The context of medicines' use in benefit-risk evaluation

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The research presented in this PhD thesis has been conducted under the umbrella of the Regulatory Science collaboration between the Dutch Medicines Evaluation Board (MEB) and the Utrecht Institute for Pharmaceutical Sciences (UIPS). The MEB is dedicated to ensure that licensed medicinal products during their whole life cycle have a positive benefit-risk. This role requires intensive collaboration with academic and clinical partners in order to develop new assessment and decision-making methods, to engage with the clinic and to strengthen regulatory science. This PhD thesis aims to go beyond its scientific merits as such by delivering science, learning and insight to promote public health.

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- World Health Organization Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, Uppsala, Sweden
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The context of medicines' use in benefit-risk evaluation

De context van geneesmiddelengebruik voor de evaluatie
van de balans tussen werkzaamheid en risico's
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 20 april 2011 des ochtends te 10.30 uur

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Contents

Chapter 1

General introduction

INTRODUCTION

The evaluation of new drugs has changed impressively with regard to efficacy, quality, and safety during the previous century. The first milestone in this field was the introduction of the Pure Food and Drug Act in 1906 in the United States [1]. This act enforced that medicines should comply with the standards as laid down in the United States Pharmacopoeia and the National Formulary regarding the strength and quality, but mainly focussed on the purity and adulterating of medicines. The Elixer Sulfanilamide tragedy was a second important landmark in the drug evaluation process [2]. It took place in 1937, shortly after the introduction of sulfanilamide, the first chemically synthesised sulfa antimicrobial drug. A solution of sulfanilamide was developed by a small company called S.E. Massengill Company. Diethylene glycol was used as a diluent and 105 patients died. Although the solution was evaluated by the company for appearance, flavour and flagrance, the toxicity of the ingredients was never tested [2]. This catastrophe led to the strengthening of the Pure Food and Drug Act from 1906 into the Federal Food, Drug and Cosmetic Act, which came into force in 1938. This law enforced pharmaceutical companies to ensure the safety of their products by conducting toxicology studies, followed by an obligatory submission of these data to the US Food and Drug Administration (FDA) for evaluation.

For most other countries in the world, it was not until the thalidomide disaster in the early 1960s that emphasis was placed on the safety of new medicines [3]. Thalidomide, initially proclaimed to be a wonder drug, turned out to cause serious birth defects when used for the treatment of morning sickness and nausea during pregnancy [4]. Toxicity studies in animals were performed, but these showed no relevant teratogenicity [5]. The case of thalidomide showed that animal experiments are not completely predictive for toxicity in humans. In the aftermath of this thalidomide disaster, new drug regulatory authorities were established (e.g. the Dutch Medicines Evaluation Board) and the authorities of already existing regulatory authorities were further strengthened (e.g. the FDA). More stringent regulations were put in place and since then manufacturers of new drugs must ensure the efficacy, quality, *and* safety of their products. The registration process subsequently became more regulated with more emphasis on the pre-registration phase, but increasingly also included requirements for monitoring of post-marketing effectiveness and safety of medicines. If post-marketing studies reveal previously unknown safety issues, appropriate actions may need to be taken, such as a written safety warning to healthcare professionals, or in the extreme cases a withdrawal of the product. Several studies showed that the number of safety-related withdrawals of new drugs is relatively stable since 1964, varying from 2% in the period 1964-1983 [6] to 3-4% in the period 1964-1983 [7] and 2.9% in the period 1975-1999 [8], while the number of written safety warnings has increased [9], indicating a more pro-active role of the regulatory authorities. During the last two decades, regulatory activities have become more and more organised in an international (International Conference on Harmonisation) or regional (European Medicines Agency) perspective.

DEVELOPMENT OF PHARMACOVIGILANCE: FROM MOLECULE TO CONTEXT

The World Health Organization defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems [10]. Recent developments have changed the field of pharmacovigilance, regarding both the tools as well as the point of view from which pharmacovigilance is being conducted. Pharmacovigilance was previously only based on the identification of signals using spontaneous reporting systems [11], but nowadays a proactive identification of risks related to medicines is also becoming more commonly used [12, 13]. In this light, the Vioxx case (described in Box 1) is considered a landmark case, from where the calls for profound changes in drug safety monitoring became stronger [14]. This pro-active approach has been put into shape by the implementation of guidelines on risk management programmes. Since 2005, a European Risk Management Plan (EU-RMP) is an obligatory part of an application for marketing authorisation in the European Union. A EU-RMP is aimed to identify, characterise, prevent and minimise the risks relating to medicinal products [15]. For each important safety concern, an action plan should be presented, in which often post authorisation safety studies (PASS) are proposed to study drug effects post-marketing.

In addition to additional requirements and the improvements in the methods that are being used for pharmacovigilance, there has also been a shift in the way pharmacovigilance is approached. In the beginning, the area was "molecule driven", implying that the detection and interpretation of adverse outcomes was based on the molecular characteristics of a drug. More recently, the role of the context in which a medicine is being used has been recognised as an important factor. This "landscaping" of drug use is also affecting regulatory decision-making. This may be illustrated with the examples in Box 1 and 2.

The context in which medicines are being used may affect (1) the detection of adverse drug reactions, (2) the benefit-risk balance of medicines and (3) regulatory decision-making. First, the detection, but also the confirmation and interpretation of (new) adverse drug reactions depend on the context in which a medicine is used. Previously, drug safety research was focussed on the detection of events (typically type A adverse reactions) with a high relative risk in patients with a low baseline risk but this is shifting towards detecting adverse drug reactions (typically type B adverse reactions) with a low(er) relative risk in populations with a high baseline risk. For adequate interpretation of these findings, the baseline risk (high versus low) of the event in the population and the excess risk induced by drug exposure are both of importance [16] and therefore information on the patient population and context of medicine use is needed.

Second, the population in which medicines are being used may affect the benefit-risk balance. Many studies already showed that the patient populations in randomised clinical trials are not comparable to the population using medicines in real life [17]. For clinical research, drug effects in patients with a less complex medical history (e.g. younger patients, with less co-morbidities, less severe disease and less concomitantly used medication) are studied. This

Box 1: Vioxx® (rofecoxib) – licensed in 1999; withdrawn in 2004 (EU)

Rofecoxib was initially licensed for the symptomatic treatment of osteoarthritis. Later, label extensions were approved for the treatment of primary dysmenorrhoea and the management of acute pain in adults. No long-term or chronic treatment had been approved. The advantage of rofecoxib was the gastrointestinal safety compared to other NSAIDs. The adherence of general practitioners (GPs) to the licensed indications was low [35], and rofecoxib tended to be prescribed for the same indications as conventional NSAIDs. Rofecoxib was prescribed to patients who not only had more frequently gastrointestinal co-morbidities, but also suffered more frequently from cardiovascular co-morbidities [36]. Eventually, a clinical trial, "APPROVe", has shown an increased risk of serious thrombotic events (including myocardial infarction and stroke) compared to placebo, following long-term use (over 18 months) [37]. This led to the voluntarily withdrawal of Vioxx by Merck in 2004 based on the results of this trial. The prescription of rofecoxib to patients with a high a priori risk of cardiovascular disease in real life [38] in combination with an increased risk of cardiovascular events negatively affected the benefit-risk balance of the product and affected the decision making process.

Box 2: Avandia® (rosiglitazone) – licensed in 2000; withdrawn in 2010 (EU)

Avandia®, containing rosiglitazone, was licensed in the EU for the treatment of type 2 diabetes mellitus [39]. At the moment of licensing, fluid retention and possibly an increased risk of heart failure were identified as risks for rosiglitazone. The regulatory authorities requested the marketing authorisation holder, GlaxoSmithKline, to perform a post-marketing cardiovascular outcome study. In 2007, a first meta-analysis was published by Nissen et al, indicating an increased risk of myocardial infarction associated with rosiglitazone [40]. Since then, more data from both clinical trials and observational studies became available and all suggested an increased risk of ischemic heart disease [41-43]. In 2010, an updated meta-analysis and a large cohort study [44, 45] both identified again an increased risk of serious cardiovascular events. These data led to the conclusion of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) that the benefits of rosiglitazone did not longer outweighed its risks [46], and the marketing authorisation for rosiglitazone was suspended. In the US, the FDA decided to restrict access to rosiglitazone by requesting a Risk Evaluation and Mitigations Strategy (REMS), for which both patients and doctors need to acknowledge that they understand the cardiovascular risks that are associated with rosiglitazone use [47]. The use of rosiglitazone in a population with a high baseline risk for cardiovascular disease together with the excess risk of rosiglitazone itself ultimately led to the withdrawals (in the EU) and the serious restrictions for use (in the US).

difference hampers extrapolation of clinical trial data with regard to efficacy, but also regarding safety to daily clinical practice. The baseline risk of patients for certain safety related outcomes therefore differs between the population in clinical trials and clinical practice, which may lead to large differences in absolute risks when used in daily practice. Consequently, the benefit-risk balance also strongly depends on the user population.

Third, regulatory decision-making has to take into account the knowledge of the context in which medicines are used. Vioxx® was not used according to its licensed indications (Box 1). This off-label use strongly affected the benefit-risk balance and ultimately led to the withdrawal of the product. The knowledge of the environment is necessary for an adequate regulatory decision-making, especially for medicines that are aimed to have effect in the long term (e.g. primary or secondary prevention of cardiovascular disease, treatment of obesity), whereas the adverse drug reactions can occur immediately following the start of a medicine.

To summarise, the context in which medicines are used, influences the benefit-risk balance, and the regulatory decisions that are based upon it. Therefore, extensive knowledge about

patient characteristics, patterns of drug use and the regulated availability of medicines is necessary for optimal regulatory decision-making.

