Review Article on Current Epidemiology and Policies of COPD Worldwide

The narrative review of chronic obstructive pulmonary disease management in Turkey: medical treatment, pulmonary rehabilitation and endobronchial volume reduction

Ipek Candemir^

Ataturk Chest Disease and Chest Surgery Education and Research Hospital, Ankara, Turkey

Correspondence to: Ipek Candemir, MD. Ataturk Chest Disease and Chest Surgery Education and Research Hospital, Ankara, Turkey. Email: ipekcayli@yahoo.com.

Abstract: Chronic obstructive pulmonary disease (COPD) is one of the most common chronic diseases. In Turkey, the prevalence of COPD has been shown at rates of 9.1% to 19.1%, and COPD was found to be the third leading cause of mortality and eighth leading cause of disability. In several national multicentral studies, a high rate of non-adherence to pharmacologic treatment according to GOLD was found to be high, and the most commonly prescribed treatment was the triple regimen. The most important non-pharmacologic treatment of COPD is pulmonary rehabilitation (PR), which is also highly recommended in Turkey, but it is also underutilized, like in other countries. Awareness of healthcare professionals and patients should increase in Turkey. The recommendations in content and modality of programs are similar to international guidelines. Another non-pharmacologic treatment is endobronchial volume reduction (EBVR). Although there is limited number of studies about EBVR, in national reports, the importance of patient selection, method, close follow-up after intervention, and applications in experienced centers are emphasized to decrease the economic burden of this expensive treatment. There is still great need for further randomized studies about pharmacologic and non-pharmacologic treatment and additionally, a close collaboration between healthcare professionals, physicians, professional societies of pulmonology, planners of reimbursement system, patients, patient advocacy groups and the general public should be established.

Keywords: Pharmacologic treatment; pulmonary rehabilitation; endobronchial volume reduction

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable airway disease with persistent and progressive respiratory symptoms and air flow limitations. Risk factors for COPD are smoking, outdoor, indoor and occupational air pollution, and aging of the world's population (1,2). In a subgroup analysis of the ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints), the rate of current smokers was found to range from 25% to 42% (3). As expected, the prevalence of the number of current smokers was higher in patients with COPD than healthy subjects in previous international studies (4,5). The Global Adult Tobacco Survey in Turkey conducted in 2012 showed that the total prevalence of current smoking was 27.1%, and 41.5% in men and 13.1% in women (6). In a study published in 2018, the rate of current smokers in patients with COPD was 49% (50% among males and 33.3% among females) in the Eastern Black Sea region of Turkey (7). The rate was similar to previous

^ ORCID: 0000-0002-9877-3516.

national studies (8,9). In a recent multicenter study from Turkey, it was found that 56.3% of 776 patients with newly diagnosed COPD were current smokers, 38.1% of whom were ex-smokers and 7.2% had history of biomass exposure (10). Biomass such as organic fuels usually cause indoor air pollution in rural areas of Turkey. In a study that was conducted in women from rural and urban areas of Turkey, women living in rural areas with exposure to biomass fumes were more likely to be diagnosed as having COPD than urban women (12.4% *vs.* 3.9%), in spite of the prevalence of smoking being higher in the urban group (11). Another important risk factor is air pollution. A strong association has been shown between ambient levels of particulate matter (PM 2.5/10) and the prevalence of COPD (12,13). According to measurements performed in 2019, air pollution level was over 20 μg/m^3 PM_{10} in 98% of Turkey which was recommended over the upper limit according to World Health Organisation (14).

Prevalence, morbidity, and mortality of COPD vary across countries. The estimated number of patients with COPD was 384 million in 2010, and the estimated global prevalence of post-bronchodilator COPD was reported as 12.16% (10.91–13.40%) (15). Similarly, in studies conducted in Turkey, prevalence of COPD has been shown to range from 9.1% to 19.1% in subjects who were aged over 40 years (16-18). Additionally, mortality rates have been found to be high worldwide, but vary among countries. Since 2016, COPD has been the third leading cause of death worldwide, with an estimated 3 million deaths (5.3% of all deaths) (19). Similarly, according to the Turkish national disease burden report, it was shown that COPD was the third leading cause of mortality and eighth leading cause of disability, which causes a great national burden (20).

