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Effectiveness and safety of medicines used in COPD patients

Wang, Yuanyuan

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CHAPTER 10



Summary

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SUMMARY

Chronic obstructive pulmonary disease (COPD) is a very common chronic progressive disease that affects millions of middle-aged and older smokers. COPD patients frequently suffer from exacerbations (worsening of their respiratory symptoms). As bacterial infection is the primary trigger of exacerbations, antibiotics can be given to those patients with potential infections. However, the effects of antibiotics on COPD exacerbations in both treatment and prevention have not been consistently reported and are especially unclear in real-world settings. Smoking is an important risk factor for COPD. Stopping smoking, especially by means of pharmaceutical treatment with varenicline, is a vital intervention to improve the quality of life and reduce smoking-related disease among COPD patients. However, concerns about varenicline's neuropsychiatric safety for patients still exist due to conflicting evidence obtained from randomized controlled trials and case-report systems. It is necessary to evaluate the risk of the neuropsychiatric adverse events (NPAEs) due to varenicline by studies based on a large observational database.

The aim of the first part of this thesis was to evaluate the effectiveness of antibiotic use to treat COPD exacerbations and explore the potential drug-drug interactions (DDIs) related to antibiotics use among COPD patients. The results from a systematic review described in Chapter 2 show that prophylactic antibiotics are effective in preventing COPD exacerbations and improve the quality of life of stable COPD patients. Concerning the effects of antibiotics treatment for COPD exacerbations, however, the cohort study based on the prescription database described in Chapter 3 shows that the short-term benefits of doxycycline in addition to oral corticosteroids are only observed in COPD patients of advanced age. No long-term benefits were observed. Clinicians should take the patients' age into consideration when prescribing antibiotics to patients with acute exacerbation of COPD (AECOPD). Another cohort study, described in Chapter 4 and concerning clinically diagnosed COPD, confirmed the short-term protective effects of doxycycline use with AECOPD. However, the treatment effects of other antibiotics in real-world settings are still unclear and need to be explored further in more extensive research. In general practice, physicians may prescribe antibiotics erroneously or improperly, which may underestimate the real-world effects of antibiotic use on AECOPD. In addition, since comorbidities and polypharmacy are common among COPD patients, associated DDIs— of which there are many and which are summarized in a systematic review described in Chapter 5 – may also influence the effects of antibiotics by directly altering their pharmacokinetics or by indirectly influencing patient compliance due to adverse drug reactions (ADRs) due to DDIs.

The second part of this thesis focused on the neuropsychiatric safety of varenicline to aid smoking cessation among patients in general and COPD patients in particular.

The findings from a cohort study described in Chapter 6 do not indicate an increased risk of NPAEs associated with varenicline in either the general or the COPD population, irrespective of the psychiatric status of the patients. Considering the limitation for controlling of time-invariant confounders in traditional observational research, Chapter 7 reports a self-controlled study of a prescription sequence symmetry analysis (PSSA) to explore the varenicline's risk of NPAEs further. The PSSA results also confirm the neuropsychiatric safety of varenicline use. Remarkably, a transient increased risk of varenicline-induced sleep disorder was observed, which clinicians should take into account to reduce its influence on the adherence of patients taking varenicline. In the last chapter of the thesis, the effect estimate of the PSSA was compared with parallel group study designs, showing that the effects estimated by the PSSA may be lower than those in the parallel group study designs. However, since only two studies were included, more comparisons are necessary to draw solid conclusions.

In this thesis, we confirm the beneficial effects of prophylactic antibiotic use to prevent COPD exacerbations. However, the antibiotic treatment effects on AECOPD were only seen with doxycycline. Although other antibiotics also showed benefits, these were not statistically significant and need be investigated further. We confirm the safety of varenicline use for smoking cessation, varenicline as an effective treatment should be used widely to reduce the burden of smoking-related diseases. However, patients with neuropsychiatric disease in their history must be monitored closely considering their higher risk of NPAEs. Since the PSSA is an effective tool for identifying ADRs, it could be applied more widely to better evaluate the effectiveness and safety of medications. Other study designs and methodologies should be explored to achieve better control of related confounders in observational studies based on real-world data.

