Effectiveness and safety of medicines used in COPD patients

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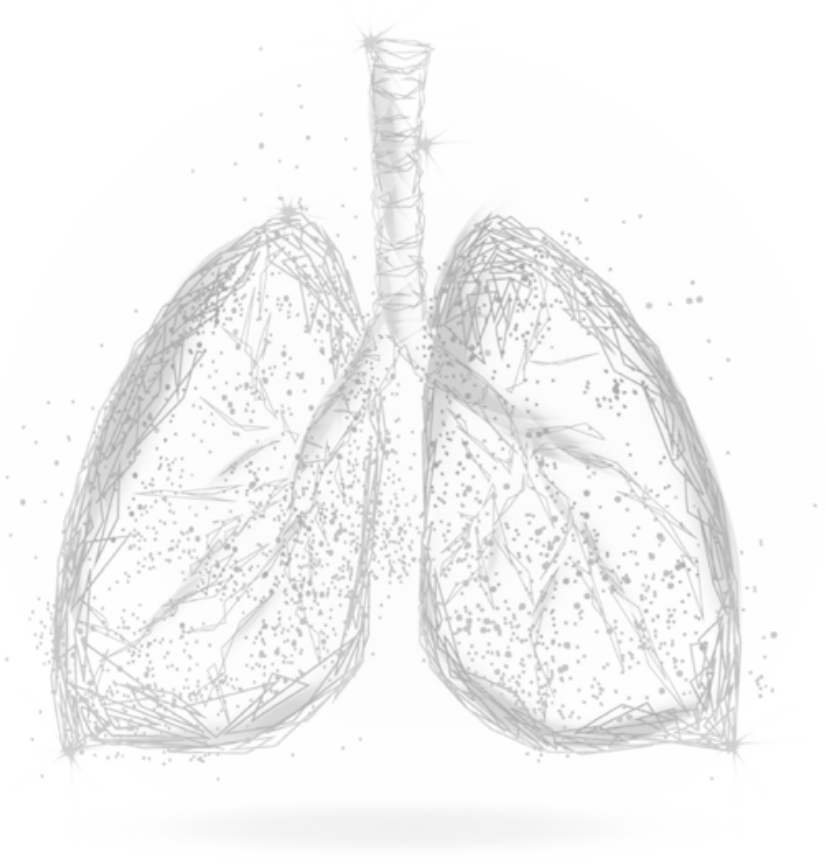
CHAPTER 9



General discussion

GENERAL DISCUSSION

The objective of this thesis was to provide a comprehensive profile about the effectiveness and safety of some drugs commonly used by COPD patients, based on a range of pharmacoepidemiological studies. In the **first part** of this thesis, we evaluated the effects of several antibiotics for the prevention and treatment of acute exacerbations of COPD (AECOPD), and the potential for drug-drug-interactions (DDIs) during antibiotic therapeutic management. We conducted a systematic review and meta-analysis to provide a benefit-risk profile of prophylactic antibiotics for AECOPD. The influence of the drug schedule (continuous vs intermittent) and treatment duration of prophylactic antibiotics (<=6 months vs > 6months) on clinical outcomes were also explored (**Chapter 2**). The effects of doxycycline in addition to oral corticosteroids in AECOPD and possible influence of age were explored in **Chapter 3**. To further reduce the influence of possible unmeasured confounding bias as potentially present in **Chapter 3**, a cohort study with complete information on COPD clinical diagnosis and lung function was conducted to explore the effects of therapy with any or a specific first-line antibiotic in AECOPD (**Chapter 4**). Considering the frequent occurrence of polypharmacy in COPD drug management, we presented a systematic DDI review focused on frequently used antibiotics among COPD patients to optimize drug treatment (**Chapter 5**). In the **second part** of this thesis, we assessed the neuropsychiatric safety of varenicline for smoking cessation in a real-world setting. Using a traditional cohort study, we especially explored the neuropsychiatric safety in COPD patients and those with previous psychiatric disorders as these are high-risk populations for psychiatric events (**Chapter 6**). Since conventional cohort studies may be vulnerable to potential for confounding bias, we further explored the neuropsychiatric safety of varenicline by use of a self-controlled study design, called Prescription Sequence Symmetry Analysis (PSSA, **Chapter 7**). Finally, we performed a systematic review comparing the effect estimates between PSSA and traditional parallel group studies with correlation analysis, agreement and discrepancy analysis (**Chapter 8**).

