

Canadian Geriatrics Society

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### THE OLDER PATIENT AND OBSTRUCTIVE AIRWAY DISEASES: LIMITATIONS FROM SPIROMETRY TO DEVICES

#### Abstract

Asthma and COPD are common in older patients, but there are unique challenges that must be considered for this age group. The ability to adequately perform spirometric manoeuvres must be assessed and responded to. Other diagnostic options such as questionnaires and peak flow measurements can be considered when spirometry cannot be done. As medications need to be properly delivered to the lung for maximal efficacy, it is important to assess if this is happening and to choose the inhaler with the best likelihood of treatment success. Issues of cognition, hand strength, dosing simplicity, number and types of inhalers prescribed, and peak inspiratory flow should all be considered.

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#### Epidemiology

Obstructive airway diseases, mostly asthma and chronic obstructive pulmonary disease (COPD), are highly prevalent in the older population<sup>1</sup>,<sup>2</sup>. By 2025, the World Health Organization (WHO) estimates that the proportion of persons over 65 years of age will represent 17% of the total world population<sup>3</sup>. COPD prevalence increases with aging, with an estimated prevalence of 20% to 30% in patients >70 years of age<sup>4</sup>. The prevalence of asthma in the elderly is also high, with studies showing it affecting >10% of patients 60 years of age or older<sup>5</sup>.

#### Diagnosis

The presentation of asthma and COPD can be subtle in the elderly, especially those with multiple other conditions that can affect respiratory symptoms<sup>6</sup>. Symptoms are often underestimated by patients. Older patients with moderate or severe respiratory disease and impairment may not appear to be disabled compared to those with more obvious issues such as cerebrovascular or musculoskeletal issues. They do not occupy rehabilitation beds for long periods or rely greatly on community services for physical support, other than post exacerbations when the diagnosis is already clear. Most can wash, dress and mobilize independently within the home, although simple acts of washing and dressing may take long periods of time and leave them exhausted. Assessment and treatment require accurate diagnosis<sup>7</sup>, which for the most part means spirometry.

Can your older and possibly frail patient adequately perform spirometry? Can we predict those that can and those that cannot perform adequate spirometry? If they cannot, what should be done?

Spirometry is relatively underutilized in the elderly. Factors shown to impact negatively on the ability to do proper spirometry include lower scores on cognitive and functional testing, or a lower level of educational attainment. Age alone was not an independent determining factor in some studies<sup>8</sup>, though it was in others<sup>9</sup>, possibly related to different study designs and factors such as education and cognitive status being accounted for.

A Mini Mental State Examination (MMSE) score of  $<24/30^{10}$  and inability to copy intersecting pentagons (IP), as well as clock drawing tests predicts inability to perform spirometry<sup>11</sup>. Please <u>see</u>.

Fortunately, most older patients can have meaningful measurements made of FEV1 and FVC if there is careful attention to technique and data quality. These tests, when combined with an informed evaluation of respiratory symptoms, should lead to the timely and accurate diagnosis of asthma and COPD in older patients. The association between pulmonary function measured by spirometry and the presence of frailty phenotype in community-dwelling older patients interestingly did not show a relationship between frailty and lung function, although the prognosis of COPD patients who are 'frail' is significantly worse<sup>12</sup>.

That being said, as many as one-fifth of patients cannot perform proper spirometry, most commonly in the very elderly, and those with lower cognitive and functional scores in whom respiratory symptom reporting might be expected to be reduced or inconsistent. Alternative objective measurements such as forced oscillometry could be useful<sup>13</sup>, but is not readily available in most locations. Oscillometry is a <u>non-invasive</u> technique to characterize the airway through the superimposition of pressure fluctuations into the airway during normal tidal breathing, which can be done on children and older adults and does not require any forced maneuvers or technical teaching.

There are several different questionnaires that have been assessed for both asthma and COPD. The use of simple screening tools (e.g., questionnaires, hand-held spirometers) that have been validated in the primary care setting has been proved to be an effective method for case finding of COPD<sup>14,15,16,17</sup>. Studies of three questionnaires<sup>18</sup> including the International Primary Care Airways Group (IPAG) <u>questionnaire</u>, the COPD



Population Screener (COPDPS) <u>questionnaire</u>, and the Lung Function <u>Questionnaire</u> (LFQ) have shown high negative predictive values (94–96%), so in this case the diagnosis of COPD could be safely excluded, but poor positive predictive values. The IPAG questionnaire had the best sensitivity of the questionnaires (58.7%).



