Effectiveness and safety of medicines used in COPD patients

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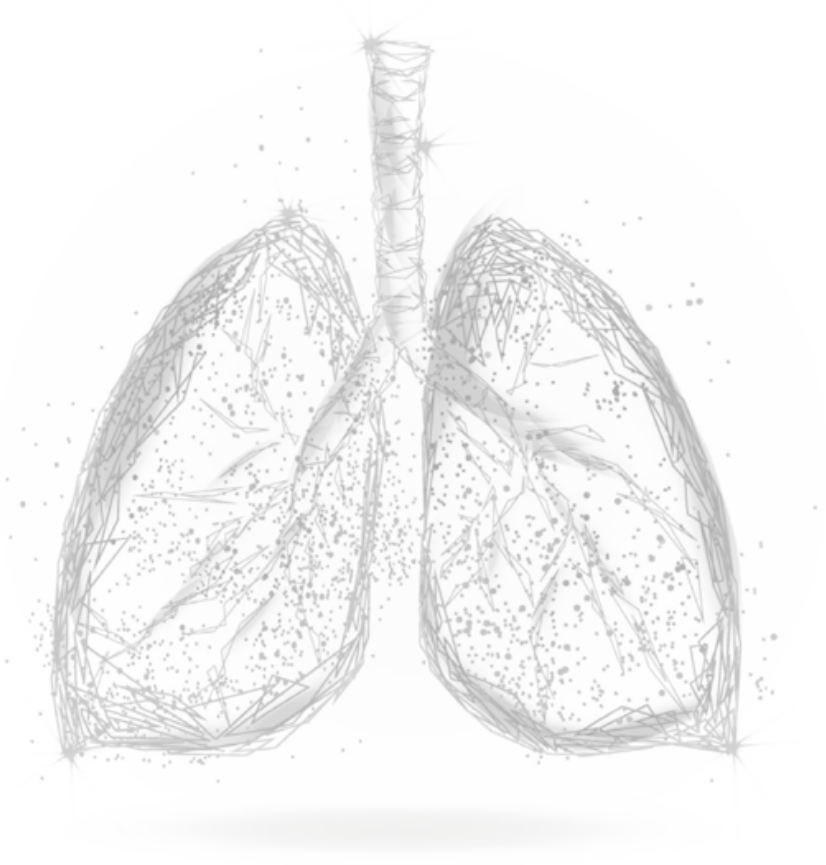
CHAPTER 1



General Introduction

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Chronic obstructive pulmonary disease

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report 2020, Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation. Such symptoms are caused by airway and/or alveolar abnormalities usually triggered by significant exposure to noxious particles or gases.[1] Cigarette smoking is the main independent causal risk factor for COPD with indoor and outdoor air pollution and occupational exposure to dust and noxious particles also being the risk factors for COPD.[2] Moreover, host factors that may contribute to the development of COPD include age, genetics, airway hyper responsiveness and abnormal lung development.[3-5]

The prevalence of COPD varies across countries as well as regions within countries. According to the findings of a global meta-analysis, the number of COPD cases increased to 384 million in 2010, with a global prevalence of 12% (ranging between 8% and 15%).[6] COPD is commonly diagnosed in individuals aged 40 years or older based on the presence of associated symptoms and risk factors. However, a definitive COPD diagnosis requires the performance of spirometry. The presence of a post-bronchodilator $FEV_1/FVC < 0.7$ confirms the presence of airflow limitation and results in a COPD diagnosis. COPD patients are currently categorized into four GOLD stages of severity of airflow limitations based on the predicted value of FEV_1: mild (stage I, $FEV_1 \geq 80\%$ predicted), moderate (stage II, $50\% \leq FEV_1 < 80\%$ predicted), severe (stage III, $30\% \leq FEV_1 < 80\%$ predicted) and very severe (stage IV, FEV1 < 30% predicted).[1] A large prevalence study estimated that the rate of COPD for GOLD stage II and higher is around 10% in the general population, and a little higher in men than women (11.8% and 8.5%, respectively).[7]