Antibiotics in management of COPD exacerbations

As respiratory bacterial infection is a major risk factor of COPD exacerbations,[1,2] antibiotics can be part of the drug management of COPD according to recent guidelines.[3] However, these recommendations are based on a limited body of evidence from randomized controlled trials (RCTs) and lack of consistent results from studies in a real-world setting. Therefore, we conducted four separate scientific studies to provide more evidence for the optimal use of antibiotics among COPD patients.

Effects of antibiotics for preventive use

In **Chapter 2**, we conducted a systematic review to evaluate all possible beneficial and side effects of prophylactic antibiotics in stable COPD patients. Pooled results from

twelve RCTs showed that the frequency of AECOPD and the number of patients with AECOPD were significantly reduced, independent of the drug schedule (continuous vs intermittent) and duration of treatment (<=6 months vs >6 months). However, when we examined specific antibiotics, we could only confirm the superiority of macrolides in preventing exacerbations of COPD and erythromycin and azithromycin appeared the most effective, a finding which is in line with clinical recommendations.[4,5] Previous research suggested properties of anti-inflammation and immune-modulation by macrolides,[6,7] however, this was not supported by findings from our review, where we observed changes in neither bacterial load nor airway inflammation. Despite the direct beneficial effects of prophylactic antibiotics regarding the reduction of exacerbations, the patients' quality of life was only improved by longer use (> 6 months) of prophylactic antibiotics. There were no differences in the rate of hospitalization, adverse events and the time to next exacerbation between patients with prophylactic antibiotics and those on placebo.

Of note, antibiotic resistance problems always come along with antibiotic use, especially for macrolides, for which the review data showed an increase in resistance.[8] Weighing benefits and risks of prophylactic antibiotic therapy, the long and continuous use of such therapy should be advised carefully, and it should be used preferably by the high-risk patient population who are at risk for development of severe infections such as patients who are older, with high-risk comorbidities and with higher frequency of exacerbations in the previous year, and those with more severe AECOPD.

Effects of antibiotics for therapeutic use

According to the GOLD guideline, amino-penicillin with clavulanic acid, macrolide, or tetracycline antibiotics are recommended as the initial empirical choice of antibiotic treatment for AECOPD.[3] In the Netherlands, according to the Dutch primary care guideline, doxycycline or amoxicillin are recommended as the first choice in AECOPD treatment.[9] These recommendations were basically based on results of RCTs. Real-world evidence from observational studies is valuable to evaluate the applicability of the findings from RCTs for the real-world setting, and these were presented in **chapter 3 and 4**.

In **chapter 3**, we conducted a cohort study including the outpatient population from the University of Groningen's prescription database IADB.nl, to explore the real-world effects of doxycycline for AECOPD and the influence of age. We found a 23% reduced risk of treatment failure by doxycycline in addition to systemic corticosteroids among COPD outpatients aged 75 years and older; a finding consistent with results from few previous RCTs about doxycycline for AECOPD among outpatients.[10] However, in younger patients with COPD, we did not find any difference between additional antibiotic use and oral corticosteroids use only, which is consistent with our hypothesis that older people may

benefit more from antibiotics due to their susceptibility to bacterial infections and inflammations. The fact that the natural lung function, the natural defense mechanism and mucocilliary clearance are reduced with increasing age is also in line with this hypothesis.[11-13]

