received consultancy fees from Steve Data/PELyon Clinical Research Organisation; has received research support from Merck, GlaxoSmithKline, ALK Abello, Bristol-Myers Squibb, and Bayer; has received lecture fees from BMS; has stock/stock options in Peylong; and has received travel support from Novartis, AstraZeneca, and Boehringer Ingelheim. J. F. M. van Boven has received travel support from the Respiratory Effectiveness Group and European Chronic Obstructive Pulmonary Disease Coalition; has received consultancy fees from AstraZeneca; and has received research support from AstraZeneca, GlaxoSmithKline, Boerhinger Ingelheim, and Chiesi. M. N. Eakin has received travel support from the Respiratory Effectiveness Group; has received consultancy fees from Praxis Pharmaceuticals; and has received research support from the National Institutes of Health and the Cystic Fibrosis Foundation. J. M. Foster has received travel support from the Respiratory Effectiveness Group and European Academy of Allergy and Clinical Immunology; is on the Vertex Pharmaceuticals advisory board; and has received research support from GlaxoSmithKline and AstraZeneca. D. Price is on the boards for Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva; has received consultancy fees from Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Pfizer, and Teva; has received research support from UK National Health Service, British Lung Foundation, Aerocrine, AKL Ltd, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly, GlaxoSmithKline, Meda, Merck, Mundipharma, Napp, Novartis, Orion, Pfizer, Respiratory Effectiveness Group, Takeda, Teva, Zentiva; has received lecture fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Meda, Merck, Mundipharma, Novartis, Pfizer, SkyePharma, Takeda, and Teva; has received payment for manuscript preparation from Mundipharma and Teva; has a patent with AKL Ltd; has received payment for developing educational presentations from GlaxoSmithkline and Novartis; has stock in AKL Ltd; has received travel support from Aerocrine, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva; has received funding for patient enrolment or completion of research from Almirall, Chiesi, Teva, and Zentiva; is a peer reviewer for grant committees for Medical Research Council (2014), Efficacy and Mechanism Evaluation programme (2012), Health Technology Appraisal (2014); and owns 80% of Research in Real Life, Ltd (and its subsidiary social enterprise Optimum Patient Care), which receives unrestricted funding for investigator-initiated studies from Aerocrine, AKL Ltd, Almirall, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, Zentiva. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication February 24, 2016; revised May 19, 2016; accepted for publication May 27, 2016.

Corresponding author: Bernard Vrijens, PhD, WestRock Healthcare, Rue des Cyclistes Frontière 24, Visé 4600, Belgium. E-mail: bernard.vrijens@westrock.com.

2213-2198

http://dx.doi.org/10.1016/j.jaip.2016.05.019

Abbreviations used
ABC- Ascertaining barriers to compliance
CMA- Continuous multiple-interval measures of medication availability
COPD- Chronic obstructive pulmonary disease
EMD- Electronic monitoring devices
EMR- Electronic medical records
FDC- Fixed dose combination
ICS- Inhaled corticosteroids
LABA- Long-acting β_2-agonists
MPR- Medication possession ratio
RCT- Randomized controlled trial
TTD- Time to discontinuation

Keywords: *Medication adherence; Asthma; Chronic obstructive pulmonary disease (COPD); Initiation; Implementation; Persistence; ABC taxonomy*

Respiratory clinicians have access to a wide range of efficacious therapies. Randomized controlled trials (RCTs) have repeatedly demonstrated the efficacy of licensed asthma and chronic obstructive pulmonary disease (COPD) therapies in terms of their ability to minimize symptom burden, improve health-related quality of life, and maintain or slow disease progression.[1,2] Yet reports of numerous asthma and COPD exacerbations and related pressures on emergency and respiratory services persist.[3,4] This apparent disconnect is primarily explained by the gap between efficacy results derived from well-controlled, short-term RCTs involving highly selected populations and effectiveness evaluations conducted in more every day, real-life settings, typically involving diverse patient populations, across a wide range of care settings and patient characteristics and evaluated over longer time intervals than are used in RCTs.[5]

One of the important differentiating factors between efficacy RCTs and real-world effectiveness studies is medication adherence optimized in RCTs, but commonly suboptimal in everyday routine care. Through registration RCTs, regulatory authorities require an estimate of efficacy (or "method-effectiveness") that assumes perfect adherence while, in practice, payers are often more interested in "use effectiveness" to inform cost-effectiveness analyses and guide market access and reimbursement decisions through pragmatic RCTs or noninterventional studies. All study designs reflect some aspect of the real world, but the ability to extrapolate the findings of registration RCTs to more routine clinical environments must be treated with caution.[6] The real-world implications of differences between registration RCTs and routine care adherence behaviors depend on the characteristics of both the disease and the medications as drug actions are inherently dose and time dependent. As a result, variable underdosing (which is the norm) diminishes the actions of medications in real life by various degrees compared with RCT settings.[7]

The importance of optimizing asthma medication in the context of routine ("real-world") practice was recognized and stressed by the World Allergy Organization and Interasma in their joint manifesto on adherence to asthma treatment in respiratory allergy (also endorsed by Allergic Rhinitis and Its Impact on Asthma and the Global Allergy and Asthma European Network).[8]

The Ascertaining Barriers to Compliance (ABC) taxonomy began as an initiative of the European Union to standardize adherence-related terminology for clinical and research use.[9] The publication of the ABC taxonomy marked an important step forward in the standardization and future development of adherence research. To facilitate its use in respiratory research and practice, it is now important to consider its applicability and relevance to the real-life complexities of respiratory care.

Although sharing many of the common barriers to optimal adherence reported in other chronic diseases,[10,11] asthma and COPD stand apart because of the central role that inhaled therapy plays in their management, and the associated challenges that the effective inhaler technique presents to optimum therapy delivery and adherence.[12] Furthermore, the 2 conditions differ in their age of onset, pattern of symptoms, and disease course giving rise to potential differences in respective medication adherence behaviors. We consider the value of the ABC taxonomy in differentiating between adherence behaviors and clinical settings in these respiratory conditions, as a way to both understand behavior-specific determinants and establish a new standard for future respiratory adherence research. Finally, evidence gaps and unmet needs are outlined to act as a guide for future respiratory adherence researchers.

TOWARDS A COMMON ADHERENCE TAXONOMY

On the basis of a systematic review of the medication adherence literature, Vrijens et al's[9] proposed ABC taxonomy conceptualizes adherence to medications in line with principles of behavioral and pharmacological science. This proposal was developed as a response to a 2003 World Health Organization call for action to address the disease burden associated with poor medication adherence.[13] It also furthered the thinking laid out by the International Society for Pharmacoeconomics and Outcomes Research in their 2008 consensus statement on adherence definitions.[14,15]

The ABC taxonomy defines the overarching concept of "medication adherence" as the process by which patients take their medication as prescribed and subdivides it into 3 essential elements: (A) initiation; (B) implementation, and (C) persistence (see Figure 1). This subdivision outlines the sequence of events that have to occur for a patient to experience the optimal benefit from his or her prescribed treatment regimen.

Step "A" in the process, "initiation"—when the patient takes the first dose of a prescribed medication—is typically a binary event (patients either start taking their medication or not in a given time period). In contrast, step "B," "implementation"—the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken—is a longitudinal description of patient behavior over time, that is, his or her dosing history. The final step "C," defined within the taxonomy, "persistence," is the time elapsed from initiation, until eventual