SAMENVATTING

Chronic Obstructive Pulmonary Disease, oftewel COPD, is een veelvoorkomende chronische en progressieve ziekte waar miljoenen rokers op middelbare en hogere leeftijd last van krijgen. COPD-patiënten lijden regelmatig aan exacerbaties (verergering van hun ademhalingsklachten). Omdat bacteriële infecties vaak de hoofdoorzaak zijn van exacerbaties, kunnen antibiotica toegediend worden bij patiënten met potentiële infecties. De effecten van antibiotica op COPD exacerbaties bij zowel behandeling als preventie zijn echter niet nauwkeurig geschat en zijn met name onduidelijk in de praktijk. Roken is een belangrijke risicofactor voor COPD. Stoppen met roken, vooral met behulp van farmaceutische behandeling met varenicline, is een essentiële ingreep om de kwaliteit van leven te verbeteren en om ziektes die verband houden met roken te verminderen bij COPD-patiënten. Echter, bezorgdheid om de neuropsychiatrische veiligheid van varenicline voor de patiënten blijft bestaan door tegenstrijdig bewijs dat voortkomt uit *randomized controlled trials en case-reports*. Het is van belang om het risico op neuropsychiatrische bijwerkingen bij vareniclinegebruik te evalueren met behulp van grootschalige observationele databases.

Het doel van het eerste deel van deze thesis is het evalueren van de effectiviteit van antibiotica voor de behandeling van COPD-exacerbaties, en om de potentiële interacties tussen geneesmiddelen (*drug-drug interactions* ofwel DDI's) in relatie tot antibioticagebruik bij COPD-patiënten te onderzoeken. De resultaten van een systematisch onderzoek in hoofdstuk 2 laten zien dat profylactische antibiotica effectief zijn in het voorkomen van COPD-exacerbaties en de kwaliteit van leven bij stabiele COPD-patiënten kan verbeteren. We kijken verder naar van de effecten van antibioticabehandelingen tijdens COPD-exacerbaties in hoofdstuk 3 met behulp van een cohort onderzoek dat gebaseerd is op een prescriptie-database. Dit onderzoek toont aan dat naast het gebruik van orale corticosteroiden de voordelen van doxycycline op korte termijn alleen zichtbaar zijn bij COPD-patiënten op hogere leeftijd. Er werden geen voordelen op de lange termijn gevonden. Clinici zouden daarom de leeftijd van de patiënten in acht moeten nemen als zij antibiotica voorschrijven aan patiënten met acute exacerbatie van COPD (AECOPD). Een vervolgstudie met klinisch gediagnostiseerde COPD, beschreven in hoofdstuk 4, bevestigt dat er kortdurende beschermende effecten van doxycyclinegebruik bij AECOPD zijn. De effecten van andere antibiotica in de praktijk zijn echter nog steeds onduidelijk en moeten nader onderzocht worden in een uitgebreider onderzoek. In het dagelijks leven kan het voorkomen dat artsen antibiotica onterecht of onjuist voorschrijven, wat ervoor kan zorgen dat de effecten van antibiotica op AECOPD in de praktijk onderschat worden. Daar komt nog bij dat comorbiditeiten en polyfarmacie gebruikelijk zijn bij COPD-patiënten. Daardoor kunnen geassocieerde DDI's – die in groten getale voorkomen en zijn samengevat in een systematisch overzicht in hoofdstuk 5 – ook invloed hebben

op de effecten van antibiotica door directe veranderingen te induceren in hun farmacokinetiek of door het indirect beïnvloeden van de therapietrouw van patiënten door bijwerkingen ten gevolge van de DDI.