Since COPD is a preventable, treatable, frequent and important disease, it is important to reduce the risk factors and establish optimal management for these patients. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) documents, which are reported in most literature, and are accepted globally, have been revised regularly. In Turkey, the updates and recommendations of GOLD are followed and discussed. In this review, it is aimed to present national recommendations and studies about pharmacologic treatment according to GOLD document and non-pharmacologic treatment consisting of pulmonary rehabilitation (PR) and endobronchial volume reduction in Turkey.

The search engines including PubMed, Science Direct, and Google Scholar were used for search terms included 'Turkey' AND 'COPD' OR 'Chronic obstructive pulmonary disease' AND 'pharmacologic treatment' OR 'medical treatment' OR 'pulmonary rehabilitation' OR 'endobronchial valve and coil implantation' OR 'endobronchial volume reduction' in English and Turkish. The guidelines, expert reports, review of the Turkish chest physician societies, studies were investigated.

We present the following article in accordance with the Narrative Review Reporting Checklist (available at http://dx.doi.org/10.21037/jtd-20-2271).

Pharmacologic treatment in Turkey

The target of COPD management is to decrease symptoms, disease severity, the number of exacerbations, and improve exercise capacity and health status in order to decrease the social and economic burden of the disease according to worldwide guidelines (1,21). In national reports, it was mentioned that pharmacotherapy should be arranged according to the risk of exacerbation, adverse effects of bronchodilators, patent selection, comorbidities, ability of using inhaler devices, and the cost of medications (22,23). There are several international studies including Turkish researchers, and national studies regarding COPD treatment. A multi-center, cross-sectional, observational study including 719 patients with COPD (2.2% stage I, 33.1% stage II, 48.1% stage III, and 16.6% stage IV according to GOLD 2010) showed that the most commonly prescribed medication was long-acting muscarinic antagonists+ long-acting beta-agonists + inhaled corticosteroids (LAMA + LABA + ICS) with a rate of 43.4%. The rate of using treatment containing ICS was 89%. The authors suggested that the reasons for the preference of triple-treatment were inadequate time with patients in outpatient clinics, concerns about symptom and exacerbation control, reimbursement of all bronchodilators in Turkey in 2010. It was concluded that new strategies should be developed for the treatment of COPD to avoid non-adherence and overtreatment in Turkey (24).

In another multicenter, cross-sectional study from Turkey, 307 patients with COPD were grouped according to spirometric classification and the combined classification of GOLD 2011. 7.5% of patients were stage I, 62.5% were stage II, 25.4% were stage III, and 4.6% were stage IV. According to GOLD 2011 combined classification of COPD, 23.8% of patients were in group A, 23.1% in group B, 13.4% in group C, and 39.7% in group D. It was demonstrated that one-

third of stage I and II patients were classified as group C or D. The most common type of inappropriate treatment regimen was overtreatment. The most common overprescribed medication was ICS in 58% of patients using LABA + LAMA + ICS. It was suggested that overtreatment of ICS could be due to the high use of ICS/LABA combination products in Turkey. Additionally, it was found that treatment according to the combined classification was more cost effective due to the fact that appropriate treatment in the combined classification was slightly higher than spirometric classification (97.1% *vs.* 93.1%). The authors suggested that this could have been one of the reasons for developing the new assessment system. The non-adherence to the new classification in both Turkey and other countries was mentioned, and the investigators concluded that the interaction between the guideline authorities and pulmonologists should be improved, and better strategies should be developed in order to increase physician adherence to these guidelines (25).

There are also several studies from Turkey regarding treatment based on only the GOLD combined assessment. In another the multicenter, non-interventional, prospective, real-life observational study from Turkey, 776 newly diagnosed patients were not receiving any medication before the study, and it was found that one-third of them were in group C or D according to GOLD 2011 because 12.6% of the patients had a history of frequent exacerbation before being diagnosed as having COPD. It was demonstrated that more than 70% of the patients were overtreated. The most commonly prescribed medication was LABA+LAMA+ICS with a rate of 54.9% (10). In another multi-center cross-sectional study from Turkey called ALPHABET, 1610 patients with COPD were recruited and it was reported that 41.1% of the patients with COPD were in group A according to the GOLD 2013. Similar to previous studies, 37.2% of the patients were in group C and D. Additionally, LABA + LAMA + ICS was the most frequently prescribed regimen with a rate of 62.0%. Overtreatment was found to be in 70%. It was also found that for the assessment of symptoms, the mMRC was used more often (80.1%) than CAT (1.3%), and for the assessment of risk, the number of exacerbations (52.0%) was used more commonly than FEV1 (18.9%) in the combined COPD assessment. The high rate of non-adherence and overtreatment were also mentioned, and it was concluded that the selection of symptom or risk assessments could change the categorization of patients significantly (26).