However, due to a lack of detailed clinical diagnostic information, the identification of COPD and other comorbidities in the study reported in **chapter 3** were based on drug prescriptions as proxies for these diseases, which may have biased the results. Moreover, important baseline information on GOLD stages of severity of airway limitations in COPD and smoking history was also absent, though these are vital risk factors for the prognosis of AECOPD and this may have led to unmeasured confounding.[3] Accordingly, in **Chapter 4**, we further explored the effects of both any antibiotic and some specific antibiotics in the treatment of AECOPD among outpatients based on the "PharmLines Initiative", which linked extensive clinical information from both the Lifelines Cohort Study and drug information from the IADB.nl prescription database. Within the Lifelines Cohort information on clinical diagnosis of almost all possible chronic diseases and information on parameters of physical examinations like spirometry of lung function is obtained on a regular basis.[14] Largely in line with with findings in **chapter 3**, overall the prescription of any antibiotic was associated with a statistically significant reduction of treatment failure of AECOPD. Similar trends towards protective effects were also observed for the specific antibiotics doxycycline, co-amoxiclav, and macrolides, separately, except for amoxicillin which was associated with no effect. The doxycycline treatment was even associated with a statistically significant 47% reduced risk of treatment failure of AECOPD, after adjustments in both conventional logistic regression and propensity score analysis. Indeed, in **Chapter 4**, information about the actual severity of the presented first AECOPD according to signs and symptoms at diagnosis was absent. However, we believe that antibiotics will most likely be given to more severe AECOPD, which may have biased our result towards a null finding. Further, severe exacerbations that resulted in hospitalizations were not included, but we believe that in an outpatient setting the chance of such severe cases is low.

Although previously two observational studies indicated long-term benefits from short use of antibiotics for next exacerbations,[15,16] we did not observe this in both **Chapter 3** and **Chapter 4**. A long-term effect is also doubtful given the fact that re-infections are not substantially affected by a short-course of antibiotics. Our results about the absence of long-term effects of antibiotic treatment are in line with findings from a more recent RCT reported by van Velzen et al. in 2017.[10]

Management of DDIs in AECOPD

In **chapter 3 and 4**, it has been shown that antibiotics play a vital role in the management of patients with AECOPD. However, in COPD patients many comorbidities like

cardiovascular disease, diabetes, and lung cancer coexist.[17] These comorbidities may contribute to polypharmacy and result in potential DDIs when antibiotics are prescribed simultaneously.

In **chapter 5**, based on the causal evidence from clinical trials and observational studies with a control group, we found that many drugs interact with commonly used antibiotics in the treatment of COPD. Some co-administered drugs can alter the pharmacokinetics of antibiotics, while other antibiotics can also interfere with the pharmacokinetics of co-administered drugs. DDIs may result in treatment failures of disease or lead to adverse events. For example, clarithromycin as inhibitor of CYP3A4 can increase the risk of hypoglycemia among diabetes patients by inhibition of the metabolic enzymes of related anti-diabetic drugs (e.g. glipizide, glyburide), which are substrates of CYP3A4.

We presented details of potential clinical significant DDIs with moderate to strong levels of interaction in this review according to highly prevalent comorbidities, and such information may be used to improve the sensitivity and specificity of drug-drug interaction alert systems. Importantly, it may help physicians to improve the prescription of antibiotics to COPD patients with comorbidities.

Varenicline intervention for smoking cessation

Pharmaceutical smoking cessation treatment (PSCT) is an important intervention for tobacco smoking. Varenicline as first-line drug of PSCTs has been proven effective for smoking cessation.[18] However, concerns about neuropsychiatric adverse events (NPAEs) were raised since the spontaneous reports about such events and the related warning from the FDA.[19] Due to strict selection criteria for participants in RCTs, high-risk populations of smokers like those with COPD and psychiatric disorders were usually excluded which hinders making conclusions for a real-world setting.

Neuropsychiatric safety of varenicline for smoking cessation

In **chapter 6**, the association between varenicline use and major NPAEs was explored among general and COPD patients with or without psychiatric disorder. However, we did not observed a significant association between varenicline use and the occurrence of any NPAE in high-risk populations and the general population. Although COPD patients are considered more susceptible for possible adverse drug reactions (ADEs), in our study we did not observe an increased risk of any NPAE among COPD patients using varenicline in the psychiatric and non-psychiatric cohorts. This finding was consistent with the findings from two earlier studies.[20,21]

