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REVIEW

# Improving Physiological, Physical, and Psychological Health Outcomes: A Narrative Review in US Veterans with COPD

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**Abstract:** The Veterans Health Administration (VHA) is the largest integrated healthcare system in the United States (US) providing healthcare to an increasing number of middle-aged and older adults who remain at greater risk for chronic obstructive pulmonary disease (COPD) compared to their civilian counterparts. The VHA has obligated research funds, drafted clinical guidelines, and built programmatic infrastructure to support the diagnosis, treatment, and care management of Veterans with COPD. Despite these efforts, COPD remains a leading cause of morbidity and mortality in Veterans. This paper provides a narrative review of research conducted with US Veteran samples targeting improvement in COPD outcomes. We review key physiological, physical, and psychological health outcomes and intervention research that included US Veteran samples. We conclude with a discussion of directions for future research to continue advancing the treatment of COPD in Veterans and inform advancements in COPD research within and outside the VHA.
**Keywords:** chronic obstructive pulmonary disease, U.S. Veterans, interventions

## Introduction

Approximately 7–8% of adults in the United States (US) currently identify as Veterans of the Armed Forces; of these, approximately 42–49% are recipients of Veteran Affairs (VA) benefits, which include services such as healthcare, disability compensation or pension, loan and insurance programs, and burial services.[1,2] In general, Veterans who complete a minimum 24 months of service with an honorable discharge are eligible for healthcare through the Veterans Health Administration (VHA), one of the largest nationally integrated systems. Although VA benefits are available to most Veterans, due to priority assignments for enrollment (based on service connection, disability, and income) and copays, the approximately 9 million Veterans who currently utilize VA healthcare and participate in VA-sponsored research represent a unique subset of the Veteran population.[1,2]

Recipients of VA healthcare are typically older than the general population (median age 64 versus 38 years, respectively) and are predominantly (91%) male, although enrollment of female Veterans is rising.[1,2] The proportion of Veterans who utilize VA with an annual household income less than $35,000 is higher than that of the general US population (43% versus 26%)[1,3] as is the prevalence of ever-smoking (60% versus 35–40%).[1,2,4] Economic disadvantage and increased rates of smoking, coupled with service-related and occupational exposures, have likely contributed to the high prevalence and rising incidence of chronic respiratory diseases, including chronic obstructive pulmonary disease (COPD), among Veterans.[5,6]

COPD is not objectively different in terms of disease manifestation in Veterans compared to civilians.[7] However, the prevalence of COPD among Veterans, which is currently estimated to be between 8% and 19%,[6,8] is higher than among the general population (6%).[9] Importantly, COPD is likely underdiagnosed among Veterans, with only a minority of

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individuals with objective airflow limitation on lung function testing reporting a clinical diagnosis of COPD.[10] Veterans with COPD have increased all-cause and respiratory-related health-care utilization as well as higher rates of comorbid conditions relative to Veterans without COPD.[6] Moreover, the prevalence of mental health conditions, particularly alcohol and substance abuse, is higher in Veterans compared to civilians.[11] Comorbid mental health conditions commonly serve as a barrier to utilization and/or responsiveness to evidence-based care, such as self-management interventions.[12] Given the prevalence and significant burden of COPD within the VHA, substantial resources have been applied towards both clinical and research initiatives to improve outcomes for Veterans with COPD.

The VHA provides evidence-based treatment to Veterans with COPD in order to optimize physiological, physical, and psychological health. These treatments and interventions are comprehensively described in the Global Initiative for Obstructive Lung Disease (GOLD) guidelines.[13] Notably, Veterans with COPD and VHA researchers have contributed to early research examining such treatments and interventions to improve COPD outcomes. The objective of this paper is to provide a narrative review of interventions for key physiological, physical, and psychological health outcomes in US Veterans. Articles were identified if they were conducted with US Veterans and broadly addressed interventions for physiological, physical, or psychological outcomes.

## Physiological Outcomes and Interventions to Optimize Them in Veterans with COPD

Due to the high burden of COPD within the VA, Veterans and VHA investigators have been involved in studies which have contributed to the collective knowledge on COPD physiology. Physiological and clinical outcomes which have been examined among Veterans with COPD have included lung function, hypoxemia, and systemic effects associated with disease, such as alterations in body composition and bone mineral density. These studies support current evidence-based guidelines which include both pharmacological and non-pharmacological management of both stable COPD and acute exacerbations of COPD. Key studies examining these physiological and clinical outcomes are summarized below.