In the 2015 GOLD document, due to the inconsistency between the GOLD management strategies and real life, it was recommended to modify managements according to local needs. A new flow-chart was developed by some Turkish pulmonologists because of the high rate of non-adherence to GOLD in Turkey in 2016. In this flow-chart, the assessment of dyspnea as mMRC ≥2 was recommended initially, and if answered as yes then patients were put in group B or D; if no, patients were in A or C. Secondly, the assessment of risk (post-bronchodilator FEV1 <50% of predicted/2 or more exacerbations/1 or more exacerbations needing hospital admission) was recommended. If all was no, patients were grouped into group A or C, if there was any yes, into group B or D. Finally, the recommended first-choice treatment in group A was short-acting muscarinic antagonists (SAMA) or short-acting beta-agonists (SABA), in group B LAMA or LABA, in group C ICS + LABA or LAMA, and in group DICS + LABA and/or LAMA (27).

After the 2017 GOLD criteria were launched, in the view of the Turkish Thoracic Society (TTS) in the Report of the GOLD 2017 Global Strategy for the Diagnosis, Management, and Prevention of COPD, it was mentioned that GOLD 2017 treatment recommendations had some limitations, especially in groups C and D. The Turkish authors suggested that the recommendations of GOLD were based on studies containing heterogeneous patients, and there was no study that was prospectively designed according to the definition of groups C or D. Additionally, although spirometric stage was removed in GOLD 2017, primary outcome in most clinical trials was change of FEV1. Furthermore, most studies on exacerbation had recruited patients with one or more exacerbations (22). Only in the FLAME study 19% of the patients have two or more exacerbations. In patients with severe exacerbations, comparable results were shown between the LABA + LAMA and ICS + LABA treatment groups. In this study, it was also found that most exacerbations were seen during the follow-up period (28). In the TTS report, it was concluded that the evidence levels of the recommendations were low due to these reasons. In Turkey, because ICS are overprescribed (27), the TTS recommended to start pharmacologic therapy with one bronchodilator (LABA or LAMA), and during follow-up, in the event of the presence of persistent symptoms, the other bronchodilator group might be added. It was also recommended that ICS could be added in the event of two moderate or one severe exacerbation. Otherwise, when the patient had fewer exacerbations, ICS might be removed from the treatment. The need of close follow-up to optimize treatment was mentioned (22).

According to COPD assembly of the Turkish Respiratory Society 2017 report, in group A patients, a short or long-

acting bronchodilator was recommended; in group B, LABA or LAMA, if persisting symptoms LABA + LAMA; in group C, LAMA, if persisting symptoms LABA + LAMA or ICS+LABA; in group D, LABA + LAMA, if persisting symptoms LABA + LAMA + ICS or ICS + LABA. It was recommended that when there were persisting symptoms despite triple-therapy, ICS might be stopped and theophylline, roflumilast or macrolide could be added (23).

Since September 2019, the LABA + LAMA + ICS triple combination has received reimbursement by the Turkish Institution of Social Insurance in patients who have been treated with ICS and LABA for at least 3 months, but have not received adequate response, have frequent attacks (2 or more attacks per year or 1 or more history of hospitalization) and dyspnea (mMRC 2 and above or CAT score of 10 and above). It remains to be seen as to whether this adjustment will affect overtreatment of the triple combination. Nevertheless, use of ICS is still controversial in Turkey. Additionally, there has been lack of data about adherence to escalation and de-escalation of treatment.

The recommendation for the use of roflumilast and azithromycin in Turkey is similar to GOLD. Since 2014, roflumilast got has received reimbursement by the Turkish Institution of Social Insurance in patients with cough and sputum symptoms lasting at least 3 months and 2 or more exacerbations per year for at least 2 years and FEV1 ≤50% in spite of long-acting bronchodilator and/or ICS therapy. In a recent study from Turkey, 83 patients with COPD in group C and D with chronic bronchitis symptoms using roflumilast were analyzed retrospectively and a significant decrease was found in both COPD exacerbations and hospitalizations when compared with the pre-treatment period (29). Azithromycin is used more commonly in exacerbations than in stable COPD in Turkey. Although the prescription rate of theophylline is not low in Turkey, theophylline is recommended unless long-term bronchodilators are unavailable or unaffordable according to GOLD. The accurate rate of use of these molecules in stable COPD has not been shown in studies.

