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INTEGRATED STUDY MASTER'S FINAL THESIS

Impact of Smoking Cessation Programs in Patients with Chronic Obstructive Pulmonary Disease. Literature Review

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1. Abbreviations

Abbreviation	Full Form
AAT	Alpha-1 Antitrypsin
AP-1	Activator Protein 1
ATS	American Thoracic Society
BOLD	Burden of Obstructive Lung Disease (study)
CAT	COPD Assessment Test
CBT	Cognitive Behavioral Therapy
CCQ	Clinical COPD Questionnaire
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CO	Carbon Monoxide
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
DNRI	Dopamine and Noradrenaline Reuptake Inhibitor
EAGLES	Evaluating Adverse Events in a Global Smoking Cessation Study
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
eGFR	Estimated Glomerular Filtration Rate
ERS	European Respiratory Society
FDA	Food and Drug Administration (United States)
FEV1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GAD-7	Generalized Anxiety Disorder 7-item Scale
GBD	Global Burden of Disease
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HDAC2	Histone Deacetylase 2
HRQoL	Health-Related Quality of Life

Abbreviation	Full Form
IL-8	Interleukin-8
LTB4	Leukotriene B4
MAOI	Monoamine Oxidase Inhibitor
MCP-1	Monocyte Chemoattractant Protein-1
MCID	Minimum Clinically Important Difference
MI	Motivational Interviewing
mMRC	Modified Medical Research Council (dyspnea scale)
MRC	Medical Research Council
nAChR	Nicotinic Acetylcholine Receptor
NF-κB	Nuclear Factor Kappa B
NICE	National Institute for Health and Care Excellence
NRT	Nicotine Replacement Therapy
OR	Odds Ratio
PHQ-9	Patient Health Questionnaire 9-item Scale
PR	Pulmonary Rehabilitation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trial
RR	Relative Risk
SGRQ	St George's Respiratory Questionnaire
SPIROMICS	Subpopulations and Intermediate Outcomes in COPD Study
TNF-α	Tumor Necrosis Factor Alpha
WHO	World Health Organization

2. Summary

Chronic Obstructive Pulmonary Disease (COPD) is one of the most significant causes of chronic illness and premature death worldwide, affecting hundreds of millions of people and placing an enormous burden on healthcare systems globally. Cigarette smoking is responsible for the vast majority of Chronic Obstructive Pulmonary Disease cases in high income countries and remains the most important modifiable driver of disease progression, yet a striking proportion of patients continue to smoke even after receiving a formal diagnosis. This persistent

smoking behaviour reflects not simply a lack of willpower, but the deeply entrenched neurobiological, psychological, and social nature of tobacco dependence, which is consistently more severe in Chronic Obstructive Pulmonary Disease patients than in the general smoking population.

This narrative literature review was undertaken to examine and synthesise the available evidence on the impact of smoking cessation programmes in patients with established Chronic Obstructive Pulmonary Disease. A comprehensive search of PubMed, EMBASE, the Cochrane Library, and MEDLINE was conducted, covering publications from 2000 to 2024, with inclusion of earlier landmark studies where their foundational relevance justified an exception. The review draws on a broad range of study designs, including randomised controlled trials, systematic reviews, meta-analyses, and longitudinal cohort studies, and encompasses the full spectrum of cessation modalities, including pharmacological, behavioural, combined, digital and those embedded within pulmonary rehabilitation frameworks.

The central finding of this review is that smoking cessation is, without question, the most effective disease modifying intervention available in Chronic Obstructive Pulmonary Disease management. The evidence supporting this conclusion is consistent across study designs, populations and outcome measures. Cessation slows the accelerated decline in forced expiratory volume in one second that characterises active smokers with Chronic Obstructive Pulmonary Disease, reduces the frequency and severity of acute exacerbations, lowers hospitalisation rates, and improves health related quality of life. Crucially, the survival benefit associated with cessation is demonstrable even in patients with severe and very severe disease a finding that challenges the fatalistic attitudes that too often prevent cessation support from being offered or accepted at advanced stages.

Among the pharmacological options evaluated, varenicline emerges as the most efficacious single agent, achieving confirmed 12 month abstinence rates approximately three to four times higher than placebo in Chronic Obstructive Pulmonary Disease specific trials. Concerns about its neuropsychiatric safety, which previously tempered enthusiasm for its use in a population with high rates of depression and anxiety, have been comprehensively addressed by the “EAGLES” trial (8).

Combination nicotine replacement therapy and bupropion represent effective alternatives for patients in whom varenicline is contraindicated or not tolerated. Across all pharmacological options, the evidence is unambiguous that medication combined with structured behavioural support produces substantially better outcomes than pharmacotherapy alone and this combined approach is endorsed as the standard of care by the GOLD 2024 guidelines (1).

Behavioural interventions, ranging from brief opportunistic physician advice to motivational interviewing, cognitive behavioural therapy, and telephone quit lines, each contribute meaningfully to cessation outcomes, with a clear dose response relationship between the intensity of support and quit rates. Motivational interviewing is particularly suited to Chronic Obstructive Pulmonary Disease patients given the high prevalence of ambivalence, fatalism and self blame in this group. The integration of cessation support within pulmonary rehabilitation programmes is identified as an underutilised opportunity that leverages an intensive, multidisciplinary setting to provide cessation support to highly motivated patients.

The review also highlights a number of important gaps in the current literature. Patients with severe and very severe Chronic Obstructive Pulmonary Disease remain substantially underrepresented in cessation trials, as do those with significant psychiatric comorbidities. Long term follow up data beyond 12 months are limited, the evidence base for digital cessation tools in Chronic Obstructive Pulmonary Disease specific populations is underdeveloped, and the role of electronic cigarettes as a harm reduction strategy remains unresolved. On the basis of the synthesised evidence, this review makes recommendations for the universal integration of cessation support into routine Chronic Obstructive Pulmonary Disease care, routine screening for comorbid depression and anxiety and the development of disease specific cessation pathways in both primary and secondary care settings.

3. Summary (Lithuanian)

Lėtinė obstrukcinė plaučių liga (LOPL) yra viena iš svarbiausių lėtinių ligų ir priešlaikinės mirties priežasčių visame pasaulyje, paveikianti šimtus milijonų žmonių ir užkraunanti didžiulę naštą sveikatos priežiūros sistemoms visame pasaulyje. Cigarečių rūkymas yra didžiosios daugumos lėtinės obstrukcinės plaučių ligos atvejų priežastis dideles pajamas gaunančiose šalyse ir išlieka svarbiausiu koreguojamu ligos progresavimo veiksniu, tačiau didelė dalis pacientų toliau rūko net ir gavę oficialią diagnozę. Šis nuolatinis rūkymo įprotis atspindi ne tik

valios stoką, bet ir giliai įsišaknijusį neurobiologinį, psichologinį ir socialinį tabako priklausomybės pobūdį, kuris nuolat yra sunkesnis pacientams, sergantiems lėtine obstrukcine plaučių liga, nei apskritai rūkančiai populiacijai.

Ši pasakojamoji literatūros apžvalga buvo atlikta siekiant ištirti ir apibendrinti turimus įrodymus apie rūkymo metimo programų poveikį pacientams, sergantiems nustatyta lėtine obstrukcine plaučių liga. Buvo atlikta išsami PubMed, EMBASE, Cochrane bibliotekos ir MEDLINE paieška, apimanti 2000–2024 m. publikacijas, įtraukiant ankstesnius svarbius tyrimus, kurių esminis aktualumas pateisino išimtį. Apžvalga remiasi įvairiais tyrimų modeliais, įskaitant atsitiktinių imčių kontroliuojamus tyrimus, sistemines apžvalgas, metaanalizes ir išilginius kohortos tyrimus, ir apima visą metimo rūkyti būdų spektrą, įskaitant farmakologinius, elgesio, kombinuotus, skaitmeninius ir tuos, kurie yra įtraukti į plaučių reabilitacijos sistemas.

Pagrindinė šios apžvalgos išvada yra ta, kad rūkymo metimas neabejotinai yra veiksmingiausia ligos eigą modifikuojanti intervencija, prieinama gydant lėtinę obstrukcinę plaučių ligą. Šią išvadą patvirtinantys įrodymai yra nuoseklūs tarp tyrimų modelių, populiacijų ir rezultatų rodiklių. Metimas rūkyti sulėtina pagreitėjusį forsuoto iškvėpimo tūrio sumažėjimą per vieną sekundę, būdingą aktyviems rūkaliams, sergantiems lėtine obstrukcine plaučių liga, sumažina ūminių paūmėjimų dažnį ir sunkumą, sumažina hospitalizacijų skaičių ir pagerina su sveikata susijusią gyvenimo kokybę. Svarbiausia, kad su metimu rūkyti susijusi išgyvenamumo nauda yra akivaizdi net pacientams, sergantiems sunkia ir labai sunkia liga – tai atradimas, metantis iššūkį fatalistiniam požiūriui, kuris pernelyg dažnai trukdo pasiūlyti ar priimti paramą metant rūkyti vėlyvose stadijose.