Longitudinal studies based within the VHA, such as the Normative Aging Study (NAS), have resulted in an improved understanding of and delineation between healthy aging and disease processes such as COPD.[14,15] Comprised of over 2000 participants who were first enrolled in 1963 who have triennial follow-up data,[16] the NAS represents a rich source of multi-dimensional information contributing to studies which have identified environmental (eg, smoking, air pollution)[17,18] as well as genetic, epigenetic, and genomic risk factors that affect lung function and COPD susceptibility.[14,15,17,19]

## Oxygen Supplementation

VHA research was a key stakeholder in establishing the detrimental effects of hypoxemia on not only end organ function but also reactive vasoconstriction in the pulmonary vasculature leading to pulmonary hypertension and cor pulmonale. Sentinel publications supported by the VHA include a brief report by Renzetti et al[20] in 1968 which established the associations between COPD and mortality, spirometric lung function, and hypoxemia. Findings from this observational report gave rise to numerous subsequent studies, both within and outside of the VHA, which established the safety and benefit of supplemental oxygen on exercise tolerance and dyspnea,[21] cardiovascular parameters,[21] and survival[22] among COPD patients with significant hypoxemia. As research practices evolved over the decades from single-site studies to multi-center collaborative initiatives, VA investigators continued to contribute to research on the management of hypoxemia in COPD patients. Multiple VA facilities served as research study sites for the Long-Term Oxygen Treatment Trial (LOTT) which examined oxygen supplementation for COPD patients with moderate resting or exercise-induced hypoxemia.[23] While the benefits of oxygen supplementation in COPD patients with severe resting hypoxemia (defined as an oxygen saturation ($SpO_2$) <89% or an arterial oxygen tension, $PaO_2$ ≤55 mmHg, or $PaO_2$≤59 or $SpO_2$≤89% with signs of cor pulmonale) had been previously established,[24,25] LOTT demonstrated that routine supplementation in moderate resting ($SpO_2$ 89–93%) or exercise-induced hypoxemia ($SpO_2$ 80–90%) was *not* associated with improved all-cause mortality or time to first hospitalization,[23] leading to a significant revision of management guidelines issued by the VHA, professional societies, and the GOLD recommendations.[13] Current guidelines on the initiation of oxygen supplementation (as outlined above) as well as the titration of supplemental oxygen to a goal $SpO_2$ >90–92% represent the integrated results of trials conducted both within and outside the VHA.

## Pharmacological Management

Veterans and VHA investigators have contributed substantially to studies of medications, such as bronchodilators, that improve symptoms through improvements in lung function by increasing airway diameter and decreasing air trapping and hyperinflation. Early trials examined systemic bronchodilators, such as theophylline[26] and metaproterenol,[27,28] and were later supplanted by studies of inhaled beta-agonists and antimuscarinic agents,[29] the two dominant classes of bronchodilators in use today. Use of long-acting inhaled beta-agonists and antimuscarinic agents is currently recommended as first-line, evidence-based maintenance therapies for COPD.[13] Additional studies of pharmacological agents have included investigations of the effect of morphine on dyspnea,[30] an important strategy for the palliative care of Veterans with advanced chronic lung disease associated with air hunger.

Significant morbidity is attributed to acute exacerbations of COPD and investigations into pharmacological strategies to treat and prevent these events have also involved Veteran populations. In a multi-center, randomized controlled trial (RCT) sponsored by the VA Cooperative Studies Program (CSP), systemic corticosteroids for Veterans hospitalized with acute exacerbations of COPD were found to reduce the incidence of a combined endpoint of all-cause mortality, mechanical ventilation, readmission for COPD, or escalation of therapy relative to placebo.[31] Systemic corticosteroids are now considered the standard of care for management of acute exacerbations of COPD,[13] although the optimal doses and duration of therapy remain active areas of investigation.

Significant resources have also been allocated to *preventing* acute exacerbations among COPD patients. Multiple VA medical centers served as research study sites for a RCT of chronic macrolide therapy using azithromycin to target chronic airways inflammation and prevent acute exacerbations of COPD.[32] Findings from the study, which examined daily azithromycin taken for a year in addition to usual therapy, were notable for decreased COPD exacerbations and improved health-related quality of life (HRQoL), but also increased risk for hearing loss. Chronic suppressive macrolide therapy is now endorsed by the GOLD guidelines as an adjunctive maintenance medication for exacerbation-prone individuals.[13]

The performance of roflumilast, another pharmacological agent for the prevention of exacerbations, was examined relative to chronic suppressive azithromycin use among Veterans. In this observational study, the unified medical records system within the VHA, known as the Corporate Data Warehouse, was examined along with Medicare usage data for 3875 Veterans. Results showed that roflumilast, an oral selective phosphodiesterase-4 inhibitor, was associated with *increased* all-cause mortality and COPD-related hospitalizations relative to chronic suppressive macrolide therapy.[33] The findings from this study supported the need for head-to-head studies of chronic macrolide therapy relative to roflumilast which are currently being investigated through an ongoing RCT (clinicaltrials.gov NCT04069312).

## Systemic Effects of COPD

Although airflow obstruction is the defining feature of COPD, there is increasing appreciation of the extra-pulmonary and systemic consequences of COPD. Due to the higher rates of and cumulative exposure to smoking, as well as intermittent use of systemic corticosteroids, COPD has been identified as an independent risk factor for osteoporosis among Veterans.[34] The clinical consequences of the increased prevalence of osteoporosis were subsequently confirmed in a study of 87,360 Veterans aged >50 years with newly diagnosed COPD between 1999 and 2003, where high rates of hip and wrist fragility fractures were observed.[35] Additional findings from this study included low rates of bone mineral density testing and anti-resorptive treatment (eg, bisphosphonates)[35] and identified a crucial need for screening for bone health among Veterans with COPD.