COPD is one of the leading causes of morbidity and mortality worldwide.[8] Its burden is predicted to increase in the coming decades as a result of continuous exposure to risk factors in developing countries and aging of the population worldwide, particularly in high-income countries.[9] Smoking cessation interventions, increased physical activity, and early diagnosis and treatment of related comorbidities are considered key measures for reducing the health-economic burden of COPD. [10]

Up to now, the key goals of COPD treatment have been to improve patients' prognosis and prevent the disease from worsening. The main treatment used in the daily management of mild and moderate COPD is pharmacotherapy. Bronchodilators, including short- and long-acting β2-agonists (SABA and LABA) and short- and long-acting anticholinergics (SAMA and LAMA) are essential for managing and preventing symptoms, and combined treatment (SABA/SAMA, LABA/LAMA or LABA/ICS) may be used as appropriate. Non-

pharmacological treatment comprises pulmonary rehabilitation (e.g., exercise training, education, and behavioral change).[11] Oxygen therapy is necessary for patients with very severe COPD and lung surgery may also be necessary.

Exacerbations of COPD and antibiotic use

An exacerbation of COPD is defined as an acute worsening of respiratory symptoms that necessitates additional therapy.[1] COPD patients can periodically experience acute exacerbations that may accelerate the decline in lung function, reduce the quality of life, and increase mortality and health-care costs.[12,13] [14] Infections, especially bacterial infections, and inflammation are thought to be an important trigger for exacerbations of COPD. Previous studies have found that bacteria are responsible for around 40% to 50% of exacerbations.[15,16] *S. pneumoniae*, *H. influenza*, *P. aeruginosa*, *M. catarrhalis*, *A. baumannii*, and *S. aureus* were the most frequently reported bacteria that cause exacerbations of COPD.[16-18] According to the GOLD guideline, the main goals in treatment of COPD exacerbations are minimizing the negative impact of the current exacerbation and preventing subsequent exacerbations.[1] Because almost 40% of exacerbations are bacteria-caused respiratory tract infections,[16] the use of antibiotics has become a common component in the management of acute exacerbations among COPD patients, both in terms of treatment and prevention.[1,19]

Notably, recommendations in prophylactic use of antibiotics in the management of COPD exacerbations are conditional and unspecific. Only long-term macrolides are currently mentioned as first-line therapy.[1,19] Moreover, in terms of current evidence, an optimal regimen of prophylactic antibiotics for exacerbations has not been well established, and related recommendations regarding an appropriate schedule (continuous vs. intermittent) and the duration of a specific antibiotic intervention (below or equal to 6 months vs. above 6 months) are still lacking. Besides, the effects of even the most extensively researched antibiotics macrolides—let alone other potentially suitable antibiotics—on the time to the first exacerbation, changes in lung function, the bacterial load, and airway inflammation have not been adequately evaluated.[20] Knowledge of these outcomes is also vital for elucidating possible mechanisms behind the reduction of exacerbations through the prophylactic use of antibiotics, and for weighing benefits and risks.[21]

The beneficial effects of oral corticosteroids as an effective treatment for acute exacerbations of COPD (AECOPD) in improving COPD symptoms and lung function are well established.[22] However, although antibiotics have been recommended for the treatment of AECOPOD when signs of bacterial infection are present,[1] there is still uncertainty regarding the beneficial effects of antibiotic treatment used in the combination with oral glucocorticoids for AECOPD, particularly in the case of outpatients in real-world settings. In 2012, a Cochrane review that pooled the results

of five RCTs conducted among outpatients did not reveal a significantly reduced risk of treatment failure associated with antibiotics currently prescribed for outpatients.[23] However, an updated version of this Cochrane review conducted in 2018 presented statistically significant beneficial effects of current antibiotics prescribed for outpatients.[24] Two new RCTs were included in this later study in relation to the earlier review conducted in 2012.[25,26] Notably, one of the two RCTs did not support the beneficial effects of antibiotics treatment on AECOPD, although it did contribute to almost 25% of the sample size of the updated pooled results.[25]

Hence, most of the available scientific evidence on the effects of antibiotics for AECOPD is basically derived from RCTs. It is widely accepted that RCTs provide solid evidence with high internal validity, however, their generalizability in the real world, especially in outpatient settings is low. COPD is a chronic disease and is mostly managed on an outpatient basis within a population that is more heterogeneous compared with populations from RCTs. Moreover, the use of antibiotics for AECOPD treatment is not always appropriate and in line with related guidelines.[27,28] Therefore, the effect of antibiotic treatment for AECOPD in real-world settings may differ from those obtained in clinical trials and require further investigation.