Iš vertintų farmakologinių variantų vareniklinas išsiskiria kaip veiksmingiausias vienas preparatas, patvirtintas 12 mėnesių abstinencijos rodiklis, nustatytas specifiniuose lėtinės obstrukcinės plaučių ligos tyrimuose, yra maždaug tris–keturis kartus didesnis nei placebo. Abejonės dėl jo neuropsichiatrinio saugumo, kurios anksčiau slopino entuziazmą dėl jo vartojimo populiacijoje, kurioje yra didelis depresijos ir nerimo lygis, buvo išsamiai išspręstos „EAGLES“ tyrime (8).

Nikotino pakaitinės terapijos ir bupropiono derinys yra veiksmingos alternatyvos pacientams, kuriems vareniklinas yra kontraindikuotinas arba netoleruojamas. Visų farmakologinių

alternatyvų atveju įrodymai nedviprasmiški, kad vaistų vartojimas kartu su struktūrizuota elgesio palaikymu duoda žymiai geresnių rezultatų nei vien tik farmakoterapija, ir šis kombinuotas metodas yra patvirtintas kaip GOLD 2024 gairių (1) priežiūros standartas.

Elgesio intervencijos, pradedant trumpais oportunistiniais gydytojo patarimais ir baigiant motyvaciniais pokalbiais, kognityvine elgesio terapija ir telefono linijomis, padedančiomis mesti rūkyti, reikšmingai prisideda prie metimo rūkyti rezultatų, o paramos intensyvumas ir metimo rūkyti rodikliai yra aiškiai susiję su dozės ir atsako santykiu. Motyvaciniai pokalbiai ypač tinka lėtine obstrukcine plaučių liga sergantiems pacientams, atsižvelgiant į didelį ambivalentiškumo, fatalizmo ir savęs kaltinimo paplitimą šioje grupėje. Metimo rūkyti palaikymo integravimas į plaučių reabilitacijos programas įvardijamas kaip nepakankamai išnaudota galimybė, kuri pasitelkia intensyvią, daugiadisciplininę aplinką, kad būtų galima teikti metimo rūkyti paramą labai motyvuotiems pacientams.

Apžvalgoje taip pat atkreipiamas dėmesys į keletą svarbių dabartinės literatūros spragų. Pacientai, sergantys sunkia ir labai sunkia lėtine obstrukcine plaučių liga, vis dar yra gerokai mažiau atstovaujami nutraukimo tyrimuose, kaip ir tie, kurie serga reikšmingomis psichikos ligomis. Ilgalaikio stebėjimo duomenys, ilgesni nei 12 mėnesių, yra riboti, skaitmeninių nutraukimo priemonių, skirtų specifinėms lėtinės obstrukcinės plaučių ligos populiacijoms, įrodymų bazė yra nepakankamai išvystyta, o elektroninių cigarečių, kaip žalos mažinimo strategijos, vaidmuo lieka neišspręstas. Remiantis susintetintais įrodymais, šioje apžvalgoje pateikiamos rekomendacijos dėl visuotinės nutraukimo palaikymo integracijos į įprastinę lėtinės obstrukcinės plaučių ligos priežiūrą, įprastinio gretutinės depresijos ir nerimo patikrinimo bei ligai būdingų nutraukimo būdų kūrimo tiek pirminės, tiek antrinės sveikatos priežiūros įstaigose.

4. Keywords

Chronic Obstructive Pulmonary Disease; COPD; Smoking Cessation; Nicotine Replacement Therapy; Varenicline; Bupropion; Motivational Interviewing; Cognitive Behavioural Therapy; Pulmonary Rehabilitation; FEV1 Decline; Exacerbations; GOLD Guidelines; Nicotine Dependence; Health Related Quality of Life; Digital Health.

5. Introduction

It is often said in respiratory medicine that if you want to do one thing for a Chronic Obstructive Pulmonary disease patient, it should be to stop their smoking. The evidence for smoking cessation as the single most effective disease modifying intervention available in COPD management is about as solid as evidence can be in the case of chronic diseases. Yet a stroll through any outpatient clinic dealing primarily with respiratory diseases will turn up an alarming number of patients at every stage of the disease who still indulge in smoking, concerningly, it is often daily and heavily rather than an occasional relapse. This review aims to examine the gap and evaluate the evidence for closing it.

COPD is third in leading causes of death worldwide, only behind Ischaemic Heart diseases and stroke. According to World Health Organization (WHO) estimates, it kills around 3.5 million people annually (1). The prevalence figures are difficult to pin down with precision as COPD is a systematically underdiagnosed condition and the variation in estimates exists due to the spirometric criteria applied in the population studied. COPD is an indiscriminate disease, the mortal and economic tolls are staggering in both low and high income countries, with the condition affecting roughly 10% of adults over 40 with an exponential increase with advance in age (1).

The economic burden is equally staggering. In the European Union, COPD related healthcare spending is estimated at tens of billion Euros annually. The single largest cost driver being the hospitalization for treatment of acute exacerbations, each admission costing tens of thousands in high income countries and patients suffering with severe disease complications have been noted to require multiple admissions in a year.

Tobacco smoking is considered the cause for 85% to 90% of COPD in western populations. Unfortunately, this is not a case of association masquerading as causation; the biological mechanisms linking smoke exposure to airway and lung parenchymal destruction are well characterized, the dose response relationship between cumulative pack year exposure and disease is well documented and cessation trials have demonstrated reversal of disease trajectory. Even so, only about 15 to 25% of lifetime smokers ever develop clinically significant COPD, pointing to us that genetic susceptibility and early life factors play a modulating role and while tobacco exposure is necessary it is not sufficient in all cases (28).

The strongest argument for smoking cessation in the case of COPD is the FEV1 trajectory. Fletcher and Peto first described it in 1977 in a study of London bus drivers; susceptible smokers lose lung function at a rate of roughly two to three times compared to non-smokers, starting from early adulthood (5). Their data also showed, that cessation at any point of the course of the disease bends the trajectory back to normal, although not back to the baseline lung function that the patient would have had if they never smoked however to a rate that would be expected from ageing alone and this conclusion has since been substantiated by many modern and more recent studies. What is to be gleaned from this is that the damage that has already occurred stays but the damage that would have been incurred is largely averted by simply stopping smoking.

The Lung Health Study, conducted in over 5,000 participants and first reported in 1994 by Anthonisen and colleagues have put this principle to strenuous test (3). This remains the most influential cessation trial on the subject of COPD to this date, not only because it was the only one but also as it has a long and rigorous follow up with clear outcomes that threw light on something clinicians needed to hear spelled out; A highly structured cessation intervention, especially one that combines nicotine replacement with intensive behavioural support can lead to a meaningful change to the natural progression of the disease and sustained quitters have statistically longer lives. The 14.5 Year mortality data published in 2005 confirmed a statistically significant survival advantage in the intervention group as well (4).

Despite the above mentioned proven correlation, smoking cessation remains tragically underprioritized in many clinical settings. While stated reasons vary from clinicians citing time crunch, inherent sense that patients are unlikely to quit to uncertainty about the best available therapeutic options. Patients also cite fear of weight gain, anxiety related to withdrawals and most corrosively, the belief that damage is done and quitting doesn’t pose much of a benefit to their health. A broader structural issue is also quite evident; Cessation pharmacotherapy is not often funded, cessation counselling is not always accessible and the intensity of support that the evidence suggests is required is often impossible to deliver in a short consultation, especially in an outpatient setting.

Against this backdrop, this literature review was undertaken with the aim of synthesizing what the available evidence actually shows about cessation programs in COPD; what works and what fails to make a difference, for whom is this a right fit and under what conditions would

this sort of management be suited to. The goal remains not to produce another generic summary of cessation pharmacotherapy rather to examine the specific challenges and opportunities by the COPD population while translating the evidence into something that can be of meaningful use for clinicians who want to do better by their patients.

5.1 Aims and Objectives

The primary aim of this review is to evaluate the impact of smoking cessation programs on clinical outcomes in patients with established COPD and to provide evidence based guidance for clinical practice.

The specific objectives are:

1. To describe COPD as a clinical entity, including its epidemiology, classification and the burden it places on patients and the global healthcare system.
2. To examine the pathological processes and disease mechanism underpinning COPD with attention provided to how tobacco smoke drives and sustains these processes.
3. To evaluate both pharmacological cessation therapies like Nicotine Replacement Therapy (NRT), Varenicline and Bupropion and non pharmacological therapies like behavioural, digital and psychological cessation interventions in COPD patients.
4. To examine the present evidence for combined pharmacological and behavioural approaches and integration for cessation support within pulmonary rehabilitation programs.
5. To identify specific barriers and facilitators in in cessations in COPD patients that distinguish them from the general smoking population.
6. To assess the impact of cessation on key COPD outcomes, including lung function, exacerbation frequency, hospitalization, survival and quality of life.
7. To make recommendations for clinical practice based on existing evidence and to provide possible avenues for further research.

6. Literature search strategy and Methodology

This study is a narrative literature review, selected as the most appropriate design to synthesize heterogeneous evidence across multiple cessation modalities, study types, and outcome measures. A comprehensive and systematic approach was adopted for the identification and selection of literature relevant to the impact of smoking cessation programs in patients with Chronic Obstructive Pulmonary Disease. Although this review is narrative in design and

therefore does not adhere to the rigid protocols of a systematic review or a meta-analysis; transparency in the search process and explicit inclusion and exclusion criteria were applied to ensure rigor and reproducibility of the evidence synthesized.