In addition to bone health, there has been increasing attention given to the impact of differences in body mass and body composition among Veterans with COPD. Body-mass index (BMI), a widely used metric of the weight-to-height relationship, is an integral component of the BMI, obstruction, dyspnea, and exercise limitation (BODE) index, which correlates with mortality and exacerbation frequency in COPD and has been validated in Veterans.[36] In addition to body mass, the role of fat-free mass, a proxy measure for muscle mass, and its relationship with functional outcomes and exercise tolerance in Veterans with COPD represent important future areas of research.[37]

## Care Coordination Interventions

Other work in Veterans to improve physical outcomes in COPD has focused less on the individual patient, and more on the quality and type of care the patient receives. Although the majority of COPD-related care is managed by primary care providers, Veteran access to specialty care and referrals patterns to pulmonologists for COPD are comparable to those in the general community.[38] A significant proportion of the morbidity and direct costs associated with COPD within the VHA arise from hospitalizations due to acute exacerbations of COPD.[8] In an effort to develop and introduce programs to reduce COPD hospitalizations, the VHA sponsored a multicenter RCT examining the efficacy of a multidisciplinary comprehensive care management plan comprised patient and primary care provider education, the development of an action plan for exacerbation management, and proactive case management relative to usual care.[39] Unfortunately, the study was terminated prematurely in 2012 due to *increased* rates of COPD-related hospitalizations and excess all-cause mortality in the intervention (comprehensive care) arm.[39] Notably, similar results for comprehensive care programs at non-VHA hospitals have subsequently been reported,[40] supporting that additional research and alternative strategies for preventing COPD hospitalizations are needed.

While effective strategies to prevent COPD hospitalizations remain an active field of investigation, programs to reduce the length of stay and prevent re-admissions have also received priority within the VHA. VHA-wide initiatives to reduce hospital utilization through expanded outpatient care resulted in a 51% reduction in length of stay for COPD exacerbations over 1994–1998, notably without increased mortality or non-VA hospital use.[41] Additionally, individual programs focused on coordinated transitional care, a nurse-driven, telephone-based program targeting high-risk patients with comorbid COPD and congestive heart failure prior to discharge to home at an urban VA medical center resulted in a 54% reduction in 30-day re-hospitalization risk and was shown to be cost-effective.[42] Moreover, one study examined the association of using non-VA outpatient care (both VA and non-VA care [ie, dual-care], and non-VA care only) and VA-only care with 30-day re-admission among Veterans. Overall, compared to Veterans who received VA-only care, Veterans who received dual-care and non-VA care only were 20% more likely to be readmitted for a COPD-specific exacerbation.[43] These initiatives likely explain the recent finding of lower rates for 30-day re-admissions following hospitalizations for COPD at VA relative to non-VA hospitals.[44]

## Physical Outcomes and Interventions to Improve Them in Veterans with COPD

An overarching goal in the treatment of Veterans with COPD is to maximize physical function. However, the clinical course of COPD can contribute to a vicious cycle of reduced function. Patients who experience dyspnea, a major symptom of COPD, tend to avoid physical activities that worsen dyspnea, causing further muscle deconditioning and reductions in exercise capacity.[45] Pain is another common symptom of COPD, which can also contribute to lower physical function.[46] Physical outcomes, such as dyspnea, exercise capacity, physical activity (PA), and pain, reflect potentially modifiable risk factors of all-cause and respiratory-related mortality.[47] As such, there has been great interest within VHA to develop effective interventions to improve physical outcomes in Veterans with COPD. The following sections detail several of these interventions, and highlight the impact of these interventions on dyspnea, PA, exercise capacity, pain, and risk for acute COPD exacerbations.

## Pulmonary Rehabilitation

Pulmonary rehabilitation (PR) is a well-established treatment of COPD, effectively improving exercise capacity, dyspnea, and HRQoL.[48] PR is a comprehensive intervention that focuses on exercise training and self-management education. It typically occurs 2–3 times a week across 8–12 weeks. Access to traditional, in-person PR can be difficult. In the VA with regional medical centers, distance is a significant barrier. In the National Emphysema Treatment Trial, participants who lived greater than 36 miles from the treatment facility were 51% less likely to complete PR compared to those who lived less than 6 miles away.[49] In one urban VA medical center, 25% of initially evaluated Veterans never started PR, 29% dropped-out, while only 46% completed a full course of 18 sessions.[50] Some Veterans who would benefit from PR decline participation due to access-related barriers, such as time and distance to travel to the program.[50,51] Earlier work within VA compared outcomes in Veterans who completed PR to Veterans who were referred to PR but declined.[52]