Mini-spirometers (e.g., COPD 6 and PIKO 6) are portable and do a good job

of ruling out disease without the full spirometric evaluation being required. While a peak flow metre can be helpful, it is somewhat less sensitive. That being said, a 20% improvement in peak flow post bronchodilator supports a diagnosis of asthma, and a peak expiratory flow rate of less than 80% will detect more than 90%



of people with chronic obstructive pulmonary disease in the community, including all of those with moderate or severe disease, which are those that would benefit from bronchodilation<sup>19</sup>.

Ultimately, a trial of therapy in those who cannot undergo objective testing is often necessary<sup>20</sup>, but can lead to inappropriate therapy, side effects and non-treatment of other significant conditions<sup>21</sup>.

#### **Definition of the diseases**

Asthma is classically a disease of eosinophilic airway inflammation, which is reversible with time or treatment. COPD includes a heterogeneous group of clinical manifestations and diverse disease phenotypes (i.e., emphysema, chronic bronchitis), often characterized by the presence of partially reversible airflow obstruction. However, long-standing asthma often leads to airway

remodeling and partly irreversible airflow obstruction<sup>22</sup>, making the differentiation between these two entities clinically challenging at times. In addition, there can be overlap with other disease processes such as bronchiectasis, bronchiolitis, interstitial lung disease and congestive heart failure.

Management of these conditions is different and mirrors the pathophysiology with pharmacologic treatment now often reflecting the treatable traits more so than the descriptive name. That being said, eosinophilic inflammation requires treatment with inhaled corticosteroids (ICS) and hyperinflation requires treatment with bronchodilation. Therapy in asthma is stepped up from ICS to ICS/LABA (long acting beta-agonist) and potentially adding a LAMA (long acting muscarinic) with the caveat that ICS should always be included in the therapy. Therapy in COPD involves adding long acting bronchodilators, LABA, LAMA or both and adding on other agents for exacerbation prevention based on phenotypes<sup>23</sup>. To learn more <u>see</u>.

Multiple medications in the elderly can cause concern in terms of drug interactions<sup>24</sup>. Non-pharmacologic therapy includes management of comorbidities (e.g., glaucoma, cardiac disease or osteoporosis), trigger avoidance where possible, smoking cessation, vaccination, rehabilitation and proper inhaler technique, which will be further discussed.

#### Devices

Inhaled therapy ensures rapid and direct delivery to the lungs. It can be provided via a range of devices, including nebulizers, pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs) and soft mist inhalers (SMIs). To learn more <u>see</u>.

One of the main barriers to adequate therapeutic benefits of medications is appropriate and adequate inhaler technique<sup>25</sup>, <sup>26</sup> to ensure medications reach the airways they are designed to target. Studies consistently report that many patients with asthma and COPD do not use their inhaler devices correctly<sup>27</sup>, with many of those errors considered critical errors<sup>28</sup>, which significantly obviate any benefits. Unfortunately, clinicians pay more attention to the medication prescribed than to the device<sup>29</sup>.

To select the device that is most appropriate for your patient, it is important to recognize that a patient's ability to use a device may be influenced by a range of factors<sup>30</sup>. Older age increases the likelihood of comorbid conditions that may impact device selection. Physical issues including weakness, impaired dexterity, declining vision, poor hearing and low inspiratory rates may all impact on a patient's ability to use a device<sup>31</sup>. Declining cognitive function and mood disorders, which are common comorbidities for asthma and COPD<sup>32</sup>, can also impair the ability to master and recall techniques<sup>33</sup>, or even to remember when to take the medication. Furthermore, lack of effect or discomfort with the device can lead to adherence issues, which can



negatively impact on long-term outcomes<sup>34</sup>.

