(NAC) may reduce exacerbations and modestly improve health status.[1031-1034] In contrast, it has been shown that erdosteine may have a significant effect on (mild) exacerbations irrespective of concurrent treatment with ICS. Due to the heterogeneity of studied populations, treatment dosing and concomitant treatments, currently available data do not allow precise identification of the potential target population for antioxidant agents in COPD.[1035]

Phosphodiesterase 3 and 4 (PDE 3 & PDE4) inhibitors

Ensifentrine is a novel, first-in-class, inhaled dual inhibitor of PDE3 and PDE4 with both anti-inflammatory activity and bronchodilator effects. PDE3 inhibition, through modulation of cyclic GMP levels, causes smooth muscle relaxation.[1036] In parallel phase III studies, ensifentrine, delivered via standard jet nebulizer, significantly improved lung function[1036] and dyspnea but had inconsistent effects on quality of life. A reduction in exacerbation rate was suggested but the patient populations were not enriched for exacerbation risk. In addition, the studies were not designed to assess the impact of ensifentrine on top of LABA+LAMA or LABA+LAMA+ICS making it difficult to fully position this agent in our treatment algorithm (**Figure 3.9**).[501,700-702] Studies did not find safety or tolerability issues.[1037] Ensifentrine is currently only available in the United States.

Other drugs with potential to reduce exacerbations

Four large phase 3 studies have investigated the efficacy of the anti-IL-5 monoclonal antibody mepolizumab[1038] and the anti-IL-5 receptor-α antibody benralizumab[1039] in patients with COPD, who had a history of two or more exacerbations in the last year and increased blood eosinophil count. The studies showed inconsistent effects on exacerbation reduction, and none have received regulatory approval for treatment of COPD. Currently, large randomized trials are been conducted to investigate whether these and other biologic treatments are effective in a population who have more compelling evidence of eosinophilic or type II airway inflammation.[701]

Dupilumab is a fully human monoclonal antibody that blocks the shared receptor component for interleukin-4 and interleukin-13. In two large, phase 3, double-blind, randomized trials, patients with COPD, chronic bronchitis, a history of two or more moderate exacerbations or one or more severe exacerbation(s) in the last year despite treatment with LABA+LAMA+ICS, and blood eosinophil count of ≥ 300 cells/µL who received dupilumab had fewer exacerbations, better lung function and improved health status over 52 weeks.[700,701]

Nedocromil and leukotriene modifiers have not been tested adequately in COPD patients and the available evidence does not support their use. [1040,1041]

There was no evidence of benefit, and some evidence of harm, including malignancy and pneumonia, following treatment with an anti-TNF-alpha antibody (infliximab) in moderate to severe COPD.[1042]

A recent Cochrane meta-analysis did not show sufficient evidence to support the use of immunostimulants.[1043]

An RCT of the selective β1 receptor blocker metoprolol in patients with moderate or severe COPD, who did not have an established indication for beta-blocker use, showed it did not delay the time until the first COPD exacerbation compared to the placebo group and hospitalization for exacerbation was more common among the patients treated with metoprolol.[1044,1045] There is no evidence that beta-blockers should be used in people with COPD who do not have a cardiovascular indication for their use.

Simvastatin did not prevent exacerbations in people with COPD who had no metabolic or cardiovascular indication for statin treatment.[1046] An association between statin use and improved outcomes (including decreased exacerbations and mortality) has been reported in observational studies of people with COPD who received them for cardiovascular and metabolic indications.[1047]