Overall, Veterans with COPD who completed PR significantly improved exercise capacity, as measured with the 6-minute walk test (6MWT) by an average of 75 m and reported a decrease in dyspnea on the UCSD Shortness of Breath Questionnaire by 7.3 points.[52] Additionally, COPD-related acute emergency visits and hospitalizations declined post-PR.[52] More recently, predictors of Veterans' PR engagement were examined through a retrospective study of Veterans who attended their initial PR intake session between 2010 and 2018.[50] Participants who dropped out of PR (ie, dropped out before session 18) compared to completers (ie, Veterans who completed all 18 session) had worse dyspnea, as measured by the Chronic Respiratory Questionnaire-Self-Reported (CRQ-SR) at baseline, and were more likely to be current smokers and have a history of alcohol use disorder. No differences emerged between those who never started and those who dropped out.[50] Thus, while PR is unequivocally effective for improving physical outcomes, it is important that future work continue to address ongoing access barriers to PR.

## Physical Activity and Exercise Interventions

Patients with COPD tend to engage in significantly less daily PA compared to healthy-matched controls.[53] Physical activity as an outcome is important in COPD, as it is directly associated with poor health outcomes such as increased risk of acute exacerbations and increased mortality, independent of lung function.[54] Many factors can contribute to lower levels of PA, including physiologic, behavioral, and environmental factors.[55] As such, there has been a substantial amount of work within VA to develop effective interventions that promote and sustain PA and exercise.

There have been several related RCTs examining the effectiveness of a web-mediated, pedometer-based PA intervention in Veterans with COPD (Taking Healthy Steps,[56] Every Step Counts,[57] and Walking and Education to Breathe[58]). This web intervention provides Veterans with COPD personalized daily step count goals, iterative feedback, disease-specific education, motivational tips, and an online community forum. Taking Healthy Steps was a RCT conducted virtually in a national sample of Veterans with COPD identified by diagnosis code. Compared to those who were randomly assigned to use a pedometer alone, those who were assigned to the website walked on average 779 more steps per day at 4 months.[56] Every Step Counts used a more well-characterized cohort (ie, COPD diagnosis validated via spirometry). Compared to the pedometer-only control group, Veterans assigned to the website significantly increased their daily step count by 804 steps at 3 months.[57] Those assigned to the intervention also demonstrated a significant reduced risk of experiencing a COPD acute exacerbation across a 12-month follow-up.[59] Walking and Education to Breathe, the most recent RCT, evaluated the effectiveness of the intervention across two VA sites to include a more heterogeneous sample, and examined if lengthening the duration of the intervention period to 6 months would translate into improvements in exercise capacity. At 6 months, participants who were assigned to the web-based intervention walked on average 1312 more steps per day compared to those who were assigned to usual care.[58] Across these three studies, despite the significant improvements in daily step count (779–1312), there were no significant differences between the intervention and control groups in changes with respect to exercise capacity (6MWT distance) or dyspnea (mMRC).[56–58]

Additionally, a priority in PR is to facilitate behavior change so patients will sustain engagement in long-term exercise. However, it remains difficult to maintain improvements in exercise after PR. Coultas et al tested the efficacy of a 20-week, telephone-based lifestyle PA intervention compared to usual care in COPD patients eligible for PR. They did not find significant differences for their primary outcome of 6MWT distance; however, subgroup analysis found that among Veterans with moderate COPD, the intervention resulted in stability of 6MWT distance at 18 months compared to participants who received usual care.[60]

In addition to daily walking, the effectiveness of alternative exercise forms, such as Tai Chi and yoga, has been explored in Veterans with COPD. Tai Chi may be a promising intervention to support physical outcomes. Compared to a mind-body breathing intervention, a Tai Chi intervention resulted in more substantial improvements in exercise capacity (6MWT distance) among persons with COPD.[61] Similarly, a recent pilot RCT found that Tai Chi after completion of PR may support maintaining exercise capacity (6MWT distance) compared to usual care in persons with COPD after completing PR.[62] Results from another RCT suggest that Tai Chi over 6 months may help to maintain exercise capacity.[63] However, participants in the RCT reported barriers to attending the Tai Chi program similar to those reported for center-based PR (ie, distance, time).[63] One recent pilot examined the effect of yoga training on inspiratory muscle performance.[64] Inspiratory muscle strength is impaired in patients with COPD and leads to debilitating dyspnea and poor functional performance.[65] Veterans were assigned to a 6-

week yoga training program that included poses (*asana*) and controlled breathing (*pranayama*). Inspiratory muscle performance (measured via the Test of Incremental Respiratory Endurance) significantly improved from baseline, although no significant improvements were seen in exercise capacity (6MWT distance).[64]

In many patients with COPD, dynamic hyperinflation of the lungs during exercise is a major contributor to decreased exercise capacity.[66] A recent study in Veterans examined if breathing retraining coupled with exercise training, a cornerstone of PR,[48] would improve exercise capacity more than exercise training alone.[67] Exercise training occurred via treadmill and took place three times every week for 12 weeks. The researchers used a metronome to provide acoustic feedback to train participants to achieve a slower respiratory rate and prolonged exhalation. Overall, despite achieving changes in breathing pattern with breathing retraining, improvements in exercise duration and dynamic hyperinflation were not significantly different with exercise training plus breathing retraining versus with exercise training alone.[68]