Het tweede gedeelte van deze scriptie focust op de neuropsychiatrische veiligheid van varenicline als geneesmiddel om patiënten te helpen stoppen met roken, met name bij COPD-patiënten. De bevindingen van een cohortstudie, zoals beschreven in hoofdstuk 6, tonen niet aan dat er een verhoogd risico van NPAE's geassocieerd is met varenicline in zowel de algemene als de COPD-populatie, ongeacht wat hun psychiatrische status is. In hoofdstuk 7 houden we rekening met zogenaamde tijd ongebonden versturende factoren (confounding) die in traditioneel observatieonderzoek kunnen optreden. Hiertoe pasten we de zogenaamde *prescription sequence symmetry analysis (PSSA)* toe om het risico op neuropsychiatrische bijwerkingen van varenicline verder te onderzoeken. De PSSA-resultaten bevestigen ook de neuropsychiatrische veiligheid van vareniclinegebruik. Opmerkelijk is dat een kortstondig verhoogd risico op slaapstoornis werd gerapporteerd bij varenicline gebruik, waar klinici rekening mee zouden moeten houden om de invloed van varenicline op de therapietrouw van de patiënten te verminderen. In het laatste hoofdstuk van deze scriptie wordt het geschatte effect van de PSSA vergeleken met een parallelgroep-studie, die aantoont dat de geschatte effecten bij de PSSA lager zouden kunnen zijn dan die in de parallelgroep-studie. Maar omdat dit slechts twee onderzoeken omvat, zijn er meer vergelijkingen nodig om betrouwbare conclusies te trekken.

In deze scriptie bevestigen we de positieve effecten van profylactisch antibioticagebruik om COPD-exacerbaties te voorkomen. Echter, de effecten van de antibioticabehandelingen op AECOPD kwamen alleen voor bij doxycycline. Hoewel andere antibiotica ook voordelen toonden, waren deze resultaten niet statistisch significant en zullen daarom verder onderzocht moeten worden. We bevestigen de veiligheid van vareniclinegebruik voor het stoppen met roken, en varenicline als een effectieve behandeling zou veelal ingezet moeten worden om de last van ziektes die met roken verband houden te verminderen. Desalniettemin moeten patiënten met een verleden van neuropsychiatrische aandoeningen nauwlettend in de gaten gehouden worden omdat bij hen een hoger risico van neuropsychiatrische bijwerkingen bestaat. Omdat de PSSA een effectief hulpmiddel is om bijwerkingen te identificeren, zou deze techniek ook wijder verbreid toegepast kunnen worden om de effectiviteit en veiligheid van medicatie beter te kunnen inschatten. Andere methodologieën moeten onderzocht worden om betere beheersing te hebben over de versturende factoren (*confounders*) in observationele onderzoeken gebaseerd op data uit de praktijk.

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I am very excited at this moment to defend my PhD degree after four years of study at the University of Groningen. Since 2007, I have been studying in the field of Public Health for approximately twelve years, when I was so young and had never imagined to go so far towards reaching my dream as being an epidemiologist and an academic researcher. What surprised me most is that I met my Mr. Right and had my adorable son during my PhD study in the Netherlands. I am so grateful for all wonderful things that happened to me and I know that I could not achieve these without the kind help and support from many people, whom I would like to thank sincerely.

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LIST OF PUBLICATIONS

Yuanyuan Wang, Tanja R. Zijp, Muh. Akbar Bahar, Janwillem W.H. Kocks, Bob Wilffert, Eelko Hak. Effects of prophylactic antibiotics on patients with stable COPD: a systematic review and meta-analysis of randomized controlled trials. *Journal of Antimicrobial Chemotherapy*. 2018 Dec 1; 73(12): 3231-3243.

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ABOUT THE AUTHOR

Yuanyuan Wang was born on February 15th, 1988 in Henan, China. She studied Preventive Medicine at the School of Public Health for five years in Zhengzhou University, and obtained her Bachelor of Medicine degree in July 2012. Meanwhile, she was awarded another degree of Bachelor of Arts from Zhengzhou University due to her personal interest and study of the English literature. After that, she continued her master studies in the School of Public Health at the Peking University and achieved the degree of Master of Public Health with a research direction in Reproductive Epidemiology in July 2015. During her master programme, she established her research interest in the field of Epidemiology. In October of the same year, she then came to the Netherlands to pursue her PhD studies in the department of Pharmacotherapy, -Epidemiology and -Economics (PTEE) at the Groningen Research Institute of Pharmacy (GRIP) of the University of Groningen under the primary supervision of Prof. dr. Eelko Hak. Her doctoral research focused on the effectiveness and safety of medications used in COPD patients, which as described in this thesis.