6.1 Database searched

The following electronic bibliographic databases were searched: PubMed/MEDLINE (National Library of Medicine, USA); EMBASE (Elsevier); CINAHL (Cumulative Index to Nursing and Allied Health Literature); Cochrane Library, including the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL); and Google Scholar for supplementary grey literature. The search was conducted over the period from June to October 2025, covering publications from January 2000 to October 2025. For landmark studies predating this window, most notably the Lung Health Study (Anthonisen et al., 1994), exceptions were made given their foundational importance to the field.

6.2 Search terms and Boolean Strategy

Search terms were grouped into three conceptual domains, combined using Boolean operators. The condition domain included: 'chronic obstructive pulmonary disease', 'COPD', 'emphysema', 'chronic bronchitis', 'airflow limitation', and 'airflow obstruction'. The intervention domain included: 'smoking cessation', 'tobacco cessation', 'quit smoking', 'nicotine replacement therapy', 'NRT', 'varenicline', 'Champix', 'Chantix', 'bupropion', 'Zyban', 'behavioural support', 'counselling', 'motivational interviewing', 'cognitive behavioural therapy', 'CBT', 'telephone Quitline', 'mHealth', 'digital cessation', 'smartphone', and 'pulmonary rehabilitation'. The outcome domain included: 'FEV1', 'lung function decline', 'exacerbation', 'hospitalization', 'quality of life', 'mortality', 'abstinence rate', and 'quit rate'.

MeSH terms were employed in PubMed, including 'Pulmonary Disease, Chronic Obstructive' [MeSH], 'Smoking Cessation' [MeSH], 'Tobacco Use Cessation Products' [MeSH], and 'Behavior Therapy' [MeSH]. EMTREE subject headings were used in EMBASE. Search strings were adapted for each database's syntax.

6.3 Inclusion and Exclusion Criteria

Studies were included if they were published in peer reviewed journals; enrolled adult human subjects with a confirmed or physician diagnosed COPD; evaluated any cessation intervention (pharmacological, behavioural, combined, or digital); reported at least one clinically relevant outcome; and were available in English. Exclusion criteria covered case reports and case series with fewer than 10 participants; studies in exclusively non-COPD populations without a COPD subgroup analysis; opinion pieces and editorials without primary data; studies focused solely on asthma; and animal studies.

6.4 Study Selection and Quality Appraisal

Titles and abstracts of the remaining records were screened for relevance after duplicates were removed, and full texts of potentially eligible studies were then retrieved and assessed against the inclusion and exclusion criteria. Given the narrative design of this review, formal quality scoring (such as the Cochrane Risk of Bias tool or GRADE framework) was not systematically applied; however, study quality was considered in the narrative synthesis, with attention to study design, sample size, follow up duration, outcome reporting, and potential sources of bias. Priority was given to randomized controlled trials (RCTs), systematic reviews, and meta-analyses, with observational studies used to supplement where RCT data were unavailable or to address questions of real world effectiveness.

In total, approximately 193 records were identified through database searching, of which 63 full text articles were assessed for eligibility, and 36 primary studies and 27 systematic reviews or meta-analyses were ultimately included in the narrative synthesis. Additionally, the current GOLD 2024 guidelines, national smoking cessation clinical guidelines (UK NICE, US USPSTF), and the 2016 Surgeon General's Report on E-Cigarettes were incorporated as key reference documents. A PRISMA style flow diagram is included in the table below (Table 1) below for transparency.

Table 1

Stage	Records (n)
Records identified across all databases	193
Duplicates removed	48

Table 1 (continued)	
Stage	**Records (n)**
Title/abstract screening	145
Excluded at title/abstract stage	48
Full text review	97
Full text articles excluded (with reasons)	34
Primary studies included	36
Systematic reviews / meta-analyses included	27
Total included in narrative synthesis	63

7. Results

7.1 Description of the condition

7.1.1 Defining COPD and scope of the Problem

COPD is defined by the Global Initiative for Chronic Obstructive Lung Disease as a common, preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation (1). The aforementioned airflow limitation is caused by a combination of airway disease and lung parenchymal destruction and is clinically confirmed by a post bronchodilator FEV1/FVC ratio below 0.70 measured by spirometry. This definition has been for the most part stable for two decades however its implications and the recognition of how often the condition goes undiagnosed in a clinical setting has grown.

Prevalence estimates heavily depend on methodology utilized. The BOLD study, which utilized standardized spirometry in populations across 12 countries, estimated a global prevalence of approximately 10% in adults over the age of 40 (36). When extrapolated globally with the combination from the GBD study, current estimates hover around 200 to 300 million people affected with the wide range reflecting genuine uncertainty around under diagnosis, critically in low and middle income countries (59). In the United Kingdom, just over 1 million people carry a formal diagnosis however the British Lung Foundation has long argued that around 2 million more remain part of the undiagnosed group.

Mortality data shows an equally grim picture, with COPD as the third most common cause of death worldwide. It kills at disproportionate rates in low income settings where exposure to biomass fuel smoke and indoor air pollution compounds the tobacco related risk and where spirometry and necessary pharmacotherapy are often inaccessible due to a multitude of reasons. Even in high income settings, COPD mortality has not declined at the same rate as mortality as a result of other major non communicable disease, majorly influenced by the resistance of the behavioural risk factor (smoking) reduction in the population.

The economic burden of COPD warrants its own paragraph in a world run by spreadsheets and bottom lines, Hospitalization for acute exacerbations, accounts for the majority of direct COPD related costs, estimated to be sitting at 30 billion dollars in the United States of America in 2012 and certainly more in the present day (50). Indirect costs as a result of early retirement, reduced productivity and informal caregiving are more challenging to estimate and quantify but nonetheless are substantial. The point relevant to this review is that effective cessation programs are not solely clinically valuable, they stand out as cost effective and economic modelling consistently finds that investment in cessation support more than pays for itself through downstream reductions in overall hospital admissions.

7.1.2 Classification: The GOLD Framework

Spirometric severity in COPD is graded on a scale of 1 to 4, based on post bronchodilator FEV1 as a percentage of predicted normal values (in patients with confirmed FEV1/FVC below 0.70). GOLD 1 (mild) corresponds to FEV1 ≥80% predicted. GOLD 2 (moderate) is FEV1 50 to 79% predicted(1). GOLD 3 (severe) is FEV1 30 to 49% predicted(1). GOLD 4 (very severe) is FEV1<30% predicted (1). Importantly around 80% of patients with COPD in the community are in GOLD stage 1-2 at the time of diagnosis although many will have been symptomatic for years before reaching that point.

Since 2017, the GOLD framework has moved progressively away from solely spirometry based classification towards a multidimensional approach that incorporates symptom burden (assessed by the mMRC dyspnoea scale or the COPD Assessment test, CAT) and exacerbation history. The resulting ABE classification places patients into one of the three groups based on the combination of these factors, guiding the selection of pharmacological therapy independently of FEV1. This matters for this review as it underscores that lung function alone

tells only a fraction of the story, patients with similar FEV1 values can have dramatically different symptom burdens, functional limitations and exacerbations frequencies. Cessation benefits span all these dimensions rather than just the spirometric one.

Comorbidities are not incidental to COPD, they are in a very real sense, an integral part of the disease. Cardiovascular diseases, like ischaemic heart disease, heart failure, arrhythmias are present in 20 to 30% of COPD patients and share smoking as the primary etiological factor. Type 2 diabetes, osteoporosis, skeletal muscle wasting, lung cancer, depression and anxiety all occur at substantially higher rates in COPD patients than in age matched non COPD population. The presence of depression and anxiety in particular is not just a comorbidity note on a problem list, rather is a direct predictor of cessation failure and has to be actively managed in any patient attempting to quit smoking.

7.1.3 Tobacco Smoking as the Dominant Aetiological Factor

It bears repeating that roughly 85 to 90% of cases of COPD in industrialised countries are caused by cigarette smoking and tobacco exposure (31). The dose response relationship between pack year exposure and COPD risk has been well established, risk rises non linearly with cumulative exposure with a threshold of approximately 10 to 20 pack years below which risk is relatively low though lower thresholds apply to the case of populations using water pipe tobacco or experiencing high level of indoor air pollution. That said, not every heavy smoker develops COPD, only about 15 to 25% of lifetime smokers eventually end up developing clinically significant airflow obstruction, which implies substantial individual variation in susceptibility (32).

The most clearly established genetic susceptibility factor is Alpha-1 Antitrypsin (AAT) deficiency, present in roughly 1 to 3% of COPD patients (28). In AAT deficiency, the absence of adequate protease inhibitor activity, present in healthy individuals, in the lungs allows unchecked neutrophil elastase to destroy alveolar walls, producing early onset pan lobular emphysema. Interestingly, smoking dramatically accelerates this process, a patient with AAT deficiency who smokes develops emphysema decades earlier than a non-smoking AAT deficient individual and cessation of smoking in this group is arguably the most urgent intervention in all of the available COPD management strategies.