Comorbidities of COPD and potential drug-drug interactions

COPD is a chronic disease and its prevalence increases with age; around 15% of the general population over 65 years is affected by COPD.[29] Hence, age-related comorbidities frequently co-exist with COPD.[30] The most common concomitant chronic conditions associated with COPD include cardiovascular disease (e.g., heart failure, ischemic heart disease, and arrhythmias), metabolic disease (e.g., diabetes), osteoporosis, depression and anxiety, lung cancer and gastroesophageal reflux (GERD).[1,30]

COPD itself is a complex disease that entails the need for a variety of medications to improve lung function and treat exacerbations.[1] Multiple comorbidities further complicate the medical management of COPD, resulting in polypharmacy among a large section of COPD patients. Polypharmacy poses a potential risk of drug-drug interactions (DDIs) that may induce adverse events and treatment failures. Moreover, COPD is an age-related disease that generally manifests at an older age. Therefore, these older patients are more susceptible to DDIs due to gradual physiologic negative changes that may influence their pharmacokinetics and the pharmacodynamics of the drugs used.[31]

As most evidence about drug effects is from clinical trials, more attention should be paid to issues related to polypharmacy and to potential DDIs in the management of COPD in real-world settings.[32] This is especially the case for antibiotic therapy as it includes different drug classes that vary in their mechanisms relating to absorption and metabolism, making their interaction with other medications more likely. Comprehensive information for clinicians to avoid potential DDIs, however, is lacking.

Smoking cessation drug therapy and neuropsychiatric safety

Tobacco smoking is the main risk factor for COPD and other physical and mental disorders.[33-35] This preventable behavior poses huge threats to global public health.[36,37] Although in recent years, strict tobacco control policies have prompted a global decline in smoking,[36] the actual numbers of smokers and smoking-related disease burden continues to increase because of the growing population worldwide.[38] More than eight million people continue to die annually as a result of tobacco consumption.[39]

Therefore, smoking cessation strategies to prevent smoking-related diseases are imperative.[40] Varenicline, which was the first non-nicotine, pharmacotherapeutic, smoking cessation product, has been found to be more efficacious than other therapies, such as single-dose bupropion and nicotine replacement therapy (NRT).[41] However, following varenicline's approval by the FDA in 2006, safety concerns were raised relating to its neuropsychiatric adverse events, which include suicidal thoughts, aggressive behavior, depression, anxiety, and sleep disorders.[42] Numerous RCTs were subsequently conducted with varenicline to generate evidence on its safety.[43] In light of their findings, the FDA warning was removed in 2016. However, concerns remain, given the strict inclusion and exclusion criteria applied in RCTs that result in the participation of relatively healthy individuals and the lack of consistent real-world evidence. Notably, special risk populations demonstrating increased smoking prevalence, such as COPD patients, have generally been excluded from RCTs.[44]

As previously noted, most COPD patients are elderly and have multi-morbidities, making them more susceptible to adverse drug events (ADEs). Similarly, there is evidence that individuals with psychiatric disorders experience relapses of psychiatric symptoms more frequently than those without these disorders.[45,46] The safety of varenicline use for these specific populations has not been established. Although a few studies were conducted among patients with COPD or psychiatric disorders,[47,48] the results were inconsistent. Consequently, more observational studies are still needed to generate the real-world evidence relating to the safety of varenicline use.