Pressured metered dose inhalers (pMDI) were the first and are still the most commonly prescribed device. These contain a canister of medication in suspension or solution, a chamber to generate the propulsion of the medication and a mouthpiece. Accurate timing of the

inhalation after depressing the canister is necessary for successful administration. A

key component of the technique is to inhale slowly so as to not allow the medication to hit the back of the throat so it can reach the lungs.

A good breath-hold of 10 seconds is advised for all inhaled medications. Timing can be improved by newer devices such as the breath actuated MDIs (recently coming to Canada in the Respiclick device and with the use of spacers such as the Trudell Aerochambers). SABA (short acting beta agonist), LABA/ICS (long acting beta agonist/inhaled corticosteroid) and ICS are currently available in Canada in this device.

Dry powder inhalers (DPIs) are breath actuated with the patient creating the drive of the medication by inhaling through the device. This does mitigate some of the timing and requires a rapid inhalation of sufficient force to de-aggregate the powder into respirable particles. They come in two major types: a capsule that needs to be loaded one dose at a time and pierced prior to inhalation (e.g., <u>breezehaler</u>, <u>handihaler</u>), or a device that loads the dose as the activator lever or bar is clicked with multiple doses contained inside (e.g., <u>genuair</u>, <u>ellipta</u>, <u>diskus</u>, <u>twisthaler</u>). In Canada we have SABA, LABA, LAMA (long acting antimuscarinic), ICS, ICS/LABA and ICS/LABA/LAMA available in this device.





Soft mist inhalers (SMI) are the newest device using the power of a spring to create a much slower moving liquid aerosol (cf MDI) with a longer mist that makes it easier to time. In addition, particle size is generally smaller than DPI. The device (<u>Respimat</u>) creates the drive of the medication, so a slower inhalation is preferred, but the longer mist time increases probability of the medication reaching the lungs. In Canada, this is available as a SABA/SAMA (short acting muscarinic), LABA and LABA/LAMA.

Nebulizers are available and can be useful for inhalation at regular tidal breathing, needing no real coordination. They do require an outside energy source, waste a fair bit of drug, which does not get inhaled, take a longer time to complete treatment and have been recommended against due to COVID and potential aerosol generation. In Canada, they are available in SABA, SAMA and SABA/SAMA. In the U.S. there are LAMA and LABA formulations available for nebulizers.

Clearly this means there are a lot of choices that will guide how you prescribe your medications. Cost, coverage, patient and caregiver comfort, dosing frequency, availability of the drug in the class you want are all important factors. Table 1 gives you an overview of how to choose.

There is good evidence that giving different medications all in the same type of device leads to better outcomes<sup>35</sup>. Unfortunately, not all medications are available in all devices; in fact, not even all classes are available in any one device.

Clearly someone with cognitive issues would benefit from something more passive, such as a nebulizer or MDI with chamber. Family supervision may be helpful. Someone with a busy lifestyle would not want to spend the time sitting and getting a nebulized treatment. Dexterity and hand strength might limit the ability to load a capsule, compress a canister or preload the SMI canister. See Figure 1<sup>36</sup> for an algorithm to use to select the optimal device for the patient in front of you.

A newer concept gaining attention is the concept of Peak Inspiratory Flow (PIF). It has been noted that some patients do not have inspiratory capacity to activate a DPI, although the different DPIs differ in the requirements of adequate PIF. Suboptimal PIF has been associated with poorer outcomes such as hospital readmissions<sup>37</sup> so should be considered with DPI treatment when outcomes are not optimal. Figure 2 reviews a Peak Inspiratory Flow tool<sup>38</sup> I created to identify those at risk; this list includes those who are older<sup>39</sup>, hyperinflated<sup>40</sup>, female<sup>41</sup>, have poorer lung function<sup>42</sup> and post exacerbation<sup>43</sup>.

#### Switching devices

This article may well get you to consider making some changes in your patient's inhaler. With appropriate training this can lead to improved outcomes but does require a bit of work. A recently published algorithm<sup>44</sup>

suggests if you are changing inhalers, you should follow UR-RADAR. In those patient <u>uncontrolled</u> or with unaffordable medications, you should <u>r</u>eview the patient's condition (e.g., diagnosis, phenotype, comorbidities) and **a**ddress reasons for suboptimal control (e.g., triggers, smoking, non-adherence, poor inhaler technique, poor PIFR etc.), <u>d</u>iscuss inhaler switch options, patient preferences (e.g. size, daily regimen) and treatment goals, <u>a</u>llow patients' input and decide by using shared decision-making and <u>r</u>e-educate to the new device (at minimum: physical demonstration, verbal explanation and patient repetition, both verbally and physically) and prime the patient for the follow-up. See Figure 3.