CO-OCCURRENCE OF DISEASES: DIABETES MELLITUS AND OBESITY

In this thesis, we focus on two areas of disease, which are closely connected: diabetes mellitus and obesity. Studies reveal that obesity and type 2 diabetes mellitus often co-occur [18-20]. It is hypothesised that excessive weight may lead to the development of insulin resistance. When this is accompanied with dysfunction of pancreatic β-cells, type 2 diabetes will develop [21].

Diabetes mellitus is a chronic condition, with worldwide more than 220 million people currently diagnosed according to the World Health Organization [22]. There are two main types of diabetes mellitus. Approximately 5-10% of the patients with diabetes suffer from type 1 diabetes. This is an autoimmune disease, which is characterised by the deficiency of insulin production by the pancreas. The onset of type 1 diabetes is early in life, and treatment requires lifelong insulin therapy. Type 1 diabetes mellitus is therefore also referred to as insulin dependent diabetes [23]. The large majority, over ninety percent, of the patients with diabetes mellitus is suffering from type 2 diabetes mellitus, also called non-insulin dependent diabetes. Previously, this type of diabetes was mainly seen in the elderly, but nowadays the number of adults, and even children, diagnosed with this disease is increasing. This type of diabetes is a result of decreased insulin sensitivity, often caused by excess weight [21] and a sedentary lifestyle [24].

Patients suffering from overweight or obesity have excess weight and are therefore at an increased risk of developing concomitant diseases, predominantly cardiovascular disease, diabetes and some types of cancer [25]. The ratio of a patient's body weight and length, Body Mass Index (BMI, kg/m^2) is the most frequently used measure of overweight (BMI ≥ 25 kg/m^2) and obesity (BMI > 30 kg/m^2). The number of patients with obesity is increasing, not only in developed countries, but also in developing countries. The World Health Organization projects that by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese [26]. Management of excessive weight is mainly based on lifestyle interventions, e.g. diet and increased physical exercise [27]. Long-term weight maintenance is difficult because a patient should implement major changes in their lives, which need to last for a long term. Currently, there is limited place for medicines for the treatment of overweight. The only drug that is available on prescription is orlistat, and its modest effectiveness (5-10% weight loss) and gastrointestinal adverse effects limit its place in the management of excessive weight [28].

Disease severity and co-morbidities modulate the vulnerability for the development of adverse drug reactions, especially when disease, outcome, and adverse drug reaction are closely related. This is especially true for patients with obesity and/or diabetes mellitus, because both diseases are risk factors for cardiovascular disease [29] and associated with multiple

co-morbidities (e.g. cancer [30, 31], arthritis [32], depression [33, 34]). This implies that these patients are increasingly susceptible for adverse outcomes and thus that extensive information on the context in which medicines for the treatment of these diseases are being used is of importance. This information encompasses disease severity, treatment effects, medical history, and concomitantly used medication. In this thesis, we therefore study these diseases to illustrate the influence of the context of medicine use on the benefit-risk balance and the process of regulatory decision-making.

OBJECTIVES OF THIS THESIS

The objective of this thesis is to unravel how the context in which a medicine is used adds to the assessment of the benefit-risk profile, and to gain more insight in the value of this information for both drug development and regulatory decision-making. This medicines' use context (patient characteristics, patterns of drug use and the regulated availability of medicines) is studied for two disease areas that are intertwined and both involve patients with multiple co-morbidities, namely diabetes mellitus and obesity.

OUTLINE OF THE THESIS

Table 1 provides an overview of the studies presented in this thesis. All studies focus on issues that are important for the evaluation of the benefits and risks of medicines. The whole context in which medicines are used includes knowledge of patient characteristics, patterns of drug use and the regulated availability of medicines. For this, we use different data sources. Data from randomised controlled trials (RCTs) is mostly used for detecting and quantification of adverse drugs reactions that occur both frequently and relatively early during treatment. Because this type of data does not provide a complete profile of the safety and effectiveness of medicines, data from observational studies provides important information on the effects of medicines in daily clinical practice, including less prevalent adverse outcomes. Often these observational studies are preceded by hypothesis-generating spontaneous reports of unexpected drug reactions in clinical practice. In **Chapter 2**, we present eight studies addressing the above-mentioned topics. In *Chapter 2.1*, we analyse data from randomised clinical trials. In this study, three drugs that have been associated with psychiatric adverse events, bupropion, varenicline and rimonabant, are used to evaluate whether patients with a psychiatric history were included in randomised clinical trials (pre- and post-registration) of bupropion, rimonabant, and varenicline, and how this inclusion influences the reported absolute and relative incidence estimates of psychiatric adverse drug reactions.

Table 1: Overview of the studies presented in this thesis

			Important issues in benefit-risk assessment		
			Patient characteristics	**Patterns of use**	**Regulated availability**
RCTs	Chapter 2.1	Reporting of psychiatric AEs in RCTs	x		x
Spontaneous reports	Chapter 2.2	DPP-4 inhibitors and infections: disproportionality analysis	x		x
Observational studies	Chapter 2.3	Initiation of DPP-4 inhibitors and infection risk	x		x
	Chapter 2.4	Co-morbidities in patients with diabetes mellitus starting AODs	x		
	Chapter 2.5	Dynamics in health care utilisation prior to start of AODs	x		
	Chapter 2.6	Risk profiles and patterns of use in patients starting AODs	x	x	
	Chapter 2.7	Reasons for and time to discontinuation of rimonabant	x	x	
	Chapter 2.8	Orlistat: prescription-only vs. pharmacy-only	x		x

RCT: randomised clinical trial; AEs: adverse events; DPP-4: dipeptidyl peptidase-4; AOD: anti-obesity drug

Spontaneously collected case reports have been the basis of pharmacovigilance for many years. In *Chapter 2.2,* we use the spontaneous reporting system WHO Vigibase to investigate the possible association between DPP-4 inhibitors and an increased risk of infections. Because DPP-4 inhibitors are positioned as second- or third line therapy, this type of medicines may be channelled towards the more severely ill patients who might also be at an increased risk of infections. To further evaluate the risk of infections in association with DPP-4 inhibitors and infections, taking into account disease severity, we conducted an observational study using a before-after design with data from the PHARMO Record Linkage System, *Chapter 2.3*.

To analyse the context in which medicines are being used more closely, we focus in *Chapter 2.4* on patients with diabetes mellitus, who start to use an anti-obesity drug. Baseline characteristics of these patients are analysed in order to assess whether the risk of psychiatric and cardiovascular disease differs between patients with diabetes mellitus who start and those who do not start to use anti-obesity drugs. In addition, we look at the predictability of starting anti-obesity drugs, because we assume that anti-obesity drugs may be used as an alternative last line treatment for improvement of the cardiovascular profile and general (mental) well-being. Therefore, we study whether start of anti-obesity drugs is preceded by a change in overall health care utilisation (*Chapter 2.5*).

A described before, the duration of use is an important factor to consider in benefit-risk evaluations. In addition to an analysis of patient characteristics of anti-obesity drug users, we look in *Chapter 2.6* at the patterns of use of anti-obesity drugs in a general Dutch population. Also in *Chapter 2.7* the patterns of use of rimonabant are analysed and linked with reasons

for, and time to discontinuation. In addition, the association between patient characteristics and discontinuation is studied. The study presented in *Chapter 2.8* is conducted in community pharmacies in the Netherlands and focuses on the differences between users of the two available strengths of orlistat, Xenical® (120 mg, available on prescription) and Alli® (60 mg, available in pharmacies only). This information is used to study the effect of the regulated availability of medicines on the patient populations that are using these products. Finally, in **Chapter 3**, the general discussion, the results of this thesis are placed in a broader perspective. In addition, implications of this research for regulatory authorities, pharmaceutical industry, and academia are discussed and directives for the future are given.

REFERENCES

1. Barkan ID. Industry invites regulation: the passage of the Pure Food and Drug Act of 1906. Am J Public Health 1985; 75 (1): 18-26.
2. Wax PM. Elixirs, diluents, and the passage of the 1938 Federal Food, Drug, and Cosmetic Act. Ann Intern Med 1995; 122 (6): 456-461.
3. Brynner R, Stephens T. Dark remedy: the impact of thalidomide and its revival as a vital medicine. Cambridge, Massachusetts: Perseus Publishing, 2001.
4. McBride WG. Thalidomide and congenital abnormalities. Lancet 1961; 278 (7216): 1358.
5. Somers GF. Pharmacological properties of thalidomide (alpha-phthalimido glutarimide), a new sedative hypnotic drug. Br J Pharmacol Chemother 1960; 15: 111-116.
6. Bakke OM, Wardell WM, Lasagna L. Drug discontinuations in the United Kingdom and the United States, 1964 to 1983: issues of safety. Clin Pharmacol Ther 1984; 35 (5): 559-567.
7. Bakke OM, Manocchia M, de Abajo F, Kaitin KI, Lasagna L. Drug safety discontinuations in the United Kingdom, the United States, and Spain from 1974 through 1993: a regulatory perspective. Clin Pharmacol Ther 1995; 58 (1): 108-117.
8. Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. JAMA 2002; 287 (17): 2215-2220.
9. Mol PG, Straus SM, Piening S, de Vries JT, de Graeff PA, Haaijer-Ruskamp FM. A decade of safety-related regulatory action in the Netherlands: a retrospective analysis of direct healthcare professional communications from 1999 to 2009. Drug Saf 2010; 33 (6): 463-474.
10. World Health Organization and the Uppsala Monitoring Centre. The importance of pharmacovigilance: safety monitoring of medicinal products. Geneva, 2002.
11. Meyboom RH, Egberts AC, Gribnau FW, Hekster YA. Pharmacovigilance in perspective. Drug Saf 1999; 21 (6): 429-447.
12. Giezen TJ, Mantel-Teeuwisse AK, Leufkens HG. Pharmacovigilance of biopharmaceuticals: challenges remain. Drug Saf 2009; 32 (10): 811-817.
13. Eichler HG, Pignatti F, Flamion B, Leufkens HG, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. Nat Rev Drug Discov 2008; 7 (10): 818-826.
14. Frantz S. How to avoid another 'Vioxx'. Nat Rev Drug Discov 2005; 4 (1): 5-7.
15. European Commission. Volume 9A of the rules governing medicinal products in the European Union: guideline on pharmacovigilance for medicinal products for human use. Available at: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9a_09-2008.pdf (last accessed: 15 December 2010).
16. Souverein PC. Drug effects in high-risk patients; pharmacoepidemiological research in complex populations [dissertation]. Utrecht: Utrecht University; 2002.
17. Leufkens HGM, Urquhart J. Variability in patterns of drug usage. J Pharm Pharmacol 1994; 46 (Suppl 1): 433-437.
18. Heal DJ, Gosden J, Smith SL. Regulatory challenges for new drugs to treat obesity and comorbid metabolic disorders. Br J Clin Pharmacol 2009; 68 (6): 861-874.