## Psychological Outcomes and Interventions to Optimize Them in Veterans with COPD

Depressive disorders are by far the most studied psychological disorder among Veterans with COPD. Rates of depressive disorder diagnosed by structured clinical interview range from 38% to 86% based on the study sample.[69,70] Rates of diagnosed anxiety disorders range from 23% to 61%.[69,70] Despite the high prevalence of depression and anxiety in Veterans with COPD, only a third receive any mental health treatment.[69] In cross-sectional studies of Veterans, clinically significant depression symptoms were associated with low PA levels,[71] worse self-reported functional impairment,[72–74] greater dyspnea,[72] and worse HRQoL.[72,73] Moreover, epidemiological studies in large samples of Veterans with COPD have shown that depression is associated with 1.53 times higher 30-day mortality compared to Veterans without depression.[75] Depression was also associated with 1.36 times increased risk of 30-day hospital readmission for COPD acute exacerbation.[75] Clinically significant anxiety among Veterans with COPD shows similar associations to health and functional outcomes such as depression. Anxiety symptoms are associated with greater self-reported functional impairment and worse HRQoL. One study found a significant association between clinically significant anxiety and greater daily PA,[71] a finding that requires replication in prospective studies. Anxiety is associated with 1.72 times higher 30-day mortality compared to Veterans without anxiety and 1.22 times increased risk of 30-day hospital readmission for COPD acute exacerbation.[75]

Insomnia is an independent psychological disorder characterized by difficulty initiating or maintaining sleep, or early morning awakenings that cause significant distress and occur outside the diagnosis of another mental health condition.[76] Research on insomnia in Veterans remains scarce. In one study, insomnia was found to occur in 27% (50 of 183) of Veterans with COPD. A much larger percentage of Veterans reported sleep complaints with 50% of the sample reporting at least one or more sleep complaint more than three times per week.[77]

A key outcome in Veterans with COPD, HRQoL reflects an individual's perception of their quality of life when they consider their overall health (eg, 36-Item Short Form Survey (SF-36))[78] or in reference to their COPD diagnosis (eg, The Chronic Respiratory Questionnaire).[79] Illness intrusiveness, a psychological construct, describes the extent to which an individual perceives their illness to impede in their daily life and valued activities and can be assessed with self-report measures. It is a meaningful treatment outcome for Veterans with COPD who prioritize daily functioning. The VHA has prioritized intervention development to improve psychological outcomes in Veterans with COPD. The following sections describe several of these interventions and their impact on psychological outcomes.

### Cognitive Behavioral Therapy (CBT)

CBT is a time-limited, collaborative, present-focused, skills-based intervention that focuses on behavioral and cognitive change to treat psychological disorders. CBT is transdiagnostic, thus applicable in the treatment of the most common psychological disorders in COPD. Fundamental to CBT is that suffering is not directly caused by events themselves, but is a result of clients' interpretation, appraisal, meaning, and behavioral response attached to events. Thus, treatment focuses on addressing the connection between events, thoughts, emotions, and behaviors while challenging and modifying unhelpful patterns.[80]

While CBT has been studied by several research groups in civilian samples with COPD, only one research group in the US accounts for almost all empirical research on the efficacy of CBT in Veterans with COPD. Cully et al[81] conducted an RCT comparing brief cognitive behavioral therapy (bCBT) to enhanced usual care (EUC) in 302 Veterans with either heart failure (HF) or COPD and clinically significant depression and/or anxiety symptoms. The primary outcomes were depression and anxiety symptoms measured by validated self-report measures. HRQoL was the secondary outcome.

bCBT was delivered in six sessions either in-person or by telephone based on patient preference with two booster sessions provided over four months. Each session focused on a particular skill and the number of sessions varied based on patient preference and discussion with their therapist. Skill sessions focused on modification of unhelpful thinking patterns, behavioral activation, relaxation, and chronic disease self-management. Content was adapted to focus on the intersection between physical symptoms and mental health. Like traditional CBT, bCBT addressed topics such as usual and past coping styles and strengths and resources in the patient's life. Skills were taught alongside practice assignments focused on goal setting and modifying behavior and thinking patterns. Therapists for the study ranged from psychology and social work trainees to staff psychologists and physician assistants. The EUC group received assessment of mental health symptoms and a note in their chart for their primary care provider to address these concerns. Outcomes were assessed at baseline and 4 (post-intervention), 8, and 12 months.

At 4 months, there were meaningful improvements in depression and anxiety symptoms in patients with COPD or HF. Veterans with COPD showed significant improvement in all domains of HRQoL. At 12 months, differences were maintained between the treatment and control group, but there was no further improvement in symptoms.[81]

Stemming from this parent study, secondary analyses were conducted in several separate articles and provide important insights into the optimization of psychological health in Veterans with COPD. First, the impact of bCBT on illness intrusiveness was examined among Veterans with COPD in the parent study.[82] Illness intrusiveness was measured with the Illness Intrusiveness Rating Scale (IIRS) which provides a total score, as well as three validated subscales: Relationships (eg, family, civil engagement), Intimacy (eg, sexual functioning, relationship with spouse), and Instrumental (eg, health, work, active recreation). bCBT significantly improved IIRS total score at four months compared to EUC. At the subscale level, differences were found for Intimacy and Instrumental but not Relationships.