7.2 Disease Mechanisms and Pathology

7.2.1 The structural changes of COPD

One thing to note is that, the pathological changes in COPD are not uniform, they span the full length of the respiratory tract, from central airways, peripheral airways, alveolar parenchyma to the pulmonary vasculature and their relative contributions to airflow obstruction and symptoms vary in between patients, accounting in part for the clinical heterogeneity of the syndrome (26). Some patients predominantly present as “Pink Puffers” with marked emphysema and little productive cough, others present as “Blue Bloaters” with chronic bronchitis, hypercapnia and early cor pulmonale while a large cross section presents somewhere in between.

In the central airways, the dominant pathological changes are goblet cell hyperplasia, hypertrophy of submucosal mucus glands, squamous metaplasia of the airway epithelium and impairment of mucociliary clearance. These changes produce the productive cough and sputum of chronic bronchitis and in the peripheral airways, bronchioles less than 2mm in diameter, which represents the major site of airflow obstruction, the hallmark changes are peribronchiolar fibrosis, smooth muscle hypertrophy and luminal narrowing by inflammation and secretions. In the parenchyma, alveolar wall destruction; Emphysema reduces both surface area available for gas exchange and elastic recoil forces that normally hold small airways open during expiration. In the case of elastic recoil being lost, small airways collapse on expiration, thereby causing the air trapping and dynamic hyperinflation characteristic of advanced COPD (29).

These structural changes are, for the most part unfortunately irreversible, cessation cannot rebuild destroyed alveoli or unscarred peribronchiolar tissue. What it can do, and this is the core of the clinical argument for cessation, is stop new damage being added. The rate at which these pathological processes progress is substantially driven by ongoing inflammatory and oxidative activity, both of which are fuelled by continued smoke and tobacco exposure, remove the fuel and the fire is extinguished.

7.2.2 Inflammatory Pathways

The central pathophysiological process in smoking related COPD is chronic, amplified airway inflammation. Cigarette smoke activates epithelial cells and resident macrophages to release a

cascade of pro inflammatory mediators, like IL-8, TNF alpha, LTB4, MCP-1, that recruit and activate neutrophils, macrophages and CD8+ cytotoxic T lymphocytes (26). Each of these cell types contributes to tissue injury, neutrophils release serine proteases (predominantly neutrophil elastase) and matrix metalloproteinases; Alveolar macrophages in COPD are expanded 5 to10 times, compared to healthy lungs and drive both direct tissue destruction and ongoing cytokine production, CD8+ T cells release perforin and granzyme B, inducing apoptosis of airway epithelial cells.

The protease antiprotease hypothesis, originally proposed to explain AAT deficiency but now understood to operate in smoking related COPD more broadly, holds that the balance between tissue destructive enzymes and their inhibitors is shifted in COPD towards net proteolysis (26). Cigarette smoke contributes to this imbalance both by recruiting protease secreting cells and by directly oxidising and inactivating antiprotease molecules, thereby reducing their capacity to neutralise the proteolytic threat.

A clinically important observation is that airway inflammation in COPD does not simply switch off when a patient stops smoking, studies of bronchoalveolar lavage and bronchial biopsies in ex-smokers consistently show that neutrophilic inflammation attenuates with cessation, however macrophage accumulation and CD8+ T cell infiltration often persist (22). This residual inflammation likely drives the continued, although slower, FEV1 decline, that is observable even in long term ex-smokers with COPD and it provides a biological rationale for anti inflammatory pharmacological strategies that complement cessation rather than being supplanted by it.

7.2.3 Oxidative Stress

Cigarette smoke carries an extraordinary oxidant burden with estimates of free radical concentration in mainstream smoke run as high as 10 to 17th radicals per puff and this oxidative assault is compounded by the reactive oxygen species generated by the inflammatory cells recruited to the airways (26). Reactive oxygen species damage DNA, lipids and proteins directly, they activate NF-kB and AP-1 transcription factors that amplify inflammatory gene expression and perhaps most clinically relevant, they reduce the activity of histone deacetylase 2 (HDAC2), contributing to glucocorticoid resistance. The last point is a partial explaination why inhaled corticosteroids have less anti inflammatory efficacy in COPD than in asthma.

After cessation, circulating and airway markers of oxidative stress fall, though they do not reach the levels seen in population that have never smoked, The reduction in oxidative load is one of the faster acting beneficial consequence of cessation, measurable within weeks and may contribute to the early improvements in symptoms and exercise capacity that some patients notice before any change in FEV1 is detectable on spirometry.

7.2.4 Nicotine Dependence and Why COPD Patients Are Harder to Treat

To understand the reason why COPD patients are harder to treat for tobacco dependence than the general smoking population, it helps to understand the neurobiology of the process of nicotine addiction. Nicotine binds preferentially to Alpha-4 Beta-2 nicotinic acetylcholine receptors in the mesolimbic dopaminergic pathway, the brains reward system, triggering dopamine release in the nucleus accumbens and producing the feelings of reward and reinforcement that drive repeated tobacco use. With chronic exposure, receptor upregulation and desensitisation occur, the smoker needs more nicotine to achieve the same dopaminergic effect and, in its absence, experiences a neurochemical deficit characterised primarily by irritability, anxiety, poor concentration, craving and depressed mood.

COPD patients, as a group, score higher on the Fagerstrom Test for Nicotine Dependence than the smokers without lung disease (41). Several factors likely contribute, they tend to be heavier smokers with longer smoking histories, greater cumulative nicotine exposure producing more extensive receptor upregulation. They tend to inhale more deeply, maximising nicotine delivery per cigarette. They may use cigarettes as a means of managing breathlessness, anxiety and the psychological burden of chronic illness, functions that make cessation feel particularly threatening and they have higher rates of depression and anxiety, conditions in which nicotine provides pharmacological relief through dopaminergic stimulation, making the prospect of withdrawal all the more aversive.

This combination of higher physiological dependence and greater psychological reliance on smoking means that cessation pharmacotherapy needs to work harder in COPD patients and that behavioural support addressing the psychological dimensions of dependence is not optional rather essential.

7.2.5 The Fletcher-Peto Curve and What Cessation Can Realistically Achieve

It would be a grave disservice to any patient and for that matter, any reader, to overstate what cessation can do. It does not reverse COPD, it does not restore the alveoli lost to emphysema or unwind the peribronchiolar fibrosis of established small airways disease. Rather what it does is halt the accelerated progression of lung disease (22). The Fletcher-Peto model, derived from their 1977 cohort of London transport workers (5), showed that susceptible smokers follow a steeper than normal FEV1 decline trajectory from early adulthood and that quitting at any point bends this trajectory back in line with the gradual age related decline of a non-smoker. The earlier a patient quits, the more lung function is preserved, but the benefit of quitting at GOLD stage 3 is not zero, it is clinically meaningful, and the evidence reviewed in the prognosis section bears this out.

The Lung Health Study validated this model in a clinical trial setting, among sustained quitters, those who remained abstinent throughout the 5 year follow up, FEV1 decline was approximately 47 mL per year, compared to 66 mL per year in continuous smokers (3). Over 11 years, the divergence translated into a meaningful difference in functional capacity and ultimately, in survival. These numbers are not theoretical, they are drawn from over 5,000 real patients with mild to moderate COPD who were randomised to a cessation programme versus usual care (4).

7.3 Treatment Methods: Smoking Cessation Interventions in COPD

7.3.1 Nicotine Replacement Therapy

Nicotine replacement therapy (NRT) has been available since the early 1980s and remains the most widely prescribed cessation aid globally, largely because of its accessibility (9). In many countries NRT is available over the counter and in some, is provided free through public health programmes. Its mechanism is straightforward, by delivering nicotine through a non-tobacco route, NRT reduces craving and attenuates withdrawal symptoms, making the early weeks of a quit attempt more manageable without exposing the patient to the thousands of toxic and carcinogenic compounds in cigarette smoke.

Formulations include the 16 hour and 24 hour transdermal patch, nicotine gum (2mg and 4mg), sublingual tablet, oromucosal spray, nasal spray, and nicotine inhalator. The patch provides a slow and steady baseline nicotine level, the rapid acting forms (spray, gum, inhalator) allow patients to manage breakthrough cravings as they arise. Combination NRT, a patch plus a short acting formulation, consistently outperforms either product being used alone, with a Cochrane meta-analysis by Hartmann Boyce and colleagues (2018) estimating odds ratios for cessation of approximately 1.34 compared to patch alone (9). This makes clinical sense, the patch handles the tonic craving, while the short acting product handles the phasic craving triggered by specific cues or stresses.

In the general smoking population, NRT increases the odds of cessation by roughly 1.55 to 1.80 fold compared to placebo, regardless of delivery form (9). In COPD populations specifically, the picture is similar in direction but with noticeably lower absolute quit rates, highlighting the greater difficulty these patients have achieving sustained abstinence. A systematic review by Strassmann and colleagues (2009) found pooled 12 month cessation rates of roughly 12–15% with NRT versus 5–8% with placebo in COPD studies, not spectacular numbers, however clinically and statistically significant (16).

A concern sometimes raised about NRT in COPD patients, particularly those with cardiovascular comorbidities, is whether therapeutic nicotine itself might cause cardiovascular harm. The evidence here is reassuring, multiple pharmacovigilance studies and RCT safety analyses that have been conducted, have reported that NRT delivered nicotine at therapeutic doses does not significantly increase cardiovascular event rates (54). The risk benefit calculation is not close, even if NRT carried some small cardiovascular risk, it would be dwarfed by the cardiovascular harms of continued smoking.