19. Wyatt SB, Winters KP, Dubbert PM. Overweight and obesity: prevalence, consequences, and causes of a growing public health problem. Am J Med Sci 2006; 331 (4): 166-174.

20. Smyth S, Heron A. Diabetes and obesity: the twin epidemics. Nat Med 2005; 12 (1): 75-80.

21. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006; 444 (7121): 840-846.

22. World Health Organization. Fact sheet: Diabetes. Available at: http://www.who.int/mediacentre/factsheets/fs312/en/ (last accessed: 15 December 2010).

23. Daneman D. Type 1 diabetes. Lancet 2006; 367 (9513): 847-858.

24. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet 2005; 365 (9467): 1333-1346.

25. Haslam DW, James WPT. Obesity. Lancet 2005; 366 (9492): 1197-1209.

26. World Health Organization. Fact sheet: obesity and overweight. Available at: http://www.who.int/mediacentre/factsheets/fs311/en/index.html (last accessed: 15 December 2010).

27. Avenell A, Sattar N, Lean M. Management: Part I - Behaviour change, diet, and activity. BMJ 2006; 333 (7571): 740-743.

28. Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. Lancet 2007; 369 (9555): 71-77.

29. Erkens JA, Herings RMC, Stolk RP, Spoelstra JA, Grobbee DE, Leufkens HGM. Cardiovascular risk factors and diseases precede oral hypoglycaemic therapy in patients with type 2 diabetes mellitus. J Clin Epidemiol 2002; 55 (4): 345-349.

30. Grote VA, Becker S, Kaaks R. Diabetes mellitus type 2 - an independent risk factor for cancer? Exp Clin Endocrinol Diabetes 2010; 118 (1): 4-8.

31. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology 2007; 132 (6): 2208-2225.

32. Jarvholm B, Lewold S, Malchau H, Vingard E. Age, bodyweight, smoking habits and the risk of severe osteoarthritis in the hip and knee in men. Eur J Epidemiol 2005; 20 (6): 537-542.

33. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 2006; 49 (5): 837-845.

34. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 2010; 67 (3): 220-229.

35. Florentinus SR, Nielsen MW, van Dijk L, Leufkens HG, Hansen EH, Heerdink ER. Patient characteristics associated with prescribing of a newly introduced drug: the case of rofecoxib. Eur J Clin Pharmacol 2005; 61 (2): 157-159.

36. Florentinus SR, Heerdink ER, de Boer A, van Dijk L, Leufkens HG. The trade-off between cardiovascular and gastrointestinal effects of rofecoxib. Pharmacoepidemiol Drug Saf 2005; 14 (7): 437-441.

37. Merck announces voluntary worldwide withdrawal of VIOXX®. 2004. Available at: http://www.merck.com/newsroom/vioxx/pdf/vioxx_press_release_final.pdf (last accessed: 20 December 2010).

38. Layton D, Souverein PC, Heerdink ER, Shakir SA, Egberts AC. Evaluation of risk profiles for gastrointestinal and cardiovascular adverse effects in nonselective NSAID and COX-2 inhibitor users: a cohort study using pharmacy dispensing data in the Netherlands. Drug Saf 2008; 31 (2): 143-158.

39. Summary of Product Characteristics: Avandia®. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000268/WC500029108.pdf (last accessed: 20 December 2010).

40. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007; 356 (24): 2457-2471.

41. Juurlink DN, Gomes T, Lipscombe LL, Austin PC, Hux JE, Mamdani MM. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. BMJ 2009; 339 b2942.

42. Lipscombe LL, Gomes T, Levesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. JAMA 2007; 298 (22): 2634-2643.

43. Ziyadeh N, McAfee AT, Koro C, Landon J, Arnold Chan K. The thiazolidinediones rosiglitazone and pioglitazone and the risk of coronary heart disease: a retrospective cohort study using a US health insurance database. Clin Ther 2009; 31 (11): 2665-2677.

44. Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med 2010; 170 (14): 1191-1201.

45. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA 2010; 304 (4): 411-418.

46. Committee for Medicinal Products for Human Use. The European Medicines Agency recommends suspension of the marketing authorisation of Acomplia. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/acomplia/53777708en.pdf (last accessed: 15 December 2010).

47. Woodcock J, Sharfstein JM, Hamburg M. Regulatory action on rosiglitazone by the U.S. Food and Drug Administration. N Engl J Med 2010; 363 (16): 1489-1491.

Chapter 2

The context of medicines' use in benefit-risk evaluation

Chapter 2.1

Reporting of psychiatric adverse events in randomised clinical trials

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ABSTRACT

Introduction: Bupropion, varenicline, and rimonabant have all been associated with psychiatric adverse events (AEs). The objective of this study was to assess whether patients with a psychiatric history were included in RCTs (pre- and post-registration) of bupropion, rimonabant, and varenicline, and how this inclusion influenced the reported absolute and relative incidence estimates of psychiatric AEs.

Methods: Descriptive study including full clinical study reports for bupropion, varenicline, and rimonabant (study drugs). In addition to general information on these studies, information was extracted on in- and exclusion criteria for psychiatric co-morbidities, and incidence of reported (total and psychiatric) AEs. In addition to descriptive statistics, we calculated relative risks (RR), risk differences (RD) and the number needed to harm (NNH) to analyse how the in- and exclusion criteria influenced the absolute and relative incidence estimates of psychiatric AEs in relation to any AEs.

Results: We identified 27 studies for the selected study drugs, including on average 677 participants (range 52-3,045). For 24 studies (89%), psychiatric disease was an exclusion criterion; in three (11%) patients with psychiatric disease could be included. For any AE, both the RR (1.08 (95% CI 1.02-1.14) vs. 1.09 (95% CI 1.07-1.11)) and the NNH (15.9 and 13.9) were similar, whereas for psychiatric AEs, the NNH was lower for studies including patients with psychiatric disease (8.3 vs. 11.9), despite the RR being similar (1.56 (95% CI 1.33-1.84) and 1.33 (95% CI 1.25-1.41)).

Discussion: In the vast majority (89%) of the RCTs for the selected study drugs, patients with psychiatric disease were excluded. The similar RRs but diverging NNHs in studies in- and excluding patients with psychiatric disease emphasise the importance of selecting the appropriate patient population for randomised clinical trials, especially if both the pharmacological working mechanism and the expected patient population outside the clinical trial setting indicate susceptibility for certain safety issues.

INTRODUCTION

In recent years, several drugs, licensed for non-psychiatric indications have been associated with severe psychiatric adverse events (AEs) [1, 2]. Two of these are indicated for smoking cessation: Zyban® (bupropion) (approved in the European Union (EU) in 1999 [3] and Champix® (varenicline, granted marketing authorisation in the EU in 2006) [4]. A third drug, Acomplia® (rimonabant), was indicated for the treatment of obesity. This drug was approved in 2006 and has been withdrawn from the market in 2008 [2, 5]. For all these drugs, effects on the central nervous system and thus the possibility of the occurrence of psychiatric adverse drug reactions could be expected based on the mechanisms of action of these drugs.

Bupropion was initially developed as antidepressant (first registered as such in 1985 (United States)) and inhibits selectively the neuronal re-uptake of noradrenaline and dopamine. It is postulated that the effect on smoking cessation is mediated by noradrenergic and/or dopaminergic mechanisms [3]. Dopaminergic activation might explain the psychiatric events [6, 7]. The effect of varenicline is probably a result of the partial agonist activity at the α4β2 nicotinic receptor where its binding produces an effect on symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in a reduction of the rewarding and reinforcing effects of smoking by preventing nicotine binding to the receptor (antagonist activity) [8]. Several case reports of psychiatric events possibly related to the use of varenicline have been published [9, 10], and the US Food and Drug Administration has issued warnings regarding these possible psychiatric events [1]. In the EU, the Summary of Product Characteristics (SPC) and Patient Information Leaflet (PIL) has been updated several times to update the information on neuropsychiatric adverse drug reactions [4]. The exact relationship between varenicline and psychiatric AEs remains unclear. Rimonabant was the first inhibitor of the cannabinoid-1 (CB-1) receptor licensed in the EU. Inhibition of the CB-1 receptor leads to decreased food intake, resulting in weight loss. In the brain, the CB-1 receptor is involved in the regulation of cognition and mood functions, implying that it is connected to regulation of mood, anxiety, and depression [11].

Although the pharmacological working mechanisms possibly leading to psychiatric AEs were already known from (pre-) clinical research, the magnitude of the safety issues after registration appeared to surprise clinicians and regulatory authorities. However, as both tobacco dependence [12, 13] and obesity [14, 15] are closely related to psychiatric disease, it could have been expected that the drugs would be used in patients with a history of psychiatric disease. These patients are likely to be at an increased risk for developing psychiatric AEs, in addition to the effect of the drugs itself through the pharmacological mechanisms.