Second, in a separate study,[83] bCBT was found to result in a significant reduction of high-frequency suicidal ideation (SI) in the bCBT group compared to the EUC at 4- and 8-month time points after controlling for baseline SI but the treatment effect was not sustained at 12 months. Specifically, at 4 and 8 months, respectively, participants who received bCBT compared to EUC had 72% and 68% lower likelihood of reporting high-frequency SI.

Third, predictors of treatment response to bCBT were explored in secondary analysis.[84] Multivariate regression models examined whether hypothesized baseline variables including baseline depression or anxiety symptoms, functional limitations, self-efficacy for disease management, adaptive coping, maladaptive coping, number of sessions attended, and working alliance (ie, relationship between therapist and client) predicted improvement in primary outcomes of depression symptoms or anxiety symptoms. The same predictors emerged for both improvement in depression and anxiety symptoms. Participants with greater physical functioning impairment and lower self-efficacy showed less improvement in anxiety and depression symptoms. Those with greater baseline depression or anxiety showed greater improvement in symptoms.

The fourth and final study stemming from the parent study describes a utilization analysis of the content delivered in bCBT.[85] They found that participants who received the "physical health" and "thoughts" modules earlier in treatment had a greater likelihood of remaining in treatment. Results have important clinical implications suggesting that early psychoeducation and skill building should focus on the intersection between physical and mental health, as well as dysfunctional or unhelpful thought patterns to optimize treatment completion rates. Together, these studies offer important data on the efficacy of bCBT, as well as treatment predictors.

## Pulmonary Rehabilitation and Physical Activity

As described in the physical outcomes section, PR is the standard of care for Veterans with COPD targeting exercise capacity and physical functioning. However, PR also improves many psychological outcomes, but studies with Veteran samples are limited. In a retrospective study, Veterans with COPD who participated in twice weekly outpatient PR for 18 weeks demonstrated significant improvement in depression symptoms over the course of PR. Greater reduction in depression over the course of treatment was significantly associated with greater improvement in CRQ-SR total score and the following subscales: fatigue, mastery, and emotional function.[86] Similar findings were documented in a prior study examining the relation between change in depression symptoms and change in CRQ-SR subscales. In a sample of 81 Veterans enrolled in 8 weeks of biweekly PR, significant improvements were found for depression symptoms but not anxiety symptoms. Moreover, change in depression symptoms, but not anxiety symptoms, was associated with change in CRQ-SR domains of fatigue, emotion, and mastery.[87] PR, a core treatment for Veterans with COPD and significant depression symptoms, improves physical functioning and psychological outcomes. However, depression and anxiety symptoms, particularly in Veterans with more than one mental health diagnosis and/or lifetime/chronic course of psychological disorders may require more intensive outpatient therapy specifically for mental health following PR or concurrently. Re-assessment of depression and anxiety symptoms is important at the end of PR to determine treatment needs.

Other work within VA has examined the effect of PR on insomnia. A recent retrospective study examined subjective and objective sleep changes after eight weeks of conventional, in-person, structured PR and 12 months of an unstructured exercise program.[88] Despite sustained improvements in exercise capacity (measured via the 6MWT distance; mean improvement 68.8 m) and dyspnea (measured via the mMRC; mean difference −0.4 points), neither subjective sleep (measured via the Pittsburgh Sleep Quality Index) nor objective sleep (measured via actigraphy) improved.[88]

Surprisingly, research testing PA interventions in Veterans with COPD has not found significant improvements in depression or anxiety symptoms. One VA-based study compared the effects of a 4-month pedometer plus internet-mediated intervention to waitlist control (pedometer) on HRQoL in Veterans with COPD measured at 4 and 12 months.[56,89,90] While HRQoL improved in the intervention group compared to the control group at 4 months, there was no difference at 12 months. Moreover, no change in depression scores was observed at either 4 or 12 months. However, these results are confounded by the fact that the treatment of anxiety and depression was not the main focus nor well characterized in the sample. For example, participants were not recruited based on significant levels of depression and anxiety nor was the intervention personalized in any way to participants based on their depression and/or anxiety levels.