PSSA and observational study designs in drug safety evaluation

Most evidence regarding the effects of drugs is derived from strictly regulated clinical trials. However, the results from RCTs may not reflect the real-world situations, given that the participants are relatively healthy and because of the limited scope for detecting rare events with clinical trials. Therefore, real-world evidence derived from traditional, non-randomized, observational study designs is valuable for exploring such drug effects or toxicities within the field of pharmacoepidemiology. However, the evidence from observational studies is often inconsistent, and such designs have been criticized for their potential of bias (e.g., selection or information bias) and confounding (e.g. unmeasured confounding).[49]

Prescription sequence symmetry analysis (PSSA) is increasingly being used to detect adverse effects or events associated with medications. PSSA is a self-controlled study design in which genetic and other time-invariant confounding can be well controlled, it does not entail the abovementioned bias.[50,51] It compares the symmetry in the sequence of exposure medication and marker (outcome) medications as proxy for ADRs within a specific time window based on prescriptions or claims databases.[52] The sequence ratio (SR) reflects the association between exposure and outcome. However, PSSA is still sensitive to time-varying variables, notably if the follow-up time is long. The overall validity of PSSA study designs has not been fully evaluated by comparing its result with those from conventional observational parallel group study designs, and such comparisons are urgently required.

AIM OF THIS THESIS

In this thesis, we aim to develop a comprehensive profile on the effectiveness of antibiotic use for acute exacerbations of COPD both prescribed prophylactically and therapeutically, and to provide real-world data on neuropsychiatric safety of varenicline use for smoking cessation, particularly among high risk populations with COPD or psychiatric diseases.

OUTLINE OF THIS THESIS

In **part I** of this thesis, we present several studies on the role of antibiotics in acute exacerbations of COPD (AECOPD).

In **Chapter 2,** we report the results from a meta-analysis of RCTs focusing on the beneficial effects and side effects of prophylactic antibiotic therapy in COPD patients.

In **Chapter 3,** we demonstrate the real-world effects of doxycycline treatment on acute exacerbations among COPD outpatients based on data extracted from the University of Groningen's prescription database (IADB.nl) and explored the possible influence of age on the clinical outcomes.

In **Chapter 4,** we further explored the real-world effects of several antibiotic drugs used for acute exacerbations of COPD patients based on a linked database between the Lifelines Cohort biobank with extensive clinical information and the University of Groningen's prescription database (IADB.nl).

In **Chapter 5,** we present a systematic review of drug-drug interactions associated with frequently prescribed antibiotics among COPD patients based on causal evidence obtained from observational cohort studies, case-control studies and clinical studies, aimed at improving the safety of antibacterial prescriptions.

In **part II** of this thesis, we present studies on the role of varenicline for smoking cessation using different designs.

In **Chapter 6,** we present the results of a retrospective inception cohort study aimed at assessing the risk of neuropsychiatric adverse events (NPAEs) in starters with varenicline versus starters with nicotine replacement therapy (NRT) among both the general and COPD populations, with and without psychiatric disorders. This study was conducted using data extracted from the University of Groningen's prescription database (IADB.nl).

In **Chapter 7,** we further examine the association between varenicline use and the onset of NPAEs in a real-world setting using a prescription sequence symmetry analysis (PSSA) study design.

Furthermore, in **Chapter 8** we systematically compared effect estimates derived from the PSSA study with effect estimates from conventional observational parallel group study designs, to assess the validity and constraints of the PSSA study design within epidemiological research.

Last, in **Chapter 9,** we summarized the main findings of this thesis, discussed these findings in detail and provided suggestions for future research.