The aim of this study was to assess whether patients with a known psychiatric history were included in the RCTs (pre- and post-registration) for the three study drugs, i.e. bupropion, rimonabant and varenicline, and how this process of in- and exclusion of patients with a psychiatric history influenced the absolute and relative incidence estimates of psychiatric adverse events.

METHODS

Data sources and study selection

The present study was conducted as part of a regulatory science agreement between Utrecht University and the Dutch Medicines Evaluation Board. All data on the study drugs, i.e. bupropion, rimonabant, and varenicline were disclosed in a confidential way. Randomised clinical trials (RCTs) in humans for the study drugs in comparison with placebo or a reference drug were included in the analysis. Studies were eligible for inclusion in the study only if a full clinical study report (CSR) was available at: the Dutch Medicines Evaluation Board. All studies for which the CSR was available at the MEB by 01 April 2010 were identified. For rimonabant and varenicline, only studies investigating authorised indications were included [5, 8]. For bupropion, only studies assessing the treatment of smoking cessation were included [3].

Data collection

General information

We extracted information on general variables from the CSRs of the study drugs into a spreadsheet. The data sought included date of study report, timing of study in registration process, location of research setting, objectives of the studies, treatment duration, and number of included patients. All data were analysed delinked from the individual study drugs.

Other information

Additionally, information on other variables was extracted from the individual RCTs. These data comprised in- and exclusion criteria regarding predisposition to psychiatric disease, medical history of participants, including psychiatric disease and use of psychiatric medication at baseline. Individual trials used various terms to describe in- and exclusion criteria. For simplicity, the included RCTs were categorized into two groups depending on whether they stated "psychiatric disease" as such as an exclusion criteria (thus trials including patients with a psychiatric disease versus trials excluding patients with a psychiatric disease). Information was also extracted on measurement scales that were used to assess psychiatric disease.

Information was retrieved on methods of collection of adverse events, and whether the investigators retrieved information on AEs in a passive or pro-active way. To study the absolute and relative reporting of adverse events, we collected information on the numbers of reported adverse events, both overall and psychiatric AEs. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA; www.who-umc.org). In this study, we defined psychiatric AEs as all adverse events that were coded within the System Organ Class "Psychiatric disease" according to MedDRA.

Data analysis

Descriptive statistics were used for continuous variables (mean, median, range), and categorical variables were described with frequencies and percentages. Both absolute incidences of (psychiatric) adverse events and risk ratios were calculated. To assess the difference in reporting of psychiatric adverse drug reactions and compare this to the overall reporting of adverse drug reactions, we constructed forest plots in which the risk difference (RD) was presented, separately for the studies excluding and including patients with psychiatric disease. To present risk differences in a more comprehensible way, we calculated the number needed to harm (NNH). The number needed to harm is the inverse of the absolute risk difference (1/RD), and expresses the number of patients who need to be treated in order to cause harm (e.g. an adverse drug reaction) in one patient that would not have been harmed otherwise. The statistical analyses were carried out using SPSS 16.0 statistical software (SPSS Inc. Chicago, Illinois, USA) and Comprehensive Meta-Analysis version 2.0 (www.meta-analysis.com).

RESULTS

Our search yielded 33 RCTs for the selected study drugs. We excluded four trials, because no full clinical study reports were assessable for analysis. Assessment of the full text CSRs led to exclusion of two additional studies, since the CSRs were not complete. The remaining 27 RCTs were included in the study.

In Table 1, the baseline characteristics of these studies are described. Half of the studies were submitted as part of the registration dossier (n=13, 48%), the remaining 14 studies (52%) were finalised after marketing authorisation was granted. Study size ranged between 52 and 3,045 participants, with a mean of 677 patients per study. Almost half (n=13, 48%) of the studies were conducted in North America alone, and two (7%) were conducted solely in the European Union. The vast majority, 78% (n=21), of the studies compared the active substance against placebo, and there were five (19%) three-arm studies identified. Eleven studies (40%) had a duration of less than 12 weeks and three studies (11%) had a duration of more than one year (Table 1).

When looking at in- and exclusion criteria of the studies, the vast majority of the studies (n=24, 89%) excluded patients with current or recent history of psychiatric disease. Three studies (11%) were identified in which patients with psychiatric disease were not explicitly excluded. For 21 studies (78%), use of psychiatric medication at baseline was not allowed (Table 1). In five studies (19%), psychiatric medication was not explicitly mentioned as exclusion criteria.

The exclusion criteria varied largely between studies, ranging from a single statement ("Subjects currently with depression or subjects who had required treatment for depression in the previous 12 months, and subjects with a past history or current diagnosis of panic disorder, psychosis, or bipolar disorder {were excluded}.") to a very detailed description of the exclusion criteria regarding psychiatric disease ("Excluded are: subjects with current or prior diagnosis of

Table 1: Baseline characteristics of randomised clinical trials

Study characteristics	N (study)
Study	27 (100%)
Patients per study	18,291 (mean 677, range 52-3,045)
Timing in registration process	
Pre-registration trial	13 (48%)
Post-registration trial	14 (52%)
Region	
EU alone	2 (7%)
NA alone	13 (48%)
EU and NA	4 (15%)
Other countries	8 (30%)
Treatment arms	
Active substance vs. placebo	21 (78%)
Active substance vs. AC*	1 (4%)
Active substance vs. AC* vs. placebo	5 (19%)
Treatment duration	
< 12 weeks	11 (40%)
12-24 weeks	7 (26%)
24-52 weeks	6 (22%)
≥ 52 weeks	3 (11%)
Exclusion criteria – psychiatric disease	
Diagnosis of PD mentioned as exclusion criterion	23 (85%)
Diagnosis of PD not mentioned as exclusion criterion	3 (11%)
No in- or exclusion criteria mentioned	1 (4%)
Exclusion criteria – psychiatric medication	
Use of PM mentioned as exclusion criterion	21 (78%)
Use of PM not mentioned as exclusion criterion	5 (19%)
No in- or exclusion criteria mentioned	1 (3.7%)
Standardized measurement scale	
HAD	5 (19%)
Beck depression inventory data	3 (11%)
Beck depression inventory data + SCID	2 (7%)
CES-D + SADS-L+HAMD	1 (4%)
No scale reported	16 (59%)

EU: European Union; NA: North America; AC: Active Comparator; PD: Psychiatric disease; PM: Psychiatric medication; HAD: Hospital Anxiety and Depression Scale; SCID: Structured Clinical Interview for DSM Disorders; CES-D: Center for Epidemiologic Studies Depression Scale; SADS-L: Schedule for Affective Disorders and Schizophrenia-Lifetime; HAMD: Hamilton Rating Scale for Depression

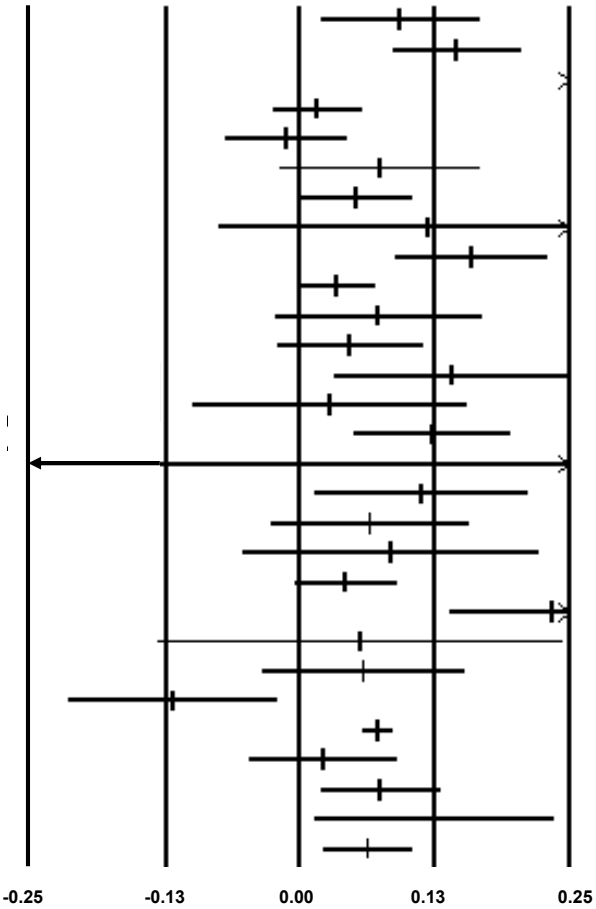
anorexia nervosa or bulimia nervosa; Subjects who had taken an monoamine oxidase (MAO) inhibitor within the past 14 days; Subjects currently or within the past 12 months requiring treatment for depression; Subjects with current or prior history of panic disorder, psychosis, or bipolar disorder; Subjects who had used a nicotine replacement product, clonidine, or nortriptyline within the previous month; Medications that were prohibited by the protocol for both episodic and chronic concomitant use including: antidepressants (including bupropion, citalopram, fluoxetine, mirtazepine, nefazodone, paroxetine, sertraline, trazodone, tricyclic

antidepressants, and venlafaxine), antipsychotic agents (including clozapine, quetiapine, olanzapine, risperidone and ziprasidone), benzodiazepines (including alprazolam, diazepam, and lorazepam), mood stabilizers/anticonvulsants (including carbamazepine, gabapentin, lamotrigine, lithium, and valproate)").

For the overall reporting of AEs, the risk difference (RD) for the trials including patients with psychiatric disease was 0.06 (95% confidence interval (CI) CI 0.02-0.10), and RD was 0.07 (95% CI 0.06-0.09) for trials excluding patients with psychiatric disease (Figure 1). However, when specifically looking at the reporting of psychiatric adverse events, in the trials excluding patients with PD, the RD was 0.08 (95% CI 0.07-0.10), while in the studies including patients with PD, we found a RD of 0.12 (95% CI 0.08-0.16)) (Figure 2).