### Pharmacotherapy

Research on pharmacotherapy to improve psychological outcomes in individuals with COPD is limited in both civilian and Veterans samples. Drawing from the general literature, a Cochrane review published in 2018 found insufficient evidence for pharmacotherapy for the treatment of depression in individuals with COPD.[91] In their review of the literature on anti-depressants for depression in COPD, no recommendation was made for any anti-depressant type. Rather, non-pharmacological treatments, such as collaborative care models and CBT, were encouraged as first-line therapy.[92]

## Future Directions to Advance COPD Research and Clinical Care in Veterans with COPD

### Advances in Physiological Outcomes

Pharmacological treatment of COPD is focused on maximizing lung function, reducing risk for acute exacerbations, and symptoms management, namely the reduction of dyspnea.[93] More recently, advances in COPD treatment have utilized precision medicine to target COPD in its early stages or before disease onset.[94] However, to our knowledge, there are few funded research studies in the VHA focused on early COPD or prevention efforts. This is notable given that Veterans of the Iraq and Afghanistan conflicts will be entering midlife and have already been identified to be at greater risk for respiratory diseases given environmental exposures.[95] Prior studies in civilians have begun to characterize those who may have "early" COPD targeting adults <50 years of age with ≥10 pack-years of smoking history with evidence of lung function abnormality by CT or spirometry that do not meet criteria for COPD.[96] Improved understanding of Preserved Ratio Impaired Spirometry, a classification of individuals who have proportional reductions in $FEV_1$ and FVC but preserved ratio, provides a group of individuals at higher risk for transitioning to COPD and may particularly benefit from early intervention.[97] Advances in imaging technology can help identify those who may be at-risk for COPD.[98] At least one funded study within the VHA is exploring the application of computation imaging technology (CT) using Quantitative Imaging Analysis (QIA) to identify structural defects in the lungs before disease onset. By targeting individuals in the early COPD stage, effective clinical management can be offered and presents a vital area for future research in Veterans.

Similarly, identification of predictive biomarkers within COPD remains an active area of research with many unanswered questions.[94] While review of the research on biomarkers of COPD is beyond the scope of this paper, more research is needed exploring COPD biomarkers in Veterans with careful delineation of endotypes connected to the proposed biomarker and clinical manifestation of disease activity.[99] For example, past research in civilians established an association between epigenetic changes and inflammatory-response cytokines in COPD patients undergoing a prolonged, 24-session exercise training regimen.[100] Early changes were observed in DNA methylation between baseline and after the first session but no changes were observed in H4 acetylation status at any point during the intervention. Inflammatory markers changed in response to the exercise intervention with an increase in interleukin-6 (IL-6) and a decrease in growth factor-beta after session 24.

In Veteran samples using a cross-sectional design, greater daily step count and higher 6MWT distance were associated with lower systematic inflammation, as measured by CRP and IL-6.[101] After controlling for age, $FEV_1$% predicted, pack-years smoked, cardiac disease, current statin use, history of acute exacerbations, and season, each 1000-step increase in daily step count was significantly associated with 0.94 mg/L and 0.96 pg/mL decrease in CRP level. Similarly, for every 30-m increase in 6MWT distance, there was a 0.94 pg/mL decrease in CRP and 0.96 pg/mL decrease in IL-6 level. While not causal, these studies point to potential epigenetic changes associated with exercise-induced inflammatory biomarkers in COPD.

Research with Veteran samples has established correlations between epigenetic markers of biological age and functioning in COPD.[102] At baseline, epigenetic age and age acceleration, measures that capture the difference between biological and chronological age, were inversely associated with 6MWT distance and PA after adjusting for chronological age, sex, race, smoking status, pack-years, BMI, cohort, and estimated cell counts. Importantly, longitudinal *change* in one of the measures of epigenetic age was inversely associated with change in 6MWT distance at 12 weeks, suggesting that epigenetic age may represent a potentially modifiable molecular signature of exercise capacity.[102] Potential applications of epigenetics and biomarkers for the prediction of clinical outcomes, such as COPD acute exacerbations or response to exercise training programs such as pulmonary rehabilitation, represent active areas of investigation.

## Advances in Physical Functioning

While PA promotion interventions show promising short- and some long-term benefit in terms of increasing daily PA and reducing COPD acute exacerbation risk, improvements in exercise capacity have not been observed.[58] In the next decade, RCTs are needed to test the dose of PA promotion (ie, duration, intensity) required to sustain functional improvements. Long-term trials testing beyond 12 months are necessary. Moreover, development and testing of novel interventions that leverage varying levels of Veteran engagement, such as hybrid approaches that combine self-guided and in-person/provider-delivered components are needed to examine the impact of frequency of promotional and supportive messages and check-ins from staff.[58] Additionally, little is known about the social context and its association with short- and long-term adoption of PA. Studies exploring the role caregivers, family members, and friends in the adoption and maintenance of PA in COPD are needed, particularly given that social context has proved important for the success of COPD self-management efforts.[103,104] Finally, it is important to consider the effects of the COVID-19 pandemic on habitual PA and exercise patterns.[105,106] Indoor walking and exercise in malls, gyms, and senior centers have been reduced and alternatives are not always available. As such, innovative research is needed to better understand how patients with COPD prefer to engage in PA in their current environments and preferences for in-home exercises.