#### Conclusion

The first step in treatment is making the right diagnosis. Spirometry can be done by most patients. If spirometry is not feasible then questionnaires help to rule out disease and a normal peak flow rules out significant COPD. Subsequently, medications must reach the lung to work. As such the delivery device is as important as the medication class. Recognize that the older adult may have challenges in device use, which may include decreased cognition, reduced dexterity and comorbidities that need to be considered in proper diagnosis and in choosing the correct device to promote improved outcomes.

Inhaler	Advantages	Disadvantages
pMDI Pressured Metered Dose Inhaler	<ul> <li>Portable and compact</li> <li>Multidose device</li> <li>Metered-dose</li> <li>Established/familiar</li> <li>Available for SABA, ICS and ICS/LABA</li> </ul>	<ul> <li>Require coordination</li> <li>High deposition in mouth and oropharynx</li> <li>'Cold Freon' effect (cold sensation of the spray hitting the back of the throat)</li> <li>Contain propellants that can lead to environmental decline</li> </ul>
pMDI + spacer	<ul> <li>Lower dependency on inspiratory effort</li> <li>Easier to coordinate</li> <li>Higher lung deposition than pMDI</li> <li>Reduced mouth and oropharynx deposition</li> <li>Can be used with MDI or SMI</li> </ul>	<ul> <li>Less portable than pMDI</li> <li>Certain spacers may acquire electrostatic charge</li> <li>Additional cost to pMDI</li> <li>Requires regular maintenance</li> </ul>
BA-MDI Breath Actuated Metered Dose Inhaler	<ul> <li>Portable and compact</li> <li>Multidose device</li> <li>Breath-actuated</li> <li>Available in ICS, ICS/LABA and SABE</li> </ul>	<ul> <li>Contain propellants that can lead to environmental decline</li> <li>'Cold Freon' effect (cold sensation of the spray hitting the back of the throat)</li> <li>Requires a moderate inspiratory effort</li> </ul>

DPI Dry Powder Inhaler	<ul> <li>Portable and compact</li> <li>Breath-actuated</li> <li>Does not contain propellants</li> <li>Multidose devices available</li> <li>Available in SABA, LABA, LAMA&lt; LABA/LAMA, iCS and ICS/LABA</li> </ul>	<ul> <li>Requires a minimum inspiratory effort</li> <li>May not be appropriate for emergency situations</li> <li>Multiple designs (maybe confusing for the patient)</li> <li>May be complicated to load</li> </ul>
SMI	Portable and compact	<ul> <li>Not breath-actuated</li> </ul>
Soft Mist	<ul> <li>Multidose device</li> <li>Lower dependency on</li> </ul>	<ul> <li>Only one device currently available</li> </ul>
Inhaler	<ul> <li>inspiratory effort</li> <li>High fine-particle fraction</li> <li>High lung deposition; low mouth and oropharynx deposition</li> <li>Does not contain propellants</li> </ul>	<ul> <li>May be complicated to load</li> </ul>
Nebulizers	<ul> <li>Can be used at any age</li> <li>Can be used by acutely ill</li> <li>No specific inhalation technique required</li> <li>Can be used to dispense drugs not available as pMDI or DPI</li> </ul>	<ul> <li>Most lack portability</li> <li>Some require an outside energy source</li> <li>Noisy</li> <li>Can result in longer treatment times</li> <li>Can be expensive</li> <li>Aerosol generating</li> </ul>

Adapted from (30)

#### Figure 1. Device selection algorithm



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WH/ Four m	AT WERE OUI	R FINDINGS	0lder age <sup>5-11</sup>	Female sex <sup>6,7,8,12</sup>	FVC, 5.11 ↓ IC, 5.6 ↓ FEV, 2.13, 14
IF-AT WH	AT IS THE PIF	ASSESSMI	ENT TOOL?		
Clinical suspicion of sPIF	Symptoms refractory to current therapy	Sex	Age	COPD disease severity	
	Yes	Female	≥65 vears	Moderate- to-very severe	Assess PIF if any factor
Yes			and the second se	Statistics of the state of the	is in the red zone