Figure 1: Risk difference for overall adverse events

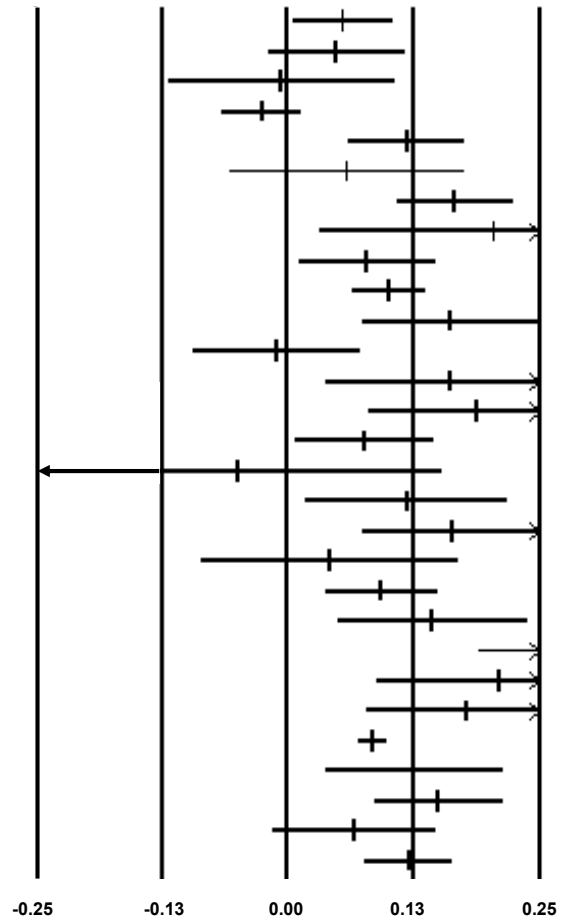
	Risk difference	Lower limit	Upper limit
Study 1	0.093	0.018	0.167
Study 2	0.146	0.087	0.205
Study 3	0.522	0.435	0.609
Study 4	0.016	-0.026	0.057
Study 5	-0.013	-0.071	0.044
Study 6	0.075	-0.019	0.168
Study 7	0.051	-0.003	0.106
Study 8	0.118	-0.075	0.312
Study 9	0.159	0.087	0.230
Study 10	0.034	-0.002	0.071
Study 11	0.073	-0.024	0.170
Study 12	0.046	-0.022	0.114
Study 13	0.141	0.033	0.250
Study 14	0.028	-0.100	0.156
Study 15	0.123	0.051	0.196
Study 16	0.000	-0.284	0.284
Study 17	0.113	0.013	0.212
Study 18	0.065	-0.028	0.158
Study 19	0.084	-0.054	0.222
Study 20	0.042	-0.005	0.090
Study 21	0.234	0.138	0.329
Study 22	0.056	-0.133	0.245
Study 23	0.059	-0.035	0.154
Study 24	-0.019	-0.216	-0.022
Overall*	0.072	0.058	0.087
Study 25	0.022	-0.048	0.091
Study 26	0.075	0.019	0.131
Study 27	0.124	0.013	0.236
Overall†	0.063	0.022	0.104



* Overall risk difference for studies excluding patients with psychiatric disease; † Overall risk difference for studies including patients with psychiatric disease

Figure 2: Risk difference for psychiatric adverse events

	Risk difference	Lower limit	Upper limit
Study 1	0.055	0.005	0.105
Study 2	0.048	-0.020	0.116
Study 3	-0.006	-0.119	0.106
Study 4	-0.026	-0.065	0.013
Study 5	0.118	0.061	0.175
Study 6	0.059	-0.057	0.175
Study 7	0.166	0.108	0.224
Study 8	0.205	0.031	0.379
Study 9	0.079	0.011	0.148
Study 10	0.100	0.063	0.137
Study 11	0.162	0.074	0.250
Study 12	-0.011	-0.094	0.073
Study 13	0.161	0.038	0.283
Study 14	0.187	0.080	0.294
Study 15	0.076	0.008	0.145
Study 16	-0.050	-0.254	0.154
Study 17	0.118	0.017	0.219
Study 18	0.163	0.074	0.252
Study 19	0.042	-0.086	0.170
Study 20	0.093	0.038	0.149
Study 21	0.144	0.050	0.239
Study 22	0.453	0.190	0.717
Study 23	0.210	0.088	0.331
Study 24	0.177	0.079	0.276
Overall*	0.084	0.069	0.098
Study 25	0.126	0.038	0.214
Study 26	0.150	0.086	0.214
Study 27	0.067	-0.015	0.148
Overall†	0.120	0.076	0.164



* Overall risk difference for studies excluding patients with psychiatric disease; † Overall risk difference for studies including patients with psychiatric disease

Calculated from the risk differences, the number needed to harm (NNH) for any adverse events in the trials' including patients with psychiatric disease was 15.9, meaning that 15.9 patients needed to be exposed to treatment to cause an AE in one patient. For trials that excluded patients with psychiatric disease the NNH was comparable (13.9). However, when specifically looking at the reporting of psychiatric adverse events, the NNH for trials excluding patients with psychiatric disease was 11.9 while for trials including patients with psychiatric disease, it was 8.3. The relative differences, (risk ratios (RRs)), were comparable for the reporting of both overall AEs (RR 1.08 (1.02-1.14) and RR 1.09 (1.07-1.12)) and psychiatric AEs (RR 1.56 (1.33-1.84) and RR 1.33 (1.25-1.41)). It was noted that for both, the RR for psychiatric AEs were significantly higher than for overall AEs.

An additional finding was that all study protocols stated that investigators recorded on (electronic) case report forms (CRFs) all reported adverse events and AEs were collected at regular intervals. In four studies (15%), including the three studies in which patients with a psychiatric history were allowed to participate, psychiatric AEs were specifically addressed by using complementary data queries (CDQs) to obtain additional information on adverse events in the neurological and psychiatric disorder system organ classes. The AE-terms used by investigators were recorded according to the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) (n=9 (33%)) and the Medical Dictionary for Regulatory Activities (MedDRA) (n=17 (59%)). In one RCT (4%), the dictionary used for the coding of AEs was not mentioned.

DISCUSSION

In the vast majority (89%) of the RCTs with the study drugs, patients with psychiatric disease were excluded. The occurrence of psychiatric adverse drug reactions was significantly higher in absolute terms for trials including patients with psychiatric disease as compared to those excluding patients with psychiatric disease (resulting in an increased NNH), but when looking at the relative risks, the risk for psychiatric AEs was comparable for trials in- and excluding patients with psychiatric disease.

Since the close relation between tobacco dependence and obesity on the one hand and mental illness on the other hand is already known for years, it can be concluded that the trials excluding patients with psychiatric disease do not reflect the real-world users. The interpretation of the safety results and the extrapolation of these results to the setting outside clinical trials are therefore difficult**.** Although already many studies in different fields of medicine pointed out the differences between trial population and real world population [16-18], the results of this study again emphasise the importance of including the right population into trials. For reasons of internal validity it is acknowledged that regulatory RCTs are designed to show efficacy of a drug, rather than providing information on the effectiveness of the drug, and therefore the choice of a "clean" population with as little as possible co-morbidities is as expected. However, for the extrapolation of the results of such trials and to anticipate on the safety of a certain drug in the real world, these trials have their limitations. We advocate therefore that in addition to regular phase III trials, additional controlled studies in normal clinical settings should be performed. These studies with less stringent in- and exclusion criteria should include a more realistic study population that more adequately reflects the real users of a drug [19, 20].

The RCTs for all three drugs investigated the efficacy and safety of a non-psychiatric indication, being smoking cessation and obesity. Although from preclinical studies as well as from already existing licensed indications the effect of these drugs on the central nervous system was known, it is likely that the focus during the design and conduct of the studies was on the efficacy and safety for the new indications, rather than on the psychiatric effect of the drugs.

It is therefore possible that there was a decreased awareness towards onset, registration, and handling of psychiatric AEs during the studies. This is supported by our finding that in only four studies specific scripted questionnaires implemented at each visit and telephone contact were used to collect information specifically focussed on psychiatric AEs. Among these four studies were the three studies that included patients with a psychiatric history. On the other hand, the increased awareness of the psychiatric potential of these drugs can also have led to the exclusion of patients with a psychiatric history. In the CSRs, no justification for the in- and exclusion criteria was given.

The increased reporting of psychiatric AEs in both absolute and relative terms in the trials including patients with psychiatric disease might, at least partly, be due to increased efforts for the systematic collection of these AEs. A similar finding was also reported by Rief et al, who investigated differences in adverse event reporting in placebo groups in SSRI- and TCA-trials, and showed that the interpretation of drug trial results depends essentially on results of placebo groups; therefore, placebo groups must be designed with care and adverse effect assessment methods need substantial improvements [21]. Additionally, patients with a psychiatric history might have had a higher predisposition to psychiatric disease and thus an increased vulnerability for the development of psychiatric AEs. With regard to the latter, our previous research already indicated that patients using pharmacotherapy for the treatment of obesity are more often having a psychiatric diagnosis in their history compared to patients not requiring obesity-treatment [22, 23]. A history of psychiatric disease likely places those patients at an increased risk for developing psychiatric adverse events.

The strength of this study is that we were able to use the full clinical study reports as submitted to the regulatory authorities by the holders of the marketing authorisations. The effect of publication bias is therefore limited which increases the validity of the study. In addition, the use of three different products with indications related to lifestyle conditions, who are all centrally acting drugs with a non-psychiatric indication, and are associated with the same type of adverse drugs reactions made it possible to conduct an analysis looking beyond one single drug thereby increasing the external validity of this study. A limitation of the study is that we took into account only those studies as present in the regulatory dossier. There may be studies, conducted independently from the marketing authorisation holders of the study drugs. A search using PubMed revealed that the number of additional published trials with the study drugs was limited (bupropion: 3 [24-26]; rimonabant: 1 [27]; and varenicline: 0).