Notably, the VHA is a leader in telemedicine and prioritized access to care well before the COVID-19 pandemic[107] which only expanded over the last two years.[108] The VHA system provides iPad, with built in internet access, at no cost to Veterans without a personal device and/or internet access. Moreover, the VA has an established Care Coordination/Home Telehealth (CCHT)[109] for chronic diseases including COPD, which provides home equipment for daily monitoring and disease management by a nurse care coordinator. In 2017, from funding through the VA's Office of Rural Health, home-based PR was offered across 13 VA medical centers. While several studies in civilians have established the efficacy of home-based PR,[110,111] until 2017 only hospital-based PR was offered in the VHA system. Based on home-based cardiac rehabilitation provided in the VA,[112] home-based PR involves an initial in-person evaluation, followed by 11 weekly telephone or video appointments, an in-person evaluation at week 12, and follow-up phone/video calls at 3 and 6 months. A final in-person evaluation occurs at 12 months from the start of the program.[112] However, the extent to virtual only rehabilitation and exercise programs are available to Veterans varies by VA. Future research is needed to demonstrate implementation of existing evidence-based PR programs delivered virtually in the VHA as part of routine clinical care.

## Advances in Psychological Functioning

There is extensive evidence documenting increased inflammatory markers in psychological disorders and, in particular, major depressive disorder. Increases in pro-inflammatory markers including peripheral blood IL-1β, IL-6, Tumor Necrosis Factor (TNF) and C-reactive protein (CRP) are well documented.[113] Yet, the role of inflammation and shared pathways between depression and COPD remain inconclusive. Limited cross-sectional research on civilians with COPD has found that greater depression symptoms are associated with higher TNF-α and sTNFR after adjusting for possible confounders.[114,115] However, one prospective study did not find a significant association between depression and inflammatory markers in individuals with stable COPD.[116] Janssen et al[116] measured several inflammatory markers (white blood cell, hsCRP, IL6, fibrinogen) in COPD patients at baseline and 36-month follow-up. They classified individuals as having persistent systemic inflammation if they had 2 or more markers elevated in the upper quartile at baseline and follow-up or no inflammation corresponding to no elevation in inflammation at either time point. They found no association between baseline depression scores and inflammation group after adjusting for confounders, and no differences were found either in change in depression scores or mean levels at follow-up between inflammation groups. Nonetheless, given the notable role of inflammation in both COPD and depression, as well as the heterogeneity of both diseases, future research examining the association between inflammation and depression in COPD utilizing prospective designs is needed. Furthermore, reduction in inflammatory markers reflects a meaningful marker of treatment response in COPD[100,101] and depression,[117] thus it is plausible that targeting both COPD symptoms and depression concurrently could result in greater reduction in inflammatory markers corresponding to treatment response compared standalone therapies that separately target physical functioning and psychological symptoms.

In order to advance interventions for psychological outcomes in COPD, it is critical that researchers begin dually targeting both physical functioning and psychological outcomes. For example, past research with patients with diabetes and HF found that combining a physical intervention (ie, exercise) with psychotherapy (ie, CBT) produced superior outcomes in both functioning and mental health symptoms.[118,119] Yet, up to this point, two independent bodies of literature have focused on separately addressing physical functioning via pulmonary rehabilitation and exercise, and mental health through psychotherapy/behavioral interventions. One funded study in the VHA is testing the integration of a pedometer-based walking intervention with CBT in a 12-week virtual intervention with Veterans with COPD, low PA levels, and clinically significant depression and/or anxiety symptoms (NCT04953806). The intervention will target daily step count and self-reported physical disability, as well as depression and anxiety symptoms.

## Future Areas for Clinical Improvement

While research establishing the efficacy of treatments for COPD has been fruitful, implementation of guideline-based care remains fraught with health-care inequities. Women Veterans hospitalized for COPD are less likely to have received inhaler therapies prior to admission compared to men.[43] In addition, women are less likely during the course of a COPD hospitalization to receive appropriate inhaler combinations and more likely to receive inappropriate inhaler combinations.[43] Moreover, women, racial and ethnic minorities, and individuals with drug and alcohol use disorders are less likely to have pulmonary function tests performed, possibly leading to delays in diagnosis and under-treatment.[120] In considering optimizing outcomes, it is imperative to consider and equally target health-care inequities that serve as barriers to guideline-based care. Similarly, enhanced recruitment of underserved groups (ie, lower socioeconomic status, racial and ethnic minorities) in COPD research studies is needed. Research and quality improvement projects are important to examine system and individual-level approaches to ensure equity in guideline-based care for all Veterans with COPD. Funding for COPD research that include focus on minority healthcare is needed.

## Conclusions

The coming decade will see an increase in COPD prevalence in US Veterans as Vietnam era Veterans fully reach older adulthood and Iraq and Afghanistan conflict Veterans enter midlife. A multi-pronged agenda targeting system-level factors that increase access and improve care delivery, as well as bench and clinical research will be needed to advance our understanding, treatment, and management of COPD in Veterans. Partnerships with all stakeholders including patients, university-affiliated hospitals, industry, and the international research community will be critical to accelerate the development and implementation of novel treatments to improve physiological, physical, and psychological health outcomes for this heterogenous disease.

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## Disclosure

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