Practical prescribing points for COPD patients include dosing adequacy, heavily dependent smokers (Fagerström Test for Nicotine Dependence ≥7) often need higher dose patches (21mg/24hr) or combination NRT from the outset and formulation choice. The nicotine nasal spray has the fastest absorption kinetics and may be most effective for managing intense cravings, however rhinitis (common in COPD) may reduce tolerability. The nicotine inhalator requires coordinated breathing technique, which may be challenging in patients with severe dyspnoea or diaphragmatic muscle weakness.

7.3.2 Varenicline

Varenicline is the most effective single pharmacotherapy for smoking cessation currently available (55). Full stop. That conclusion is consistent across the Cochrane meta-analyses, the major RCTs, and the network meta-analyses that have tried to rank cessation pharmacotherapies against each other. Its superiority to both NRT and bupropion is not marginal, rather it is statistically robust and clinically meaningful.

The mechanism is elegant in its specificity, varenicline is a selective partial agonist at the alpha 4 beta 2 neuronal nicotinic acetylcholine receptor, the same receptor subtype most implicated in nicotine reward and dependence. As a partial agonist, it does two things simultaneously, it stimulates the receptor sufficiently to maintain some dopaminergic tone (reducing craving and withdrawal symptoms), while binding tightly enough to block the full agonist effect of smoked nicotine (reducing the rewarding effect of a cigarette). The patient who smokes while taking varenicline gets significantly less from the cigarette, which erodes one of the most powerful reinforcers of continued smoking.

In the general smoking population, varenicline at 1mg twice daily (following a dose escalation week starting at 0.5mg once daily for three days, then 0.5mg twice daily for four days) increases the odds of cessation approximately 2.24 fold compared to placebo, according to the most comprehensive available Cochrane network meta-analysis (56). Six month continuous abstinence rates in clinical trials typically fall in the range of 30 to 40%, roughly double those achieved with placebo.

COPD specific evidence is compelling, the Tashkin 2011 trial enrolled 504 patients with mild to moderate COPD in a double blind, randomised, placebo controlled design and is the most frequently cited COPD specific varenicline study (6). Continuous abstinence rates at weeks 9 to 52 were 18.6% with varenicline versus 5.6% with placebo, an odds ratio of approximately 4.0, and a difference that remained statistically significant at 12 months. A second trial by the same group published in 2012 produced broadly comparable results. These figures represent realistic outcomes in a population of COPD smokers, not the optimistic scenario of a clinical trial in healthy, highly motivated smokers.

The neuropsychiatric safety controversy deserves extended attention because it directly affected clinical practice for nearly a decade. Following post marketing surveillance reports of

depression, suicidal ideation, and behaviour changes in some patients taking varenicline, the FDA issued a black box warning in 2009, this was of particular concern in COPD, where comorbid depression and anxiety are already prevalent. The EAGLES trial, a large, double blind, government mandated randomised trial in 8,144 smokers with and without stable psychiatric disorders, was designed specifically to test whether these neuropsychiatric risks were real and significant (8). The main conclusion was, varenicline did not significantly increase neuropsychiatric adverse events compared to placebo, nicotine patch, or bupropion, even in the psychiatric cohort. The FDA removed the black box warning in 2016 and clinicians can now prescribe varenicline in COPD patients with comorbid depression or anxiety without the heightened caution that was previously required, though sensible monitoring for mood changes remains appropriate, as it would be for any patient with a psychiatric history.

Practical considerations, varenicline requires dose reduction in severe renal impairment (eGFR <30 mL/min). Nausea is the most common adverse effect, occurring in around 30% of patients; it is usually mild to moderate, tends to improve after the first couple of weeks, and can be minimised by taking the medication with food and a full glass of water. Extended treatment, continuing for a further 12 weeks beyond the standard 12 week course, has been shown by Tonstad and colleagues to significantly increase 52 week abstinence rates in patients who have successfully quit on initial therapy, and should be offered to COPD patients who have quit but are concerned about relapse (19).

7.3.3 Bupropion

Bupropion hydrochloride arrived at smoking cessation almost accidentally. It was in clinical use as an atypical antidepressant when clinicians noticed that patients taking it for depression reported reduced cigarette consumption and easier quitting. Subsequent investigation established its cessation efficacy through trials specifically designed for this indication and it was approved for cessation by the FDA in 1997 (marketed as Zyban for this use, distinct from its antidepressant formulations).

Its cessation mechanism is attributed primarily to inhibition of neuronal dopamine and noradrenaline reuptake, counteracting the dopaminergic deficit of nicotine withdrawal and to a lesser degree, antagonism of nicotinic acetylcholine receptors, reducing nicotine's reinforcing properties. At the standard dose of 150mg twice daily (after a 3 day titration period at 150mg

once daily), bupropion approximately doubles the odds of cessation compared to placebo. It is inferior to varenicline in direct comparison, but clearly superior to placebo.

In COPD, Wagena and colleagues (2005) conducted an RCT in 255 COPD smokers that demonstrated 1 month CO-confirmed cessation rates of 16% versus 9% with placebo (10). A Cochrane review by Howes and colleagues subsequently confirmed bupropion's efficacy across a broader evidence base (23). Bupropion is best thought of as a second line option for COPD patients, appropriate when varenicline is contraindicated (severe renal impairment, previous hypersensitivity reaction) or not tolerated, and particularly useful in patients with comorbid depression, where its antidepressant activity provides dual benefit.

Safety considerations include the absolute contraindication in patients with a seizure history or predisposition (eating disorders, electrolyte disturbances, concurrent use of seizure lowering medications), the relative contraindication in patients taking MAOIs and the potential for modest blood pressure elevation. Insomnia and dry mouth are the most commonly reported side effects. Because COPD patients frequently have cardiovascular comorbidities, blood pressure monitoring during initiation is prudent.

7.3.4 Comparative Efficacy: A Summary

Table 2

Agent	Mechanism	12 month Abstinence (COPD)	vs. Placebo	Main Limitation
NRT monotherapy	nAChR agonist	8–15%	OR ~1.6	Adherence, dose adequacy
NRT combination	Dual nicotine	12–18%	OR ~1.9	Cost, complexity
Bupropion	DNRI + nAChR antagonist	10–16%	OR ~1.8	Seizure risk, BP
Varenicline	Partial nAChR agonist	18–22%	OR ~2.2–4.0	Nausea, renal dosing
Varenicline + NRT	Combined	22–26%	OR ~2.5+	Limited COPD data

DNRI-Dopamine and Noradrenaline Reuptake Inhibitor, **nAChR-**Nicotinic Acetylcholine Receptor, **NRT-**Nicotine Replacement Therapy, **OR-**Odds Ratio

7.3.5 Behavioural Interventions

Pharmacotherapy is only one half of the equation, the behavioural dimension of smoking, the habitual, psychological, and social aspects of tobacco use that persist independently of neurochemical dependence, dictates a different kind of treatment. A patient who stops craving nicotine still has to navigate the office colleague who smokes, the post meal cigarette ritual, the anxiety that floods in during a difficult phone call. Behavioural interventions are designed to address exactly these dimensions that are often overlooked.

The 5 A's framework, Ask, Advise, Assess, Assist, Arrange, is the most widely recommended brief intervention structure for clinicians. Its simplicity is its strength, it takes three to five minutes, can be delivered by any healthcare professional, and does not require specialist cessation training. The underlying evidence, from a Cochrane review by Stead and colleagues (2013) covering data from many thousands of patients, shows that even brief, structured physician advice significantly increases quit rates compared to no advice (18). The absolute effect is small (roughly 2–3% additional abstinence at 12 months) but given that COPD patients have frequent healthcare contacts at multiple points in the care pathway, the cumulative opportunity for brief advice is substantial.

Motivational interviewing (MI) is a more intensive, patient centred approach that engages directly with the patient's ambivalence about quitting. Rather than instructing or informing, the MI trained clinician reflects the patient's own stated reasons for and against smoking, draws out their intrinsic motivation, and explores the discrepancy between their current behaviour and their stated values and goals. This approach is grounded in the transtheoretical model of Prochaska and DiClemente, which recognises that smokers occupy different 'stages of change' and that one size fits all cessation advice is often ineffective in patients who are not yet contemplating quitting (25).

MI is particularly well suited to COPD patients. A systematic review by Heckman and colleagues (2010) found that MI significantly increased quit rates compared to brief advice (OR 1.47; 95% CI 1.23–1.75), with the benefit most pronounced in ambivalent or pre contemplative smokers, exactly the group most commonly encountered in COPD clinics (13). The fatalistic COPD patient who says 'I've smoked for 40 years, what is the point?' is not someone who will respond to a stern warning, they need a clinician who can explore their

ambivalence without judgment, help them articulate what they actually want for their health, and find their own reasons to act.

Individual and group cognitive behavioural therapy for smoking cessation focuses on identifying the thought patterns and situational triggers that maintain smoking behaviour and building concrete coping strategies. It is more intensive than brief advice or standard counselling, typically delivered over multiple sessions, but the evidence for a dose response relationship is clear, more sessions produce better outcomes. A Cochrane review by Lancaster and Stead (2017) found individual counselling significantly superior to brief advice (OR 1.57), with group CBT producing comparable results (11). Group formats carry an additional potential benefit in COPD: the shared experience of breathlessness, functional limitation, and disease related anxiety creates natural common ground that can generate peer support and normalise the cessation effort.