When we examined specific NPAEs, we observed a significantly reduced risk of anxiety among varenicline users in those with psychiatric disorders compared with NRTs users, which may be due to the combined effects of reduced withdrawal-related symptoms

and raised level of positive affect on mood due to varenicline treatment for smoking cessation. As varenicline users have higher abstinence rates and successful quitting rates than NRT users, quitting of smoking is associated with recovery in psychiatric status for smokers.[22]

Of note, although the NPAEs observed in earlier studies were defined in different ways, the incidence rates of specific NPAEs related to depression, anxiety and insomnia defined by the occurrence of prescriptions of related drugs in our study were similar to these reports.[23] Much higher rates of NPAEs were observed in the specific high-risk population with psychiatric disorders in this study, which was also consistent with previous reports.[24,25]

Role of PSSA in drug safety evaluations

To overcome the limitations of traditional cohort studies regarding the control of confounding in **chapter 6**, we conducted a PSSA study described in **chapter 7** using the same IADB.nl prescription database. PSSA has been increasingly used for detecting adverse events of medication. Due to its self-controlled study design, the PSSA design may control genetic and other time-invariant confounding effectively.

Consistent with results from **chapter 6**, results in **chapter 7** also showed that varenicline was not associated with increased risks for depression or anxiety. However, it was associated with a small significant, but transient, increase in sleep disorders, which was a well-known side effect of varenicline from RCTs and other previous studies.[23,26] However, it is difficult to identify whether sleeping problems are due to side effects of PSCTs or related to withdrawal from nicotine as difficulty falling asleep and increased number of awakenings are also common symptoms of nicotine withdrawal.[27]

Of note, most observational studies (e.g. the cohort study described in **chapter 6**) used NRT as the reference group to explore the risk of NPAEs associated with varenicline to make sure the baseline characteristics of study subjects in the comparison groups are more similar. In the PSSA all patients used varenicline and only the sequence orders of prescriptions of varenicline and marker drugs for NPAEs were compared due to its self-controlled design. The difference in outcomes between study designs may be due to either missing a transient risk in the cohort study or by the absence of a reference group in the PSSA.

Although we found consistent findings in **Chapter 6 and 7**, the validity and constraints of the PSSA study design regarding the effect estimate of drug use are never compared with conventional observational parallel group study designs (e.g. cohort, case-control), which has already been proven to be an effective design to obtain causal evidence from real-world data.

Therefore, in **chapter 8**, we compared the effect estimates from two study designs, by systematically searching for publications that explored the effects of the same drug use by applying both of these study designs. Based on the correlation analysis, agreement and discrepancy analysis, this review indicated that the effect estimates generated by the PSSA are usually lower than the effect estimates generated by parallel group designs, and PSSA usually has a lower power than the conventional study designs. However, these results should be interpreted with caution, as the effect estimates were only retrieved from two separate studies. More comparisons are needed to confirm our conclusion.

FUTURE PERSPECTIVES

Although prophylactic antibiotics, especially macrolides, were shown to be effective for preventing exacerbations of COPD in **chapter 2**, the optimal regimen of antibiotics regarding dose, duration and schedule has not been well established yet, and such treatment is still far from more personalized therapy. For the long and continuous use of antibiotics, it is still an issue how to balance its advantages towards COPD exacerbations and the development of antibacterial resistance in both the individual and the community. It is wise for clinical practitioners to limit their prescription to high-risk populations in order to reduce unnecessary bacterial resistance. Better understanding of the yet unclear mechanisms behind macrolides preventing exacerbations could help develop targeted treatment for AECOPD in the future.

Regarding the antibiotic treatment for ongoing AECOPD, related guidelines were basically depend on the evidence from RCTs.[3,28] However, in reality, it is more complicated to make decisions about antibiotic use considering the heterogeneous characteristics in outpatients and various factors that may influence the final treatment outcome. The tendency towards beneficial effects of antibiotics in the elderly COPD patients shown in **chapter 3** may offer clues for clinicians and researchers to use antibiotics in more targeted populations by considering age. A personalized specific antibiotic treatment could further improve the therapeutic effects in AECOPD, but such evidence is currently lacking.