Overtreatment, due to the over prescribing triple treatment, has been the most important problem in pharmacological treatment at least for 10 years in Turkey, even the Turkish authors, societies adjusted the GOLD recommendations for Turkish chest physicians. The chest physicians should follow national recommendations. Additionally, the further randomized multi-centered studies are needed for determining the rate of prescribing the ICS and triple treatment after the recent revised reimbursement.

Non-pharmacologic treatment: pulmonary rehabilitation in Turkey

Non-pharmacologic treatment is advised to be complementary to pharmacologic treatment and should be part of the comprehensive management of COPD. After prescribing medications, quitting smoking, vaccinations, adherence to treatments, being physically active or pulmonary rehabilitation (PR) are recommended (1). Similarly, in national reports, adjusting pharmacologic treatment, smoking cessation, comorbidity assessment, vaccinations, physical activity, and PR (22,23,27) are recommended. PR as a corner stone of integrated care and an evidenced-based effective approach is recommended for patients with COPD. PR has several benefits such as improving exercise capacity, health status, dyspnea, symptoms of anxiety and depression, recovery from exacerbations, number of hospitalizations, and health costs (1,30,31). It has been shown to be the most effective treatment to improve dyspnea, health status, and exercise in tolerance; however, it is still underutilized.

Underutilization is major problem of PR all around the world. It may be due to limited numbers of PR centers/units, reimbursement strategies, and awareness of health professionals and patients, because it is based on a country's resources. There are 22 units/centers in Turkey (32), which has 81 cities and a population of 83,154,997 people (33). Reimbursement types are different around the world. Programs are more likely to be reimbursed in Europe by governments (34), similarly in Turkey. In a study in which the records of patients with COPD who underwent PR were obtained from Turkish Institution of Social Insurance, the rate of the 3.214–18.664 COPD patients who underwent PR was about 0.32–0.59% per year, 52.0-94.8% of the programs were prescribed by a chest physician, and 62.9% of the patients received PR in secondary public hospitals between 2008 and 2016. Although these low rates could be due to the higher number of patients with COPD, the authors suggested that it was due to the low number of PR centers and units, and the low awareness of PR among both health professionals and patients (35). In other studies, it has been shown that the knowledge level of primary healthcare providers on COPD and PR were inadequate (36) and besides healthy subjects, patients with COPD did not have enough information about COPD in Turkey (37,38).

Another important problem is non-adherence to PR

programs worldwide. In most of these studies, the drop-out rate was 20–30% (39). In a recent review, those reasons were demonstrated as travel and transport problems, a lack of perceived benefit of PR, being a current smoker, illness, and depression (40). Similarly, a 2-year long study from Turkey showed the rate of drop-out as 22.3% in patients with chronic respiratory disorders. These patients had decreased exercise capacity and sensation of dyspnea (41). Similarly, in Turkey, the most common reasons for non-adherence of PR were found to be the inability of understanding the efficacy and contents of PR program, lack of motivation, and transportation problems (41,42).

According to recent guidelines, patients with remaining symptoms or limited functional capacity, and frequent exacerbations despite optimal pharmacologic treatment should receive PR (43-47). The same recommendations prevail in Turkey (48). Although smoking is not an exclusion criterion, there are also suggestions about referring patients to PR who have quit smoking (49). In Turkey, smoking is not an exclusion criterion, and there is also no cut-off value for FEV1 or age for referring or attending PR. It was also shown that PR was an effective treatment strategy for patients with COPD regardless of FEV1 values or older age (50,51).

PR program staffing also differs across countries (34,52,53), depending on the program settings and available resources. Conventional PR programs typically include one or more physiotherapists, nurses, a respiratory therapist, a respiratory physician (medical director), and may also include a health psychologist, dietician, occupational therapist, pharmacist, social worker, and other staff (34,52,53). In Turkey, multidisciplinary staff is recommended (48), but most units consist of a minimum staff structure with a physician, physiotherapists, and a nurse. There has been one multidisciplinary center integrated with a homecare unit since 2007 and a chronic respiratory failure service since 2011. This center consists of a chest physician as a medical director, on-site chest physician, three physiotherapists, a dietitian, psychologist, elderly care technician, and two nurses. In the other 21 PR units, a chest physician is the medical director in 13 units, and physical medicine and rehabilitation physicians are in other units (32).