Telephone quit lines are worth particular mention in the context of COPD because of access. COPD patients are frequently mobility limited, frequently breathless on exertion, and frequently fatigued. Expecting them to attend multiple face to face cessation counselling sessions is, in some cases, simply unrealistic. Quit lines offer proactive, structured telephone based behavioural support that is accessible from home. A Cochrane review by Stead and colleagues (2013) found that proactive telephone counselling significantly increased cessation rates compared to minimal support across 77 trials (12). Most national health systems have free quit line services, ensuring COPD patients know about and are referred to them should be routine.

7.3.6 Digital Health Interventions

The explosion of smartphones has spawned a parallel explosion of smoking cessation apps, and the evidence base, while still maturing, is increasingly substantive. A Cochrane review by Whittaker and colleagues (2019) analysed 26 trials of mobile phone based cessation interventions and found that text message programmes significantly increased short term quit rates (RR 1.54 at 6 weeks to 6 months) (14). The evidence for apps specifically is more mixed reviews have found wide heterogeneity in quality, user engagement, and reported outcomes but higher intensity, interactive digital programmes appear more effective than passive or poorly personalised tools.

COPD specific digital cessation data are genuinely sparse. Most trials of digital interventions have excluded patients with significant pulmonary or cardiovascular comorbidities, which makes direct extrapolation to COPD populations uncertain. What limited data exist, mostly from feasibility and acceptability studies, suggest that COPD patients are willing to engage with digital tools, particularly when they are integrated into broader COPD management platforms that also support symptom tracking, medication adherence and exacerbation recognition. The COVID-19 pandemic accelerated the adoption of digital health tools in COPD management broadly and this may create a practical environment in which COPD specific digital cessation interventions can be rigorously evaluated.

Electronic cigarettes (e-cigarettes, vaping devices) sit in a highly contested space, the Cochrane review by Hartmann Boyce and colleagues (2022) concluded there was moderate certainty evidence that e-cigarettes with nicotine increase cessation compared to NRT and to e-cigarettes without nicotine (38). But COPD specific data are very limited and there is legitimate concern about long term respiratory effects of vaping, which is not a clean aerosol, in patients who already have compromised lung function. The current consensus position of most respiratory societies is one of cautious agnosticism, e-cigarettes may be a harm reduction tool for COPD smokers unable to quit through other means, but they should not be recommended as a first line cessation strategy pending better evidence.

7.3.7 Combined Pharmacological and Behavioural Approaches

The case for combining pharmacotherapy with behavioural support is perhaps the clearest and most consistent finding in the entire cessation literature, the two modalities are not redundant, rather they address different dimensions of the same problem. Pharmacotherapy reduces the neurochemical discomfort of abstinence, the craving, the irritability, the hedonic deficit. Behavioural support addresses the habitual, situational, and psychological dimensions, the triggers, the thought patterns, the social pressures, the strategies for coping with difficult moments. When used together, their effects are additive.

A Cochrane meta-analysis by Stead and Lancaster (2012) analysed 41 trials combining pharmacotherapy (NRT or bupropion) with counselling and found pooled cessation rates significantly higher than pharmacotherapy alone, OR approximately 1.40, with the magnitude

of benefit increasing with counselling intensity (40). GOLD 2024 guidelines are unequivocal on this point, all COPD patients who smoke should be offered both pharmacotherapy and behavioural support (1). This is not a recommendation with asterisks, it applies across all disease stages, all ages, and all previous cessation histories.

Implementing combined therapy in practice requires coordination that is not always easy to achieve. In a busy primary care setting, the prescribing clinician may have limited time and training for behavioural counselling. The practical solution is not to attempt to deliver everything in a single consultation but to use a 'prescribe and refer' model, initiate pharmacotherapy, set a quit date, provide brief advice, and arrange referral to a specialist cessation service, quit line, or structured programme. The evidence supports this distributed approach, what matters is that both components are delivered, not that they are delivered by the same person in the same appointment.

7.3.8 Pulmonary Rehabilitation as a Cessation Setting

Pulmonary rehabilitation (PR) is a multidisciplinary, evidence based intervention comprising individualised exercise training, disease education, nutritional support, and psychosocial management. Its evidence base for improving exercise capacity, dyspnoea, and health related quality of life in COPD is robust, GOLD recommends PR for all symptomatic patients with FEV1 <50% predicted, and for selected patients at earlier stages who remain functionally limited despite pharmacotherapy (1).

What makes PR a particularly valuable setting for smoking cessation is the combination of factors it brings together, patients have enrolled voluntarily in an intensive programme, signalling motivation. They have frequent contact with a multidisciplinary team that includes physiotherapists, nurses, and often psychologists, professionals well positioned to deliver cessation counselling. They receive extensive education about their disease. And crucially, they experience directly, during supervised exercise training, the functional improvements that even early cessation can bring. The 'exertional epiphany', the patient who notices they can walk further after a few weeks of not smoking is anecdotally powerful, and represents a form of immediate, tangible feedback that abstract statistics cannot replicate.

Despite this, systematic integration of cessation support into PR remains inconsistent, studies suggest that fewer than half of PR programmes have a structured cessation component. The logical conclusion that every PR programme should include structured cessation support seems straightforward, yet implementation has been slow.

7.3.9 Barriers and facilitators Specific to COPD

Why is cessation so difficult in COPD? The biological answer is, higher nicotine dependence, which is part of it, but only part. Qualitative research with COPD patients has identified a cluster of psychological and social factors that are either absent or less pronounced in the general smoking population.

Fatalism is probably the most commonly encountered and clinically significant barrier. Patients who have smoked for 40 years, who have developed a chronic progressive lung disease as a direct consequence, and who now require inhalers, have frequent chest infections, and struggle with stairs, these patients often arrive at the question of cessation already defeated. 'What is the point? The damage is already done.' 'I've already got COPD, it can't get any worse than it already is.' 'I've tried stopping before but I always end up going back.' These beliefs are not irrational given the patient's experience, they are understandable responses to a difficult situation. But they are clinically inaccurate, the evidence for continued benefit of cessation even at advanced stages is clear and they must be addressed directly and compassionately in cessation counselling.

Comorbid depression and anxiety present in up to 40% of COPD patients, represent a second major barrier. These are not incidental findings. Depression is a direct predictor of cessation failure in COPD, with odds ratios for cessation failure of approximately 1.5–2.0 compared to non depressed smokers. The mechanism is partly pharmacological (nicotine's dopaminergic effects provide real, if temporary, relief from depressive symptoms), partly psychological (cessation feels like one more loss for a patient already grieving lost function and independence), and partly behavioural (depression reduces self efficacy and motivation). Untreated depression is a cessation saboteur, and its presence should prompt concurrent treatment not a reason to delay cessation support, but a reason to ensure it is more comprehensive.

Social factors should not be dismissed for their role in COPD. COPD disproportionately affects people from lower socioeconomic backgrounds where smoking rates are higher, social networks are more likely to include smokers, and practical barriers to accessing cessation services cost, transport, working hours are greater (33). Financial incentives for cessation have shown promise in several populations, and the provision of cessation medications at no cost to the patient is associated with substantially higher uptake (60).

On the facilitators side, the COPD diagnosis itself can be a 'teachable moment', a point at which the patient's usual defences against cessation advice are lowered by the immediacy of a medical diagnosis. Studies suggest that newly diagnosed COPD patients are particularly receptive to cessation counselling in the weeks immediately following diagnosis, before the initial shock has been replaced by normalisation. Spirometry feedback is a specific technique that leverages this moment: showing the patient their current FEV1 alongside the concept of 'lung age' (the age of a healthy non-smoker with the same FEV1) makes the abstract concrete and can powerfully motivate action. A Cochrane review by McClure and colleagues (2009) found a modest but significant effect of spirometry based feedback on quit rates (37).

7.4 Prognosis: What Cessation Actually Changes in COPD

7.4.1 Lung Function

The most rigorously studied prognostic outcome of cessation in COPD is the modification of FEV1 trajectory, as discussed in the mechanisms section, Fletcher and Peto's 1977 model demonstrated that cessation at any point produces a shift from the accelerated trajectory of the susceptible smoker towards the age related trajectory of the non-smoker (5). The Lung Health Study quantified this in a trial setting: sustained quitters lost approximately 47 mL of FEV1 per year over 5 years, versus 66 mL per year in continuous smokers (3). The difference, roughly 20 mL per year, accumulates over decades into a very large difference in functional capacity and, by extension, in symptoms, exercise tolerance, and independence.

Data from the ECLIPSE study, a large, multicentre, longitudinal observational study of COPD, confirm the relationship in a real world setting (20). Active smoking was independently associated with a faster rate of FEV1 decline across all GOLD stages, after adjustment for age, sex, baseline FEV1, and exacerbation frequency. This confirmation from observational data is

important because it validates the RCT findings in populations that include the severe and very severe COPD patients who are systematically underrepresented in RCTs.