Our choice to use the full CSRs instead of using the articles of the studies was because the latter did not contain the information that we needed for this study, and because of the large differences in presentation of safety information in the publications. This was also addressed by by Pitrou et al, who reported large heterogeneity and variability in the reporting of safety related information in publications of RCTs in general, despite the publication of the CONSORT statement [28]. Assessment of psychiatric disease and psychiatric adverse events in randomised clinical trials may be even more complicated because of the use of different methods

that are being used to measure and report psychiatric disease. Further harmonisation of both standardised measurement scales and the methods for the collection of adverse drug reactions in general will be helpful. The development of guidelines for the conduct and presentation of studies such as CONSORT (for randomised clinical trials) [29], PRISMA (meta-analysis and systemic reviews) [30] and STROBE (observational studies) [31] is supportive in this, although a more stringent approach would be helpful, also focussing more on the conduct of the studies.

From a regulatory point of view, the obligation to include Risk Management Plans as part of the registration dossier in the EU since 2005 [32] has been a step forward in the proactive identification and reduction of drug related risks. When necessary, further information on the risks is sought in post-marketing studies, e.g. randomised clinical trials, or observational studies. Bupropion has been licensed long before RMPs became obligatory, and in the RMP of varenicline, the psychiatric profile was not identified as an area of concern at the time of licensing. For rimonabant, depressive disorders and anxiety were identified as a potential safety issue for which the marketing authorisation holder committed, amongst others, to perform additional epidemiological studies as part of a risk minimisation plan [33]. The experience with RMPs is increasing with regard to feasibility and practical implications of risk minimisation activities, and we expect that this regulatory tool will become increasingly important. In particular the translation of risk identified in "clean" clinical trial data into the real world population should become increasingly important.

In conclusion, we studied exclusion of patients with psychiatric disease in RCTs with three drugs with, from a pharmacology point of view, expected susceptibility for possible CNS safety concerns. We found that in the vast majority these patients were excluded. In addition, for psychiatric AEs the NNH in trials excluding patients with psychiatric disease was higher than the NNH in trials including patients with psychiatric disease. On the contrary, the NNH in the trials in- and excluding patients with psychiatric disease was comparable for the overall reporting of AEs. Clinical drug development and regulation is always finding the right balance between internal and external validity. The results of this study also emphasise the importance of further development of Risk Management Plans in order to balance pre-marketing uncertainties on the benefit-risk, particularly when the expected patient population in the real world indicate susceptibility for certain safety issues. In addition, increased awareness is needed regarding implications of the methods that are being used in RCTs for the collecting of AEs.

REFERENCES

1. US Food and Drug Administration. FDA: Boxed Warning on Serious Mental Health Events to be Required for Chantix and Zyban. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm170100.htm (last accessed: 24 August 2010).
2. Committee for Medicinal Products for Human Use. The European Medicines Agency recommends suspension of the marketing authorisation of Acomplia. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/acomplia/53777708en.pdf (last accessed: 15 December 2010).
3. Summary of Product Characteristics: Zyban. 2001. Available at: http://db.cbg-meb.nl/IB-teksten/h24160.pdf (last accessed: 20 December 2010).
4. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Champix®. Available at: http://www.emea.europa.eu/humandocs/Humans/EPAR/champix/champix.htm (last accessed: 24 August 2010).
5. Sanofi-Aventis. Summary of Product Characteristics: Acomplia. 2006. Available at: www.emea.eu.int (last accessed: 15 December 2010).
6. Golden RN, James SP, Sherer MA, Rudorfer MV, Sack DA, Potter WZ. Psychoses associated with bupropion treatment. Am J Psychiatry 1985; 142 (12): 1459-1462.
7. Grover S, Das PP. Can bupropion unmask psychosis? Indian J Psychiatry 2009; 51 (1): 53-54.
8. Summary of Product Characteristics: Champix 2006. Available at: http://www.ema.europa.eu/humandocs/PDFs/EPAR/champix/emea-combined-h699en.pdf (last accessed: 15 December 2010).
9. Alhatem F, Black JE. Varenicline-induced mania in a bipolar patient. Clin Neuropharmacol 2009; 32 (2): 117-118.
10. Kutscher EC, Stanley M, Oehlke K. Chantix-induced mental status changes in a young healthy female. S D Med 2009; 62 (5): 193-195.
11. Parolaro D, Realini N, Vigano D, Guidali C, Rubino T. The endocannabinoid system and psychiatric disorders. Exp Neurol 2010; 224 (1): 3-14.
12. John U, Meyer C, Rumpf HJ, Hapke U. Smoking, nicotine dependence and psychiatric comorbidity--a population-based study including smoking cessation after three years. Drug Alcohol Depend 2004; 76 (3): 287-295.
13. Flensborg-Madsen T, Bay von Scholten M, Flachs EM, Mortensen EL, Prescott E, Tolstrup JS. Tobacco smoking as a risk factor for depression. A 26-year population-based follow-up study. J Psychiatr Res 2011; 45(2): 143-149.
14. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 2010; 67 (3): 220-229.
15. Sarwer DB, Wadden TA, Fabricatore AN. Psychosocial and behavioral aspects of bariatric surgery. Obes Res 2005; 13 (4): 639-648.
16. Tlusta E, Handoko KB, Majoie M, Egberts TC, Vlcek J, Heerdink ER. Clinical relevance of patients with epilepsy included in clinical trials. Epilepsia 2008; 49 (8): 1479-1480.
17. Wieringa NF, Vos R, van der Werf GT, van der Veen WJ, de Graeff PA. Co-morbidity of 'clinical trial' versus 'real-world' patients using cardiovascular drugs. Pharmacoepidemiol Drug Saf 2000; 9 (7): 569-579.

18. Storosum JG, Fouwels A, Gispen-de Wied CC, Wohlfarth T, van Zwieten BJ, van den Brink W. How real are patients in placebo-controlled studies of acute manic episode? Eur Neuropsychopharmacol 2004; 14 (4): 319-323.

19. Luce BR, Kramer JM, Goodman SN, Connor JT, Tunis S, Whicher D, et al. Rethinking randomized clinical trials for comparative effectiveness research: the need for transformational change. Ann Intern Med 2009; 151 (3): 206-209.

20. Freemantle N, Strack T. Real-world effectiveness of new medicines should be evaluated by appropriately designed clinical trials. J Clin Epidemiol 2010; 63 (10): 1053-1058.

21. Rief W, Nestoriuc Y, Von Lilienfeld-Toal A, Dogan I, Schreiber F, Hofmann SG, et al. Differences in adverse effect reporting in placebo groups in SSRI and tricyclic antidepressant trials: a systematic review and meta-analysis. Drug Saf 2009; 32 (11): 1041-1056.

22. Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Leufkens HG, Egberts AC. Psychiatric and cardiovascular co-morbidities in patients with diabetes mellitus starting anti-obesity drug Obesity (Silver Spring) 2008; 16 (10): 2331-2335.

23. Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Leufkens HG, Egberts AC, Sturkenboom MC. Cardiovascular and psychiatric risk profile and patterns of use in patients starting anti-obesity drugs. Pharmacoepidemiol Drug Saf 2009; 18 (7): 631-638.

24. Simon JA, Duncan C, Carmody TP, Hudes ES. Bupropion for smoking cessation: a randomized trial. Arch Intern Med 2004; 164 (16): 1797-1803.

25. Simon JA, Duncan C, Huggins J, Solkowitz S, Carmody TP. Sustained-release bupropion for hospital-based smoking cessation: a randomized trial. Nicotine Tob Res 2009; 11 (6): 663-669.

26. Zernig G, Wallner R, Grohs U, Kriechbaum N, Kemmler G, Saria A. A randomized trial of short psychotherapy versus sustained-release bupropion for smoking cessation. Addiction 2008; 103 (12): 2024-2031.

27. Florentin M, Kostapanos MS, Nakou ES, Elisaf M, Liberopoulos EN. Efficacy and safety of ezetimibe plus orlistat or rimonabant in statin-intolerant nondiabetic overweight/obese patients with dyslipidemia. J Cardiovasc Pharmacol Ther 2009; 14 (4): 274-282.

28. Pitrou I, Boutron I, Ahmad N, Ravaud P. Reporting of safety results in published reports of randomized controlled trials. Arch Intern Med 2009; 169 (19): 1756-1761.

29. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010; 152 (11): 726-732.

30. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339 b2700.

31. Von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007; 370 (9596): 1453-1457.

32. European Commission. Volume 9A of the rules governing medicinal products in the European Union: guideline on pharmacovigilance for medicinal products for human use. Available at: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9a_09-2008.pdf (last accessed: 23 August 2010).

33. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Acomplia®. Available at: http://www.emea.europa.eu/humandocs/Humans/EPAR/acomplia/acomplia.htm (last accessed: 03 December 2010).

Chapter 2.2

Use of DPP-4 inhibitors and the reporting of infections: a disproportionality analysis in WHO Vigibase

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ABSTRACT

Introduction: Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of antidiabetic drugs. They inactivate incretin hormones, but also have many other effects throughout the body, among which are effects on the immune system. This might results in an increased infection risk. The objective of this study was to assess the association between use of DPP-4 inhibitors and the reporting of infections.

Methods: A nested case-control was conducted using the WHO-ADR database VigiBase. The base cohort consisted of adverse drug reactions (ADRs) for antidiabetic drugs (ATC-code A10). Cases were defined as ADRs of infection according to the MedDRA classification system. All other ADRs were considered controls. Reporting odds ratios (RORs) were calculated to estimate the strength of the association between different classes of antidiabetic drugs and the reporting of infections.