- Metered-dose inhalers + spacers, slow-mist inhalers, and nebulizers require a lower PIFR and can be considered for patients with sPIFR
   PIF-AT could help identify patients at risk of sPIF but requires further evaluation and validation

#### Figure 3



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#### **REFERENCES**:

<sup>1</sup> Dow L, Fowler L, Phelps L, et al. Prevalence of untreated asthma in a population sample of 6000 older adults in Bristol, UK. *Thorax* 2001; 56:472-6.

<sup>2</sup> Renwick DS, Connolly MJ. Prevalence and treatment of chronic airways obstruction in adults over the age of 45. *Thorax* 1996; 51: 27-32.

<sup>3</sup> Kalache A, Keller I. The WHO perspective on active ageing. *Promot Educ* 1999;6: 20-3, 44, 54.

<sup>4</sup> Hardie JA, Vollmer WM, Buist AS, Bakke P, Morkve O. Respiratory symptoms and obstructive pulmonary disease in a population aged over 70 years. *Respir Med* 2005; 99: 186-95.

<sup>5</sup> Murtagh E, Heaney L, Gingles J, Shepherd R, Kee F, Patterson C, et al. Prevalence of obstructive lung disease in a general population sample: the NICECOPD study. *Eur J Epidemiol* 2005; 20: 443-53.

<sup>6</sup> Dow L, Coggon D, Holgate ST. Respiratory symptoms as predictors of airways lability in an elderly population. *Respir Med* 1992;86:27-32.

<sup>7</sup> Renwick DS, Connolly MJ. Do respiratory symptoms predict chronic airflow obstruction and bronchial hyperresponsiveness in older adults? *J Gerontol* 1999; 54A: M136-9.

<sup>8</sup> Pezzoli L, Giardini G, Consonni S, et al. Quality of spirometric performance in older people. *Age and Ageing* 2003; 32: 43-6.

<sup>9</sup> Bellia V, Pistelli R, Catalano F, et al. Quality control of spirometry in the elderly – the SARA study. *Am J Respir Crit Care Med* 2000; 161: 1094-1100.

<sup>10</sup> Turkeshi, E., Zelenukha, D., Vaes, B, et al. Predictors of poor-quality spirometry in two cohorts of older adults in Russia and Belgium: a cross-sectional study. *NPJ Prim Care Resp Med* 25, 15048 (2015). https://doi.org/10.1038/npjpcrm.2015.48

<sup>11</sup> Allen S, Baxter M. A comparison of four tests of cognition as predictors of inability to perform spirometry in old age. *Age and Ageing* 2009; 38: 537-541 doi: 10.1093/ageing/afp104 (Link; https://academic.oup.com/ageing/article/38/5/537/2462151)

<sup>12</sup> Carrerra M, Mejia A, Guevara X. Association between pulmonary function measured by spirometry and frailty phenotype in community-dwelling elderly patients. *Eur Resp J* Sep 2019, 54 (suppl 63) PA807; DOI: 10.1183/13993003.

<sup>13</sup> Carvalhaes-Neto N, Lorino H, Gallinari C, et al. Cognitive function and assessment of lung function in the elderly. *Am J Respir Crit Care Med* 1995; 152: 1611-5.

<sup>14</sup> Price DB, Tinkelman DG, Halbert RJ, Nordyke RJ, Isonaka S, Nonikov D, Juniper EF, Freeman D, Hausen T, Levy ML, Ostrem A, van der Molen T, van Schayck CP: Symptom-based questionnaire for identifying COPD in smokers. *Respiration* 2006; 73: 285-295.

<sup>15</sup> Martinez FJ, Raczek AE, Seifer FD, Conoscenti CS, Curtice TG, D'Eletto T, et al.: Development and initial validation of a self-scored COPD Population Screener Questionnaire (COPD-PS). *COPD* 2008; 5: 85-95.