One nuance worth noting: FEV1 sometimes shows a modest improvement in the first 3 to 6 months after cessation, particularly in patients with significant bronchial hyperresponsiveness and reversibility (22). This early improvement reflects resolution of acute airway inflammation and oedema rather than structural reversal, and it does not persist indefinitely. After the initial period, the slope of FEV1 decline in ex-smokers is parallel to that of non-smokers rather than tracking back to the pre disease trajectory. Managing patient expectations about this, explaining that the improvement in the trajectory, not a reversal of the disease, is what they are working towards is part of honest cessation counselling.

7.4.2 Acute Exacerbations

Acute exacerbations of COPD are events of outsized clinical importance. They cause acute deterioration in quality of life and gas exchange, require intensification of treatment and often hospitalisation, carry a mortality rate of 2 to 11% per admission, and are associated with accelerated long term FEV1 decline (43). Patients who suffer frequent severe exacerbations, defined as those requiring hospitalisation, have dramatically worse prognoses than those with infrequent exacerbations, and this relationship is largely independent of baseline FEV1.

The evidence that smoking cessation reduces exacerbation frequency is observational but consistent. The SPIROMICS cohort, a large, multicentre US study of COPD natural history, found that current smokers had significantly higher exacerbation rates than ex-smokers after adjustment for multiple covariates, and that longer duration of abstinence was associated with progressively lower exacerbation risk (61). The mechanisms are biologically plausible: cessation attenuates airway inflammation, reduces bacterial colonisation, improves mucociliary clearance, and reduces the epithelial vulnerability to respiratory viruses that drives a substantial proportion of exacerbations.

Hospitalisation rates follow the same pattern, Groenewegen and colleagues (2003) found significantly fewer COPD related hospital admissions in sustained ex-smokers compared to current smokers over a 12 month observation period (48). Given that each COPD hospitalisation costs tens of thousands of dollars in direct healthcare costs, even modest

reductions in admission frequency translate into substantial cost savings at the health system level, an argument that healthcare funders and commissioners should take seriously when considering investment in cessation programmes.

7.4.3 Health Related Quality of Life

Health related quality of life (HRQoL) in COPD is measured by validated instruments including the St George's Respiratory Questionnaire (SGRQ, scored 0–100 with higher scores indicating worse quality of life), the COPD Assessment Test (CAT, 0–40), and the Clinical COPD Questionnaire (CCQ, 0–6). The minimum clinically important difference (MCID) on the SGRQ is 4 units, a helpful benchmark for interpreting the magnitude of any reported change (60).

Several studies have demonstrated HRQoL improvements following cessation in COPD patients. An analysis by Willemse and colleagues (2005) found significant SGRQ improvements in successful quitters compared to continued smokers at 12 months, with mean improvements exceeding the 4 unit MCID (63). These improvements occurred across all SGRQ domains, symptoms, activity, and impact, suggesting a broad quality of life benefit rather than improvement in one narrow dimension.

An important clinical point for patient counselling is that HRQoL may temporarily worsen in the first few weeks after cessation, as recovering mucociliary function leads to a transient increase in cough and sputum production. Some patients interpret this as evidence that quitting has made them worse and use it as a reason to relapse. Proactive counselling, explaining that this is expected, normal, and temporary, can prevent early dropout from cessation attempts driven by this misinterpretation.

7.4.4 Mortality and Survival

At 14.5 years of follow up in the Lung Health Study, all cause mortality was significantly lower in the intervention group than in the control group (HR 0.88; 95% CI 0.78–0.99) (4). The survival benefit was driven primarily by lung cancer, COPD patients who continued smoking had markedly higher lung cancer rates, with a smaller contribution from COPD specific mortality. The absolute difference in survival may appear modest in percentage terms, but for an individual patient it represents a meaningful extension of life.

Observational data from multiple cohort studies confirm this survival benefit in real world COPD populations. Consistently, former smokers with COPD have better survival than current smokers, after adjustment for confounders including baseline FEV1, exacerbation history, and comorbidities (35).It offers less benefit than cessation at an earlier stage, yes, however 'less benefit' is not 'no benefit' and the clinical significance of even a modest survival extension increases with disease severity.

7.4.5 Prognosis in Specific Subpopulations

Patients with COPD and comorbid psychiatric disease present the most difficult challenge for cessation. In patients with severe mental illness, schizophrenia, bipolar disorder, severe recurrent depression, smoking rates are extraordinarily high (up to 60 to 70% in some populations), cessation rates are lower, and relapse rates are higher (64). Yet the evidence that cessation benefits apply to these patients on a disease trajectory level is not in doubt. What is needed is collaborative care that treats psychiatric illness, tobacco dependence, and COPD concurrently, not sequentially. The traditional practice of deferring cessation support 'until the psychiatric situation is stable' is not evidence based and may represent a form of therapeutic nihilism that disproportionately harms patients who already face significant health inequalities.

Elderly COPD patients (loosely defined as over 65) may have specific concerns: the perceived irrelevance of cessation benefits at their age, the challenge of changing a lifelong habit, reduced social support. What the evidence shows is that the benefits of cessation, particularly exacerbation reduction and symptom improvement, accrue rapidly and within a timeframe that is clinically meaningful even for an 80 year old. Age should not be a barrier to offering cessation support (34).

Patients with COPD and confirmed AAT deficiency who continue to smoke have a particularly bleak prognosis; their rate of FEV1 decline on continued smoking is among the most rapid of any patient group. In this population, cessation is not just recommended, it is urgent, and every clinical encounter is an opportunity to reinforce that urgency with compassionate directness.

8. Summary of Results

Taken together, the evidence reviewed here paints a consistent and, on the whole, optimistic picture, or at least as optimistic as the literature on a serious progressive disease can be. Smoking cessation works in COPD. It works pharmacologically, behaviourally, and in combination. It works at GOLD stage 1 and GOLD stage 4, it works in patients who are 50 and patients who are 75. The benefits span the full range of clinically relevant outcomes, the rate at which the lungs deteriorate, the frequency of dangerous exacerbations, the quality of day to day life, and the probability of surviving to see the next five years.

Varenicline is the most effective single pharmacotherapy, a finding that is robust and consistent enough that it has moved into first line position in all major guidelines (56). Its neuropsychiatric safety is now established by large prospective trial data (EAGLES), resolving the decade long shadow of the FDA black box warning (8). Bupropion and combination NRT are genuine alternatives for patients who cannot use varenicline; they are not merely second best options but clinically effective treatments in their own right (30).

Behavioural support is not optional. The evidence for dose response, more intensive support yields better outcomes, is evident (11). Brief advice is valuable because it is delivered at scale. Motivational interviewing is particularly suited to the COPD population because it addresses ambivalence directly. Group CBT is effective and carries the additional benefit of peer support. Quit lines extend access to patients who cannot attend face to face services. Digital tools are promising but require COPD specific evaluation.

The combination of pharmacotherapy and behavioural support consistently outperforms either alone (40). This is the standard of care. Pulmonary rehabilitation is an underutilised but high potential setting for delivering this combined approach, and structured cessation support should be a routine component of every PR programme.

The barriers, higher nicotine dependence, psychiatric comorbidity, fatalism, socioeconomic disadvantage, are real and clinically significant. They explain why COPD patients have lower absolute cessation rates than healthier smokers, and why more intensive and sustained support is required. They do not provide a justification for not trying.

Important gaps remain in the literature, particularly regarding severe-stage patients and long-term follow-up, which are addressed in the recommendations below.

9. Conclusions and Recommendations

9.1 Conclusions

This narrative literature review has drawn together evidence from across pharmacological, behavioural and combined cessation modalities to arrive at what is, ultimately, an unambiguous conclusion: smoking cessation is the single most important intervention a clinician can offer to a patient with Chronic Obstructive Pulmonary Disease. The breadth and consistency of this evidence is striking, from the molecular disruption of the protease antiprotease balance through to the population level mortality data from the Lung Health Study, the same message emerges regardless of the level of analysis (3). Cessation works and it works across every stage of the disease.

The clinical benefits are wide ranging. Smoking cessation attenuates the accelerated decline in FEV1 that characterises active smokers with Chronic Obstructive Pulmonary Disease, bringing the trajectory of lung function loss closer to that of a healthy ageing non-smoker. It reduces the frequency and severity of acute exacerbations, the events most responsible for hospital admissions, deterioration in quality of life, and the enormous financial burden of Chronic Obstructive Pulmonary Disease management. It improves health related quality of life through reductions in cough, sputum production, and respiratory infection susceptibility, as well as through the broader psychological benefits of achieving what many patients regard as an impossible goal. It also extends survival, with the mortality benefit now demonstrated even in patients with severe and very severe airflow obstruction, a finding that directly contradicts the nihilistic belief, disturbingly prevalent among both patients and clinicians, that cessation at an advanced stage of disease is a futile endeavour.

It is worth dwelling on this last point, because clinical nihilism around cessation in Chronic Obstructive Pulmonary Disease is not a minor problem, it is arguably the most significant barrier to effective implementation of the evidence base reviewed here. When clinicians do not routinely offer cessation support, because they assume the patient won't engage, or that the

disease is already too advanced, or that previous failed attempts mean future ones are equally doomed, the consequence is that patients are denied an intervention that would, on the balance of evidence, meaningfully extend and improve their lives. The data do not support this nihilism. Every clinical encounter with a Chronic Obstructive Pulmonary Disease patient who smokes is an opportunity and treating it as such requires an active shift in clinical culture.