Results: We identified 305,415 suspected ADRs involving antidiabetic drugs in 106,469 case reports, of which 8,083 involved DPP-4 inhibitors monotherapy. Overall, the reporting of infections was higher for patients using DPP-4 inhibitors compared to users of biguanides (ROR 2.3 (95% CI 1.9-2.7)). Especially reporting of upper respiratory tract infections (URTI) (ROR 12.3 (95% CI 8.6-17.5)) was significantly associated with use of DPP-4 inhibitors.

Conclusions: This study indicates an increased reporting of infections in particular URTI for users of DPP-4 inhibitors compared to users of other antidiabetic drugs. However, the limitations of spontaneous reporting systems (e.g. underreporting, the "Weber"-effect, reporting bias) should be taken into account. Therefore, further research is needed to evaluate this suspicion and the underlying mechanism.

INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of antidiabetic drugs with currently three products available on the market (sitagliptin, vildagliptin, and saxagliptin) [1-3]. The inactivation of incretin hormones (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)) by DPP-4 inhibitors results in a rise in insulin from pancreatic ß-cells and a decrease in glucagon from pancreatic α-cells. Consequently, DPP-4 inhibitors improve glycaemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes [1].

DPP-4 is assumed to have many other functions in the human physiology due to its presence on the surface of many different cell types, but these effects are still largely unknown. The role of DPP-4 in immune regulation is better defined and includes induction of TGF-β1 in activated T-cells and suppression of production of inflammatory cytokines by T-cells [4], effects on cell growth, differentiation and apoptosis [5, 6]. The immunomodulating effect has given rise to concerns regarding a possible increase in the occurrence of infections [1-3].

Nasopharyngitis, upper respiratory tract, and related infections ((acute) bronchitis, pharyngitis, sinusitis, and rhinitis) were the most commonly reported infections for the active substances in comparison to the reference intervention in the clinical trial programmes [1-3]. However, pooled analyses for vildagliptin and saxagliptin did not indicate an increased risk of infections compared with the reference group [7, 8]. In the three EU Risk Management Plans (mandatory part of the marketing applications since November 2005 [9]) for the approved DPP-4 inhibitors, "infections" were defined as important identified risks that require further evaluation. Post-authorisation safety studies (PASS) specifically evaluating the risk of (hospitalisation due to) infections are currently being conducted for vildagliptin and saxagliptin [2, 3]. For sitagliptin, the risk for infections will be further evaluated through an in-depth analysis of the safety results of the ongoing and planned clinical trials [1].

Data on a possible direct relation between diabetes mellitus and infections are not yet conclusive. Several studies investigated a possible association between diabetes mellitus and alterations of the immune system [10, 11]. Some epidemiologic studies showed that these patients are at an increased risk for common infections [12-15], but evidence from clinical trials is limited and inconsistent [16]. As disease progression may have an effect on the occurrence of infections, more severely ill patients might be at an increased risk of infections [17]. To our knowledge, no studies have specifically investigated the relation between the use of DPP-4 inhibitors and infections as adverse drug reactions (ADRs). Therefore, the aim of the present study is to assess the relation between different classes of antidiabetic drugs and the reporting of infections.

METHODS

Setting and study design

Data were obtained from the International Drug Monitoring Program of the WHO. The WHO global individual case safety report (ICSR) database VigiBase is maintained by the Uppsala Monitoring Centre and contains summaries of suspected spontaneous case reports originally summated by health care professionals and patients to national pharmacovigilance centers in 98 countries worldwide. As of May 2010, this database contained over 5 million case reports of suspected ADRs regarding specific, but anonymous, patients. The reports contain administrative data, patient data, ADR data, medication data and additional information. The information in these reports is not homogenous, at least with regard to origin, completeness of documentation or the likelihood that the suspected drug caused the adverse events [18]. ADRs are coded according to the Adverse Reaction Terminology (WHO-ART) and Medical Dictionary for Regulatory Activities (MedDRA; www.who-umc.org).

This study was designed as a nested case-control study. The base cohort consisted of all ADRs associated with the use of any antidiabetic drug (ATC-code: A10), including both oral antidiabetic drugs and insulins in the period 1999-2009.

Definition of cases and controls

Cases were defined as ADRs classified as an infection. Infections were defined by means of MedDRA adverse reaction terms, including all relevant high level terms and lower level terms. All infections from the System Organ Class (SOC) "Infections and infestations" and infections reported in other SOCs (identified through a manual search) were defined as cases. All reports containing other ADRs were considered as controls. We grouped the infections on the first sub-level (High Level Group Term (HLGT)) of MedDRA and looked at upper respiratory tract infections (including for example sinusitis and nasopharyngitis), lower respiratory tract infections (e.g. bronchitis and pneumonia), and urinary tract infections (e.g. cystitis and pyelonephritis). Because of low numbers, all other infections were combined.

Exposure definition

Exposure to antidiabetic drugs was the determinant that was investigated. Antidiabetic drugs were subclassified based on the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization (www.whocc.no): biguanides (ATC-code A10BA), sulfonylurea derivates (A10BB), thiazolidinediones (A10BG), DPP-4 inhibitors (A10BH), insulins and analogues (A10A). When multiple antidiabetic drugs were reported for a certain ADR, this was classified as combination therapy, irrespective of whether a drug was reported was classified as "suspected" or was reported as co-medication.

Potential confounding factors

The following potential confounding factors were retrieved from the case reports: age and gender of patient, reporting year, reporting region (Europe, North America, rest of the world), and reporter type (physician, pharmacist, other care giver, pharmaceutical company (indirectly obtained from a health care professional), and patient/consumer). Additionally, concomitant use of medication affecting the immune system (defined as reporting one of these drugs as concomitant drug for an ADR) was taken into account when recorded, including antibiotics (ATC-code J01), corticosteroids for systemic use (H02) and immunosuppressants (L04).

Data analysis

Descriptive statistics were used to summarise the baseline characteristics of the case reports. Unconditional logistic regression analysis was used to estimate the strength of the association between use of antidiabetic drugs and reporting of infections and expressed as reporting odds ratios (RORs) with corresponding 95% confidence intervals (95% CI). Biguanides were the reference group. Due to low numbers, combination therapy was analysed on an aggregated level, not on individual drug-drug combination level. We focused on infections in general and more specific on the HLGTs upper respiratory tract infections, lower respiratory tract infections, urinary tract infection. Adjusted analyses were conducted with all potential confounders included in the model.

Usually, more adverse drug reactions were reported for one case report, and therefore it was possible that one case report contained more than one ADR of an infection. To test the effect of multiple ADRs reported in one case report, we analysed the data on the level of case reports (one case report represented in general one patient).

DPP-4 inhibitors are in the US indicated for monotherapy for the treatment of diabetes mellitus, while in the EU these medicines are only indicated for combination therapies. To check whether this affected the results of this study, we performed a sensitivity analysis in which we analysed the data for the US and the rest of the world separately. In addition, to study the effect of the type of reporter (health care professional or consumer) on the outcome, we performed a sensitivity analysis in which assessed the reports according to the type of reporter. Statistical analysis was carried out using SPSS 16.0 statistical software (SPSS Inc. Chicago, Illinois, USA).

RESULTS

In the WHO VigiBase, a total of 305,415 suspected ADRs related to the use of antidiabetic drugs were identified in 106,469 case reports in the study period 1999-2009. Mean age of the patients was 59.7 years (standard deviation (sd) 14.3) and the majority were females (59.6%). The vast majority of reports involved one antidiabetic drug (n=288,434 (94.4%)); 14,057 (4.6%) reported a combination of two antidiabetic drugs and in 2,924 (1.0%) reports three or more antidiabetic

drugs were reported (Table 1). Overall, the most commonly reported infections on the level of MedDRA lower level terms were pneumonia (11.8%), nasopharyngitis (10.1%), urinary tract infections (6.2%), infection (not otherwise specified) (5.5%), sinusitis (5.1%), and bronchitis (4.8%). All other types of infections were reported in less than 4.5% of the reports related to infections.

Table 1: Baseline characteristics of all spontaneous reports for antidiabetic drugs in the WHO VigiBase (1999-2009)

	Spontaneous reports n=305,415 (100%)
Age of the patient (mean (sd))	59.7 (14.3)
Age (missing)	63,212 (20.7%)
Female gender	182,130 (59.6%)
Gender (missing)	9,100 (3.0%)
Reporter	
HCP	92,896 (30.4%)
Non-HCP	129,287 (42.3%)
Study/literature	218 (0.1%)
Unknown	45,308 (14.8%)
Other	37,706 (12.3%)
Reporting year	
1999-2004	93,255 (30.5%)
2005-2009	212,160 (69.5%)
Region	
Europe	19,252 (6.3%)
United States	273,079 (89.4%)
Other	13,084 (4.3%)
Number of antidiabetic drugs involved	
Monotherapy	288,434 (94.4%)
Biguanides	21,763 (7.1%)
SU-derivates	16,675 (5.5%)
Thiazolidinediones	57,814 (18.9%)
DPP-4 inhibitors	8,083 (2.6%)
Insulin	80,347 (26.3%)
Dual therapy	14,057 (4.6%)
2 oral antidiabetics	11,991 (3.9%)
Biguanide, SU-derivate	2,413 (0.8%)
Biguanide, thiazolidinediones	1,087 (0.4%)
SU-derivate, thiazolidinediones	866 (0.3%)
Oral antidiabetic + insulin	2,066 (0.7%)
Triple therapy	2,924 (1.0%)
Concomitant medication	
Antibiotics (J01)	5,072 (1.7%)
Immunosuppressants (L04)	2,013 (0.7%)
Corticosteroids for systemic use (H02)	4,527 (1.5%)

HCP: Health care professional; SU: sulfonylurea derivates; DPP-4: dipeptidyl peptidase

A total of 242 infections were reported as MedDRA term for DPP-4 inhibitors in 212 case reports, of which 188 (88.7%) case reports reported a single infection. Of the case reports with multiple infections (n=24, 11.3%), half (n=12, 50%) reported a non-specific infection term (such as "infection" or "upper respiratory tract infection") in combination with a more specific infection term (e.g. "nasopharyngitis" or "cystitis") (see appendix 1 for a summary of the infections (according to the MedDRA lower level term).