Of note, antibiotics were not always properly prescribed in line with the guidelines.[29,30] Some antibiotics could have been used in AECOPD without actual bacterial infection. Hence, the beneficial effects as reported in **chapter 4** may underestimate the true effects in bacterially confirmed AECOPD. In the future, how to improve the appropriate personalized use of antibiotics is a problem that needs to be studied. From a pragmatic perspective, clinicians may reduce unnecessary antibiotic therapy for AECOPD by using sputum color as a predictor of potentially pathogenic bacterial infection in practice.[3] A procalcitonin-guided algorithm or C-reactive protein (CPR) test can also be considered,

if applicable, as a way to better instruct antibiotic use.[31] However, both application and accuracy of bacterial tests come with limitations for the outpatient setting, and more practical tests should be developed.

Consistent with the Dutch primary guideline,[9] the findings in **chapter 4** confirmed the beneficial effect of doxycycline treatment for AECOPD among outpatients. However, no definite conclusion can be drawn for other antibiotics from this study. Considering the variability between GP practices in the prescriptions of antibiotics to patients with AECOPD,[32] larger studies of high quality with extensive control for confounding by indication are needed to confirm and support their role in the management of AECOPD. Notably, the final antibiotic choice for AECOPD treatment should always consider the local bacterial resistance patterns and possibility of resistant pathogens by performing culture of sputum especially among high risk patients with frequent exacerbations and severe airflow limitations.[3]

Chapter 5 showed that there is a variety of clinically significant DDIs between antibiotics and a wide range of drugs that are used to treat related comorbidities in COPD. Clinicians should pay attention to these drug interactions when prescribing antibiotics by assessing the present comorbidities and polypharmacy of patients to ensure therapeutic effect and reduce the possibility of adverse effects. However, the evidence base for clinical adverse outcomes due to DDIs is still weak, and warrants further study in larger cohorts.

Based on previous evidence and the results from our studies in both cohort and PSSA study design in **chapter 6 and 7**, varenicline is safe to use for smoking cessation among general and COPD populations. Although there was no increased risk of NPAEs by varenicline compared with NRTs among patients with psychiatric disorders, considering the relatively high rate of NPAEs in smokers with psychiatric disorders, these patients should be instructed carefully. Notably, sleeping disorder is a well-recorded and common adverse event of varenicline, especially in the first three to six months after varenicline initiation. Although sleep disorders do not belong to the "severe" adverse events, it could influence the uptake and adherence of varenicline. As a result, it may finally result in the failure of smoking cessation. However, up to now, it is still not clear whether sleep disorders are caused by varenicline itself or are more related to withdrawal of nicotine. The distinction between these causes is important for pharmacists and clinicians to take appropriate actions to improve compliance and adherence of varenicline use.

Based on the findings from **chapter 8**, the lack of a wider variety of comparisons between PSSA and parallel group designs that cover more topics make it difficult to make definite conclusions about the validity of PSSA in establishing associations between drug use and related events. Thus, more studies that explore the association between drug use and adverse events by using both of these study designs based on

the same database or populations are needed. Ideally, comparisons with high-quality pragmatic trials with similar populations, exposure and outcomes could help to specify the validity of the PSSA design even better.

CONCLUSION

In the first part of this thesis, we confirmed the beneficial effects of antibiotics both in the prevention and treatment of AECOPD. Macrolides should be prescribed as the first-line antibiotic to prevent recurrence of exacerbations and doxycycline appeared the best choice for preventing treatment failure of a current exacerbation. Those with a higher risk of bacterial infections such as older patients among COPD outpatients benefit the most and personalizing therapy for these patients may possibly reduce the development of antibiotic resistance. Considering the polypharmacy among COPD patients, clinicians should pay attention to related DDIs while prescribing antibiotics to avoid treatment failure or adverse events. In the second part of our thesis, neither traditional cohort nor prescription sequence symmetry analysis showed a potential neuropsychiatric risk of varenicline use for smoking cessation among general and COPD patients. Attention should be given to patients with psychiatric disorders. The PSSA design has shown significant promise in detecting related drug adverse events, however, due to the limited available comparisons between PSSA and other traditional studies, it is still necessary to test its validity by comparisons with parallel controlled studies and clinical trials.

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