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease: 2020 Report. https://goldcopd.org/gold-reports/. Date last accessed: December 17, 2019.
2. Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. *Lancet*. 2015;385(9971):899-909.
3. Lange P, Celli B, Agusti A, et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med*. 2015;373(2):111-122.
4. Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet*. 2007;370(9589):758-764.
5. Tashkin DP, Altose MD, Bleecker ER, et al. The lung health study: airway responsiveness to inhaled methacholine in smokers with mild to moderate airflow limitation. The Lung Health Study Research Group. *Am Rev Respir Dis*. 1992;145(2 Pt 1):301-310.
6. Adeloye D, Chua S, Lee C, et al. Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. *J Glob Health*. 2015;5(2):020415.
7. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet*. 2007;370(9589):741-750.
8. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2095-2128.
9. Lopez AD, Shibuya K, Rao C, et al. Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J*. 2006;27(2):397-412.
10. Rabe KF, Watz H. Chronic obstructive pulmonary disease. *Lancet*. 2017;389(10082):1931-1940.
11. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188(8):e13-64.
12. Wedzicha JA, Seemungal TAR. COPD exacerbations: defining their cause and prevention. *Lancet*. 2007;370(9589):786-796.
13. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax*. 2005;60(11):925-931.
14. O'Reilly JF, Williams AE, Rice L. Health status impairment and costs associated with COPD exacerbation managed in hospital. *Int J Clin Pract*. 2007;61(7):1112-1120.
15. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(22):2355-2365.
16. Moghoofei M, Azimzadeh Jamalkandi S, Moein M, Salimian J, Ahmadi A. Bacterial infections in acute exacerbation of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Infection*. 2019.
17. Wilkinson TMA, Aris E, Bourne SC, et al. Drivers of year-to-year variation in exacerbation frequency of COPD: analysis of the AERIS cohort. *ERJ Open Res*. 2019;5(1).
18. Monso E, Garcia-Aymerich J, Soler N, et al. Bacterial infection in exacerbated COPD with changes in sputum characteristics. *Epidemiol Infect*. 2003;131(1):799-804.
19. Wedzicha JA, Calverley PMA, Albert RK, et al. Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. 2017;50(3).
20. Ni WT, Shao XD, Cai XJ, et al. Prophylactic Use of Macrolide Antibiotics for the Prevention of Chronic Obstructive Pulmonary Disease

Exacerbation: A Meta-Analysis. *Plos One.* 2015;10(3).

21. Cameron EJ, McSharry C, Chaudhuri R, Farrow S, Thomson NC. Long-term macrolide treatment of chronic inflammatory airway diseases: risks, benefits and future developments. *Clin Exp Allergy.* 2012;42(9):1302-1312.
22. Walters JA, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2014(9):CD001288.
23. Vollenweider DJ, Jarrett H, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Db Syst Rev.* 2012(12).
24. Vollenweider DJ, Frei A, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Db Syst Rev.* 2018(10).
25. van Velzen P, Ter Riet G, Bresser P, et al. Doxycycline for outpatient-treated acute exacerbations of COPD: a randomised double-blind placebo-controlled trial. *Lancet Respir Med.* 2017;5(6):492-499.
26. Hassan WA, Shalan I, Elsobhy M. Impact of antibiotics on acute exacerbations of COPD. *Egypt J Chest Dis Tu.* 2015;64(3):579-585.
27. Bathoorn E, Groenhof F, Hendrix R, et al. Real-life data on antibiotic prescription and sputum culture diagnostics in acute exacerbations of COPD in primary care. *Int J Chron Obstruct Pulmon Dis.* 2017;12:285-290.
28. Roede BM, Bindels PJ, Brouwer HJ, Bresser P, de Borgie CA, Prins JM. Antibiotics and steroids for exacerbations of COPD in primary care: compliance with Dutch guidelines. *Br J Gen Pract.* 2006;56(530):662-665.
29. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J.* 2006;28(3):523-532.
30. Chetty U, McLean G, Morrison D, Agur K, Guthrie B, Mercer SW. Chronic obstructive pulmonary disease and comorbidities: a large cross-sectional study in primary care. *Br J Gen Pract.* 2017;67(658):e321-e328.
31. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol.* 2004;57(1):6-14.
32. Hanlon P, Nicholl BI, Jani BD, et al. Examining patterns of multimorbidity, polypharmacy and risk of adverse drug reactions in chronic obstructive pulmonary disease: a cross-sectional UK Biobank study. *BMJ Open.* 2018;8(1):e018404.
33. Banks E, Joshy G, Korda RJ, et al. Tobacco smoking and risk of 36 cardiovascular disease subtypes: fatal and non-fatal outcomes in a large prospective Australian study. *BMC Med.* 2019;17(1):128.
34. Gaudet MM, Carter BD, Brinton LA, et al. Pooled analysis of active cigarette smoking and invasive breast cancer risk in 14 cohort studies. *Int J Epidemiol.* 2017;46(3):881-893.
35. Tjora T, Hetland J, Aaro LE, Wold B, Wiium N, Overland S. The association between smoking and depression from adolescence to adulthood. *Addiction.* 2014;109(6):1022-1030.
36. Collaborators GBDT. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990-2015: a systematic analysis from the Global Burden of Disease Study 2015. *Lancet.* 2017;389(10082):1885-1906.
37. Thun MJ, Carter BD, Feskanich D, et al. 50-Year Trends in Smoking-Related Mortality in the United States. *New Engl J Med.* 2013;368(4):351-364.
38. The L. Progress towards a tobacco-free world. *Lancet.* 2018;392(10141):1.
39. World Health Organisation. WHO report on the global tobacco epidemic 2019: offer help to quit tobacco use. Geneva: World Health Organisation, 2019: 17-21.
40. Mehrotra R, Yadav A, Sinha DN, et al. Smokeless tobacco control in 180 countries across the globe: call to action for full implementation of WHO FCTC measures. *Lancet Oncol.* 2019;20(4):e208-e217.
41. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of

varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet*. 2016;387(10037):2507-2520.

42. Moore TJ, Furberg CD, Glenmullen J, Maltsberger JT, Singh S. Suicidal behavior and depression in smoking cessation treatments. *Plos One*. 2011;6(11):e27016.
43. Thomas KH, Martin RM, Knipe DW, Higgins JP, Gunnell D. Risk of neuropsychiatric adverse events associated with varenicline: systematic review and meta-analysis. *BMJ*. 2015;350:h1109.
44. Lawrence D, Mitrou F, Zubrick SR. Smoking and mental illness: results from population surveys in Australia and the United States. *Bmc Public Health*. 2009;9.
45. Garza D, Murphy M, Tseng LJ, Riordan HJ, Chatterjee A. A double-blind randomized placebo-controlled pilot study of neuropsychiatric adverse events in abstinent smokers treated with varenicline or placebo. *Biol Psychiatry*. 2011;69(11):1075-1082.
46. Tonstad S, Davies S, Flammer M, Russ C, Hughes J. Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: a pooled analysis. *Drug Saf*. 2010;33(4):289-301.
47. Kotz D, Viechtbauer W, Simpson CR, van Schayck OCP, West R, Sheikh A. Cardiovascular and neuropsychiatric risks of varenicline and bupropion in smokers with chronic obstructive pulmonary disease. *Thorax*. 2017;72(10):905-911.
48. Evins AE, Benowitz NL, West R, et al. Neuropsychiatric Safety and Efficacy of Varenicline, Bupropion, and Nicotine Patch in Smokers With Psychotic, Anxiety, and Mood Disorders in the EAGLES Trial. *J Clin Psychopharmacol*. 2019;39(2):108-116.
49. Boyko EJ. Observational research--opportunities and limitations. *J Diabetes Complications*. 2013;27(6):642-648.
50. Wahab IA, Pratt NL, Wiese MD, Kalisch LM, Roughead EE. The validity of sequence symmetry analysis (SSA) for adverse drug reaction signal detection. *Pharmacoepidemiol Drug Saf*. 2013;22(5):496-502.
51. Lai ECC, Pratt N, Hsieh CY, et al. Sequence symmetry analysis in pharmacovigilance and pharmacoepidemiologic studies. *European Journal of Epidemiology*. 2017;32(7):567-582.
52. Hallas J. Evidence of depression provoked by cardiovascular medication: a prescription sequence symmetry analysis. *Epidemiology*. 1996;7(5):478-484.

PART I

Effects of antibiotic use for COPD exacerbations and potential DDIs during COPD exacerbation management