<sup>16</sup> Sichletidis L, Spyratos D, Papaioannou M, Chloros D, Tsiotsios A, Tsagaraki V, Haidich AB: A combination of the IPAG questionnaire and PiKo-6<sup>®</sup> flow meter is a valuable screening tool for COPD in the primary care setting. *Prim Care Respir J* 2011; 20: 184-189.

<sup>17</sup> Hanania NA, Mannino DM, Yawn BP, Mapel DW, Martinez FJ, Donohue JF, Kosinski M, Rendas-Baum R, Mintz M, Samuels S, Jhingran P, Dalal AA: Predicting risk of airflow obstruction in primary care: validation of the lung function questionnaire (LFQ). *Respir Med* 2010; 104: 1160-1170.

<sup>18</sup> Spyratos D, et al. Comparison of Three Screening Questionnaires for Chronic Obstructive Pulmonary Disease in the Primary Care. *Respiration* 2017; 93:83-89 DOI: 10.1159/000453586.

<sup>19</sup> Jackson H, Hubbard R. Detecting chronic obstructive pulmonary disease using peak flow rate: cross sectional survey. *BMJ*. 2003; 327(7416):653-654. doi:10.1136/bmj.327.7416.653.
 <sup>20</sup> Kaplan AG, Balter MS, Bell AD, Kim H, McIvor RA. <u>Diagnosis of asthma in adults</u>. *CMAJ*. 2009 Nov 10; 181(10):E210-20. PMID: 19770241.

<sup>21</sup> Aaron S, Boulet LP, Reddel H, and Gershon A. Underdiagnosis and Overdiagnosis of Asthma. *Am J Respir Crit*. <u>https://doi.org/10.1164/rccm.201804-0682CI.</u>

<sup>22</sup> James AL, Wenzel S. Clinical relevance of airway remodelling in airway diseases. *Eur Respir J* 2007; 30:134-55.

<sup>23</sup> Kaplan A. What is new in COPD in 2018? *Canadian Geriatric Society Journal*. 2018 Jan 23; 8(1), 24-33. <a href="http://canadiangeriatrics.ca/2018/01/cme-journal-volume-8-issue-1/">http://canadiangeriatrics.ca/2018/01/cme-journal-volume-8-issue-1/</a>

<sup>24</sup> Guzman-Diaz E, Mannino D. Airway obstructive diseases in older adults: From detection to treatment. *J Allergy Clin Immunol* 2010;126:702-9.

<sup>25</sup> A. Dudvarski Ilic, V. Zugic, B. Zvezdin, et al. Influence of inhaler technique on asthma and COPD control: a multicenter experience. *Int J Chron Obstruct Pulmon Dis*, vol. 11, pp. 2509-2517, 201.

<sup>26</sup> Levy ML, Hardwell A, McKnight E, Holmes J. Asthma patients' inability to use a pressurised metered-dose inhaler (pMDI) correctly correlates with poor asthma control as defined by the Global Initiative for Asthma (GINA) strategy: a retrospective analysis. *Prim Care Respir J*, vol. 22, no. 4, pp. 406-411, 2013.

<sup>27</sup> Chrystyn H, van der Palen J, Sharma R, et al. Device errors in asthma and COPD: systematic literature review and metaanalysis. *NPJ Prim Care Respir Med*, vol. 27, no. 1, p. 22, 2017.

<sup>28</sup> Price DB, Roman-Rodriguez M, McQueen RB, et al. Inhaler errors in the CRITIKAL study: type, frequency, and association with asthma outcomes. *J Allergy Clin Immunol Pract*, vol. 5, no. 4, pp. 1071-1081, 2017.

<sup>29</sup> Hanania NA., Braman S, Adams SG, Adewuya R, Ari A, Brooks J, Mahler DA, Ohar JA, Peters J, Sanjar S. The Role of Inhalation Delivery Devices in COPD: Perspectives of Patients and Health Care Providers. *Chronic Obstr Pulm Dis* 5, no. 2 (2018): 111-23. <u>https://doi.org/10.15326/jcopdf.5.2.2017.0168</u>.
 <sup>30</sup> Kaplan A, Price D. Matching Inhaler Devices with Patients: The Role of the Primary Care Physician. *Can Respir J* Volume 2018, Article ID 9473051, https://doi.org/10.1155/2018/9473051.