The structure and the setting of PR is also different across countries. PR programs can be performed as in inpatient, hospital or community-based outpatient or home-based settings (54-56). The most common is hospital-based outpatient programs (43,54) similar to Turkey. Community-based outpatient programs do not exist in Turkey yet. Synchronized video conferencing tele-PR has been performed recently. A home-based model has been performed, supervised home-PR is performed by another center, but unsupervised home-PR is more common. In Turkey, similar to other countries, home-based programs have been found to be effective, but not as effective as out- and inpatient supervised programs (43,54,57).

Although there is no international or national recommendation about optimum duration of PR programs, 8 to 10 weeks of PR has been shown to improve dyspnea, fatigue, anxiety and/or depression, physical capacity, and quality of life in patients with COPD (58-61). The most of the PR programs in Turkey last 6–8 week. It is recommended that the duration of individualized programs should be based on achieving goals and patient-centered outcomes according to assessments (48). In a recent review from Turkey, the initial examination was recommended to include medical history, smoking habit, symptoms, medications, comorbidities, routine laboratory blood tests, chest X-ray, electro and echocardiography, pulmonary function tests, arterial blood gas analysis; a physical examination comprising assessment of exercise capacity, nutritional evaluation, assessment of life quality, psychosocial status (anxiety, depression), daily living activities, occupational performance, motivation level, need for social support, need for devices (oxygen treatment, non-invasive mechanical ventilation, walker, wheelchair); and determination of transportation problems, social support, and financial resources (48). After initial assessments, comprehensive individual programs should be structured.

Exercise training is main components of PR. International recommendations about exercise training are similar to Turkey (48,62-67) in order to increase exercise capacity, muscle strength, and endurance, which was found to be related with 8-year mortality in patients with COPD in a study from Turkey (68). Like lower limb exercise training, upper limb exercise training is also important. In studies from Turkey, upper limb strength, which was found to correlate with exercise capacity, quality of life, and dyspnea in patients with COPD (69), and upper limb strength training was shown to improve quality of life and occupational performance in patients with COPD (70). Additionally, patients with severe dyspnea and those who are unable to train at target intensity, neuromuscular electrical stimulation (NMES) can be performed. However, NMES was not found as effective as conventional PR in exercise capacity, but similar improvements in dyspnea, quality of

life and anxiety, and depression scores were observed (71). In another study from Turkey, similar gains in exercise capacity were found in patients with COPD (72). In patients with COPD, inspiratory muscle weakness may also exist like peripheral muscle weakness. Inspiratory muscle training (IMT) is recommended in these patients according to national and international recommendations. In a recent review from Turkey, IMT is recommended in patients with inspiratory muscle weakness [maximal inspiratory pressure (PImax) ≤60 cmH_2O] with initial intensity with 30% of PImax and to increase the intensity gradually (48). It was shown that IMT performed with exercise training provided more benefit on inspiratory muscle strength and endurance, and exercise capacity (73).

Other important components of multidisciplinary PR are psychological and nutritional status, body composition assessment, and support if needed, and education of patients and care givers. In national and international studies, more gains in body weight were found after nutritional supplementation as a component of multidisciplinary PR, than with nutritional support alone (74-77).

As it is recommended in Turkey, education of patients and their families, and care givers should be part of the PR program. Patient education should be planned in accordance with the patient's previous experiences, education level, beliefs, attitudes, education, and social and cultural level. Simple booklets, brochures, videotapes, and real applications are used for educational purposes. The training can be performed in small groups or individually according to the needs of the patients, the content of the rehabilitation program, location, and resources (67). In a recent study from Turkey, it was shown that self-management training improved the quality of life and reduced the symptoms of depression and anxiety in patients with COPD (78).

Immediately after multidisciplinary comprehensive PR programs, an assessment of efficacy is recommended (48). Due to the decreasing benefits of PR in time, follow-up programs or maintenance strategies should be structured; however, no recommended maintenance program has been identified in Turkey or other countries yet.