The efficacy and safety profile of varenicline now leaves little clinical justification for defaulting to less effective alternatives, the data support its routine first line use across all Chronic Obstructive Pulmonary Disease patient groups, including those with comorbid psychiatric conditions. Combination nicotine replacement therapy and bupropion offer effective alternatives for patients in whom varenicline is not appropriate. The practical implication is that prescribing pharmacotherapy without arranging behavioral support is an incomplete intervention, a gap that a 'prescribe and refer' model can close even within time-limited consultations. The mechanism is intuitive, pharmacotherapy addresses the neurochemical dimension of addiction, while behavioural support addresses the habitual, emotional, and social dimensions that pharmacotherapy alone cannot reach.

Behavioural approaches deserve particular emphasis in the Chronic Obstructive Pulmonary Disease context, the high prevalence of depression, anxiety, and fatalistic cognition in this population creates a pattern of cessation difficulty that goes beyond nicotine dependence alone. Chronic Obstructive Pulmonary Disease patients do not simply find it harder to quit because they smoke more heavily, though they do. They also find it harder because their relationship with smoking is entangled with grief over their diagnosis, shame about causation, and hopelessness about their future. Motivational interviewing, with its nonjudgmental, patient centred exploration of the patient's own values and ambivalence, is particularly well suited to this clinical reality. It does not require patients to already want to quit; it starts with them where they are.

Digital cessation tools represent an area of genuine promise that the current evidence base has not yet adequately evaluated in Chronic Obstructive Pulmonary Disease populations. Given the mobility limitations, dyspnoea, and geographic barriers to in person services that many Chronic Obstructive Pulmonary Disease patients face, the potential of app based and remote cessation support is considerable. The pandemic period demonstrated that patients with chronic respiratory conditions are both willing and able to engage with digital healthcare delivery. The

gap in the evidence is not lack of patient interest but lack of well designed, adequately powered, Chronic Obstructive Pulmonary Disease specific trials, a gap that future research must address as a priority.

Pulmonary rehabilitation occupies a special position in this discussion, it is an intensive, structured intervention that places healthcare professionals and motivated patients in sustained, repeated contact, precisely the conditions under which cessation support is most effective. The integration of smoking cessation into pulmonary rehabilitation is not merely advisable; it is a missed opportunity when it does not happen. The 'exertional epiphany', the lived experience of improved breathing capacity during pulmonary rehabilitation that cessation facilitates, is a motivational resource that no amount of abstract statistics can replicate, and it remains an underutilised tool in cessation counselling.

Finally, this review has identified a number of important limitations in the current evidence base that temper the confidence with which some conclusions can be drawn. The underrepresentation of patients with GOLD stage III and IV Chronic Obstructive Pulmonary Disease in cessation trials is a substantial gap: these are the patients with the most to gain from cessation support and the most complex barriers to address, yet they are systematically excluded from the studies that might most directly inform their management. Long term follow up data beyond 12 months remain sparse, leaving questions about the durability of cessation effects on exacerbation rates and survival inadequately answered. The role of electronic cigarettes as a harm reduction strategy in Chronic Obstructive Pulmonary Disease patients who cannot achieve complete cessation remains controversial and unresolved, with the available evidence insufficient to support a definitive recommendation in either direction.

9.2 Recommendations for Clinical Practice

Based on the totality of evidence synthesised in this review, the following recommendations are offered for clinical practice in the management of tobacco dependence in patients with Chronic Obstructive Pulmonary Disease:

1. **Universal, routine enquiry at every encounter:** Every healthcare professional involved in the care of a Chronic Obstructive Pulmonary Disease patient, regardless of specialty, care setting, or the primary purpose of the consultation, should ask about

smoking status at every encounter and document this clearly. The Chronic Obstructive Pulmonary Disease diagnosis should be actively used as a 'teachable moment' rather than allowed to pass without a cessation discussion. A brief, clear, and nonjudgmental recommendation to quit, delivered by a trusted clinician, has a measurable and reproducible effect on cessation rates even when it lasts only three to five minutes.

2. **First line pharmacotherapy with varenicline:** All Chronic Obstructive Pulmonary Disease patients who smoke and express any willingness to make a cessation attempt should be offered varenicline as the first line pharmacological option, unless there is a specific contraindication such as severe renal impairment. Clinicians should be aware that the neuropsychiatric concerns historically associated with varenicline have been comprehensively addressed by the “EAGLES” trial data and should not be used as a reason to withhold the most effective available medication (8). Dosage should be individualised, with consideration of extended treatment courses for patients who achieve initial cessation.

3. **Combination Nicotine Replacement Therapy as an effective alternative:** Where varenicline is not tolerated or is contraindicated, combination nicotine replacement therapy, a long acting patch with a short acting formulation for breakthrough cravings, should be offered rather than single agent nicotine replacement therapy. The evidence for superior efficacy of combination nicotine replacement therapy over monotherapy is consistent and clinically significant.

4. **Bupropion in patients with comorbid depression:** In patients with Chronic Obstructive Pulmonary Disease and comorbid depression, bupropion should be considered as a pharmacological option, both for its cessation efficacy and its antidepressant activity. Concurrent identification and treatment of depression and anxiety using validated screening tools (PHQ-9, GAD-7) should be routine in all Chronic Obstructive Pulmonary Disease patients, not simply those who report psychological symptoms.

5. **Mandatory behavioural support alongside all pharmacotherapy:** No pharmacological cessation aid should be prescribed without accompanying behavioural support. Where intensive face to face counselling is not available, as is frequently the

case in primary care, telephone quit line referral is a well evidenced, accessible alternative that should be offered proactively rather than as an afterthought. The intensity of behavioural support should be escalated in line with patient need and the complexity of barriers present.

6. **Motivational interviewing as the default counselling approach in Chronic Obstructive Pulmonary Disease:** Given the high prevalence of ambivalence and fatalistic attitudes in this population, motivational interviewing techniques should be the default framework for cessation counselling, particularly in patients who are not yet ready to make a quit attempt. Clinicians should receive basic training in MI techniques and should understand that a patient in the precontemplation stage is not a clinical dead end they are a patient whose stage requires a different, staged appropriate intervention.

7. **Active counteraction of nihilism, in patients and clinicians:** Evidence based information about the benefits of cessation at all Chronic Obstructive Pulmonary Disease stages including, survival benefit in severe disease, should be incorporated into every cessation discussion. The use of spirometry feedback and lung age visualisation is a simple, feasible, and evidenced motivational tool that should be more widely deployed. Patients who express the belief that it is 'too late' to benefit from cessation should receive specific, personalised evidence to the contrary.

8. **Mandatory integration of cessation into pulmonary rehabilitation:** Pulmonary rehabilitation programmes should include a structured, evidence based smoking cessation component as a standard element, not an optional addition. Programme coordinators should ensure that all eligible patients are offered pharmacotherapy and behavioural support within the pulmonary rehabilitation framework and that the physical improvements experienced during pulmonary rehabilitation are explicitly linked to cessation in patient education sessions.

9. **Long term, relapse sensitive follow up:** Smoking cessation should be treated as a component of ongoing Chronic Obstructive Pulmonary Disease management rather than a onetime intervention with a binary outcome. Patients who relapse should be offered renewed cessation attempts without judgement, with recognition that the average smoker makes multiple attempts before achieving sustained abstinence and that

each prior attempt carries forward learning and motivation. Repeat prescribing of pharmacotherapy after relapse is appropriate and evidence based.

10. **Addressing socioeconomic determinants:** Where possible, prescribers should ensure that cessation medications are accessible and financially feasible for patients, advocating for subsidised provision in healthcare systems where this is not already guaranteed. Chronic Obstructive Pulmonary Disease disproportionately affects individuals from lower socioeconomic backgrounds and the cost of cessation medications should not constitute a barrier to accessing the most effective disease modifying intervention available.

11. **Specific attention to Chronic Obstructive Pulmonary Disease patients with alpha-1 antitrypsin deficiency:** Given the particularly rapid and severe disease progression associated with smoking in Alpha-1 Antitrypsin deficient Chronic Obstructive Pulmonary Disease patients, cessation should be communicated to these individuals as an absolute clinical priority. Specialist multidisciplinary input should be sought early, and cessation support should be offered at the earliest possible stage, ideally at the point of genetic diagnosis.

9.3 Recommendations for Future Research

The field would benefit substantially from well powered randomized controlled trials of cessation interventions specifically enrolling GOLD stage III–IV patients, with follow up extended to 24 to 36 months and inclusion of disease specific outcomes beyond quit rate. Rigorous evaluation of Chronic Obstructive Pulmonary Disease specific digital cessation tools including smartphone applications and AI driven support, trials of cessation strategies tailored to Chronic Obstructive Pulmonary Disease patients with comorbid severe mental illness. High quality prospective studies on the respiratory effects of e-cigarettes in Chronic Obstructive Pulmonary Disease patients, pharmacogenomic research to support individualised pharmacotherapy selection and implementation science research examining how guideline recommendations can be more consistently translated into routine clinical practice across different healthcare system contexts.

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