<sup>31</sup> Yawn BP, Colice GL, Hodder R. Practical aspects of inhaler use in the management of chronic obstructive pulmonary disease in the primary care setting. *Int J Chron Obstruct Pulmon Dis*, vol. 7, pp. 495-502, 2012.

<sup>32</sup> Kauppi P, Linna M, Jantunen J, et al. Chronic comorbidities contribute to the burden and costs of persistent asthma. *Mediators Inflamm*, vol. 2015, Article ID 819194, 2015.

<sup>33</sup> Allen SC, Jain M, Ragab S, Malik N. Acquisition and short-term retention of inhaler techniques require intact executive function in elderly subjects. *Age and Ageing*, vol. 32, no. 3, pp. 299-302, 2003

<sup>34</sup> Yawn BP, Colice GL, Hodder R. Practical aspects of inhaler use in the management of chronic obstructive pulmonary disease in the primary care setting. *Int J Chron Obstruct Pulmon Dis*, vol. 7, pp. 495-502, 2012.

<sup>35</sup> Bosnic-Anticevich S, Chrystyn H, Costello RW, et al. The use of multiple respiratory inhalers requiring different inhalation techniques has an adverse effect on COPD outcomes [published correction appears in *Int J Chron Obstruct Pulmon Dis.* 2019 Aug 02; 14:1739]. *Int J Chron Obstruct Pulmon Dis.* 2016;12:59-71. doi:10.2147/COPD.S117196.

<sup>36</sup> Dekhuijzen PN, Lavorini F and Usmani OS, Patients' perspectives and preferences in the choice of inhalers: The case for Respimat<sup>®</sup> or HandiHaler<sup>®</sup>, *Patient Preference and Adherence* vol. 10, pp. 1561-1572, 2016.

<sup>37</sup> Loh CH, Peters SP, Lovings TM, Ohar JA. Suboptimal Inspiratory Flow Rates Are Associated with Chronic Obstructive Pulmonary Disease and All-Cause Readmissions. *Ann Am Thorac Soc.* 2017 Aug; 14(8):1305-1311. doi: 10.1513/AnnalsATS.201611-9030C.

<sup>38</sup> Kaplan A, Hess M, Price D. Peak inspiratory flow (PIF) assessment tool: a simple tool for assessing the risk of suboptimal PIF (sPIF) in chronic obstructive pulmonary disease (COPD) [abstract American Academy of Family Physicians, AAFP, conference 2019].

<sup>39</sup> Jarvis S, Ind PW, Shiner RJ. Inhaled therapy in elderly COPD patients; time for re-evaluation? *Age and Ageing*. 2007 Mar; 36(2):213-8. doi: 10.1093/ageing/afl174.

<sup>40</sup> Mahler DA, Waterman LA, Gifford AH. Prevalence and COPD phenotype for a suboptimal peak inspiratory flow rate against the simulated resistance of the Diskus® dry powder inhaler. *J Aerosol Med Pulm Drug Deliv*. 2013 Jun; 26(3):174-9. doi: 10.1089/jamp.2012.0987.

<sup>41</sup> Sharma G, et al. Prevalence of Low Peak Inspiratory Flow Rate at Discharge in Patients Hospitalized for COPD Exacerbation. *Chronic Obstr Pulm Dis* vol. 4, 3 217-224. 15 Jul. 2017, doi:10.15326/jcopdf.4.3.2017.0183.

<sup>42</sup> Mahler DA. Peak Inspiratory Flow Rate as a Criterion for Dry Powder Inhaler Use in Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* 2017 Jul; 14(7):1103-1107. doi: 10.1513/AnnalsATS.201702-156PS. PMID: 28481631.

<sup>43</sup> Broeders ME, Molema J, Hop WC, Vermue NA, Folgering HT. The course of inhalation profiles during an exacerbation of obstructive lung disease. *Respir Med.* 2004 Dec; 98(12):1173-9. doi: 10.1016/j.rmed.2004.04.010. PMID: 15588037.

<sup>44</sup> Kaplan A, van Boven J. Switching inhalers: a practical approach to keep on UR RADAR *Pulmonary Therapy (in press).*