The most important problem is limited number of PR center/units. It is probably due to the low demand associated with the decreased awareness of chest physicians, healthcare providers, patients, payers. The professional societies should be encouraged to participate in education in after mentioned groups. Health policies that will ensure equity in health care should be developed about PR in patients with chronic respiratory disease. An increase in funding and resources for PR is essential. The resources should be provided for the establishment of PR units in hospitals in all over the country. The further randomized studies on long-term benefits, cost effectiveness and mortality are needed and the reimbursement should also be revised.

Non-pharmacologic treatment: endobronchial volume reduction in Turkey

Another non-pharmacologic treatment for emphysema is endobronchial bronchoscopic volume reduction. Endobronchial valve replacement and coil implantation are the main bronchoscopic interventions. In selected cases, this treatment reduces end-expiratory lung volume and improves exercise capacity, lung function, and health status after 6–12 months (1). The most common complications are pneumothorax, pneumonia, hemoptysis, and exacerbation of COPD (1). Similarly, in a single-center study from Turkey, significant improvement was shown in pulmonary functions and quality of life in selected patients with advanced emphysema after endobronchial coil implantation who had lower morbidity and mortality than with lung volume reduction surgery after intervention (79). In a recent study from Turkey, the data from patients who underwent endobronchial valve or coil placement were analyzed. It was found that the presence of more than one comorbidity in patients who underwent coil treatment was related to mortality. The mortality rate was higher (37.5% *vs.* 10.5%) in patients with coils than in those with valves in the presence of multiple comorbidities, but it was not found to be statistically significant. Authors concluded that in patients with severe emphysema with more than one comorbidity, valves were likely to be a better choice than coils (80).

In another single center study from Turkey, authors compared the complications and outcomes such as pulmonary functional tests and exercise capacity in 60 COPD patients. They found similar outcomes and no mortality was observed following neither of interventions. Pneumothorax was the most prevalent complication [3 patients (9.7%)] followed by cardiac arrhythmia in 2 patients (6.5%) after endobronchial valve placement while complications after coil implantations were pneumonia in 3 patients (10.3%), COPD exacerbation in 2 patients (6.9%) and pneumothorax in one patient (3.4%). Hypernatremia and arrhythmia have been not reported previously in national literature. As the authors mentioned, it could be due to the small number of patient

groups, underlying comorbidities and the experience of the team performing the procedure (81). In another single-center study, endobronchial valve placement was performed in 15 patients. Early complications were observed in five patients (33.3%) during the 3-month follow-up period after the EBV treatment (three chronic obstructive pulmonary disease exacerbation, one pneumothorax, and one pneumonia) (82).

In recommendations from national society consensus reports, it is declared that patient selection criteria should be evaluated before each procedure and PR should be planned before and after the procedure. Appropriate patient and method selection should be made by the decision of the multidisciplinary council (pulmonologist, radiologist, pulmonary rehabilitation specialist, thoracic surgeon, and if possible, a nuclear medicine specialist) (83).

Since September 2019, endobronchial volume reduction treatment has been reimbursed under the directives of Ministry of Health which required a report from a medical board including chest disease and/or thoracic surgery specialists in tertiary hospitals, for patients with documented advanced stage COPD completing a PR program.

Endobronchial therapy has also recently become very popular in Turkey, but the exact utilization figures is not currently known. But still, the number of experienced centers in Turkey is quite limited. On the other hand, this treatment modality is still very expensive and have potentially drastic complications. Therefore, the importance of optimal patient and method selection for endobronchial bronchoscopic volume reduction treatments, close follow-ups, and performing these procedures in selected experienced centers have also been mentioned in national reports in order to reduce the economical burden (22,84). But still, there is need for further studies.

Limitations of this review mainly include limited number of published studies especially about endobronchial volume reduction.

Conclusions

The Turkish recommendations for pharmacologic treatment of COPD, PR and endobronchial volume reduction are in line with international guidelines. Similar problems and obstacles are also seemingly present in most countries as well as Turkey. The chest physicians should follow national recommendations about COPD treatment, PR and endobronchial volume reduction. The awareness of physicians, patients, stakeholders of reimbursement system is both the most important issue and solution for the increasing the number of patients receiving effective PR, and selection criteria for endobronchial valve replacement and coil implantation should be implemented in detail. There is still great need for further randomized studies about pharmacologic and non-pharmacologic treatment and additionally, a close collaboration between healthcare professionals, physicians, professional societies of pulmonology, planners of reimbursement system, patients, patient advocacy groups and the general public should be established.

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Footnote

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