Table 2 shows the RORs of infections (overall) per antidiabetic drug as compared to biguanides. The use of DPP-4 inhibitors as monotherapy (ROR 2.3 (95% CI 1.9-2.7)), insulins as monotherapy (ROR 1.6 (95% CI 1.4-1.8)) and the combination of any oral antidiabetic drug and insulin therapy (ROR 1.8 (95% CI 1.3-2.4)) were all statistically significant associated with ADR reports of infections compared to biguanides. A slightly increased reporting of infections for patients using thiazolidinediones was found (ROR 1.2 (95% CI 1.1-1.4)), but no increased reporting of infections was found for SU-derivates (ROR 1.2 (95% CI 1.0-1.4), combination therapy of two oral antidiabetic drugs (ROR 1.0 (95% CI 0.8-1.2)) or for concomitant use of three or more antidiabetic drugs (ROR 1.0 (95% CI 0.7-1.4)). Adjustment for the potential confounding factors did not affect the results.

Table 2: Crude and adjusted reporting odds ratios for any infection

	Number of reports	Number of reports of infections	ROR (95% CI) (crude)	ROR (95% CI) (adjusted*)
Biguanides	21,763	289	Reference	Reference
SU-derivates	16,675	258	1.2 (1.0-1.4)	1.1 (0.9-1.3)
TZDs	57,814	919	1.2 (1.1-1.4)	1.3 (1.1-1.5)
DPP-4 inhibitors	8,083	242	2.3 (1.9-2.7)	2.3 (1.9-2.9)
Insulins	80,347	1,703	1.6 (1.4-1.8)	1.5 (1.3-1.7)
OAD + OAD	11,991	155	1.0 (0.8-1.2)	0.9 (0.7-1.1)
OAD + insulin	2,066	48	1.8 (1.3-2.4)	1.5 (1.1-2.2)
≥ 3 ADs	2,924	39	1.0 (0.7-1.4)	1.1 (0.9-1.4)

SU: sulfonylurea, TZD: thiazolidinediones, DPP-4: dipeptidyl peptidase, OAD: oral antidiabetic drug, AD: antidiabetic drug; * adjusted for age, gender, reporting year, reporting region, reporter type and co-medication affecting the immune system (antibiotics (J01), corticosteroids for systemic use (H02) and immunosuppressants (L04))

Assessment of different types of infections (Table 3) showed an increased reporting of upper respiratory tract infections (URTI) (ROR 12.3 (95% CI 8.6-17.5)) for the DPP-4 inhibitors, whereas the reporting for other types of infections (lower respiratory tract infections (LRTI), urinary tract infections (UTI) and other infections) was not increased. In addition, an increased reporting of URTI was found for users of TZDs (ROR 2.3 (95% CI 1.7-3.3)), and for concomitant use of three or more antidiabetic drugs (ROR 2.5 (95% CI 1.3-4.7). Slightly increased RORs were found for the use of insulin monotherapy and the reporting of URTI (ROR 1.5 (95% CI 1.1-2.2)) and UTI (ROR 1.7 (95% CI 1.1-2.5)). Also the reporting of LRTI (ROR 1.8 (95% CI 1.4-2.3)) and other infections (ROR 1.7 (95% CI 1.4-2.0)) was increased for insulin monotherapy. For the combination of an oral antidiabetic drug and insulin, increased reporting of UTI (ROR 3.5 (95% CI 1.7-7.2)) and other

infections (ROR 1.7 (95% CI 1.1-2.6)) was noted. The other associations between antidiabetic drugs and infections were non-significant (Table 3).

For DPP-4 inhibitors, the crude ROR was lower, but still significantly increased (ROR 1.6 (95% CI 1.3-1.9) in the analysis of the data on the level of case reports. The RORs for other antidiabetic drugs did not change, except for insulin. The ROR for insulin monotherapy increased to 2.1 (95% CI 1.8-2.4). Both sensitivity analyses, concerning the country from which the case reports originates and the type of reporter did not have a major impact on the results (data not shown). The point estimates changed only slightly, but due to the decreased numbers the confidence intervals became wider.

Table 3: Reporting odds ratios for specific infections

	URTI		LRTI		UTI		Other infections	
	N	ROR_{crude} (95% CI)	N	ROR_{crude} (95% CI)	N	ROR_{crude} (95% CI)	N	ROR_{crude} (95% CI)
Biguanides	38	Reference	65	Reference	30	Reference	166	Reference
SU-derivates	35	1.2 (0.8-1.9)	58	1.2 (0.8-1.7)	35	1.5 (0.9-2.5)	141	1.1 (0.9-1.4)
TZDs	233	2.3 (1.7-3.3)	232	1.4 (1.0-1.8)	113	1.4 (1.0-2.1)	367	0.8 (0.7-1.0)
DPP-4 inhibitors	171	12.3 (8.6-17.5)	20	0.8 (0.5-1.4)	13	1.2 (0.6-2.3)	51	0.8 (0.6-1.2)
Insulins	215	1.5 (1.1-2.2)	425	1.8 (1.4-2.3)	186	1.7 (1.1-2.5)	1,015	1.7 (1.4-2.0)
OAD + OAD	33	1.6 (1.0-2.5)	33	0.9 (0.6-1.4)	29	1.7 (1.0-2.9)	65	0.7 (0.5-0.9)
OAD + insulin	4	1.1 (0.4-3.1)	8	1.3 (0.6-2.7)	10	3.5 (1.7-7.2)	27	1.7 (1.1-2.6)
≥ 3 ADs	13	2.5 (1.3-4.7)	8	0.9 (0.4-1.9)	6	1.5 (0.6-3.6)	16	0.7 (0.4-1.2)

URTI: upper respiratory tract infection, LRTI: lower respiratory tract infection, UTI: urinary tract infection, SU: sulfonylurea, TZDs: thiazolidinediones, DPP-4: dipeptidyl peptidase, OAD: oral antidiabetic drug, AD: antidiabetic drug

DISCUSSION

This study showed that infections were approximately two times more frequently reported for DPP-4 inhibitors compared to biguanides in the WHO Vigibase. In particular, upper respiratory tract infections (including amongst others nasopharyngitis and sinusitis) were reported more frequently for DPP-4 inhibitors although the reporting of URTI was also increased for users of TZDs, insulin monotherapy and concomitant use of three or more antidiabetic drugs, but to a much lesser extent than for the DPP-4 inhibitors.

Based on the results of the present study it may be hypothesised that the effect of DPP-4 inhibitors results in a slight imbalance of the immune system, causing an increased risk of common, less severe infections such as (viral) upper respiratory infections. This is supported by the results of the pivotal randomised clinical trials, where also increased numbers of common infections were reported, rather than serious infections [1-3]. As far as we are aware, no studies reporting serious infections in association with the use of DPP-4 inhibitors have been reported. At this time, the magnitude of the effects of DPP-4 inhibitors on the immune system may not be compared to the magnitude of the effects as seen for example with biologic agents, resulting

in rather serious infections such as tuberculosis or histoplasmosis due to TNF-α antagonists [19, 20]. With the current data, however, it was not possible to further differentiate between infections of different nature and causes (viral, bacterial, or fungal).

The strength of this study is that the WHO VigiBase allows studying the association between use of antidiabetic drugs and infections outside the highly controlled environment of clinical trials. Nevertheless, some limitations of this study needs to be addressed. Besides the known issue of underreporting in spontaneous reporting systems [21], the reporting pattern of ADRs may differ between new and old drugs, with the most vigorous monitoring at the time of marketing and shortly thereafter, as described by Weber [21]. Both the DPP-4 inhibitors and TZDs were introduced in the study period (1999-2009), which might explain the relatively large number of reports for those drugs. However, it is unknown whether the type of ADRs that is reported changes over time and how this affects the results of this study. Nonetheless, adjustment for year of reporting did not affect the results.

Secondly, the results of this study may be subject to reporting bias, as infections are listed in both the EU and US Summaries of Product Characteristics (SPCs) for all three DPP-4 inhibitors. This may have led to differential monitoring and reporting of infections for the DPP-4 inhibitors compared to other antidiabetic drugs. Either increased reporting (physicians report ADRs that are likely to occur) or decreased reporting (physicians do not report ADRs that are already mentioned in SPCs) may have occurred. In absolute terms the number of reported infections is low as only 3% of the cases for DPP-4 inhibitors reports involved an infection (242 reports of infection out of 8,083 case reports).

Furthermore, differences in classification strategies or misclassification may have occurred by the translation from clinical terminology to the classification systems used by the WHO Vigibase (WHO-ART or MedDRA terms). We do not expect, however, that this misclassification is different for different antidiabetic medicines, and the effect of this non-differential misclassification on the results of this study will therefore be limited. There were several case reports in which more than one infection term was recorded, mainly consisting of a specific infection term (e.g. nasopharyngitis) and an a-specific term (e.g. upper respiratory tract infection), which might influence the results. However, we performed an analysis on case report level and showed that the overall results did not change.

Unfortunately, we were not able to analyse the risk of infections for combination therapy on an individual drug-drug combination level due to the low number of cases reporting each possible combination therapy. This is probably because in most case reports, co-medication is only poorly reported.

Finally, we reasoned that the different indications for the DPP-4 inhibitors in the US versus the rest of the world and a possible effect of the type of reporter (health care professional, consumer or industry) on the case reports may have influenced the results of this study. However, we found that both excluding reports from the US and excluding reporting from consumers and industry, did not affect the results.

Another explanation for our results can be the fact that diabetes itself, and its progression, are often associated with an increased risk of infections. Although literature is not yet conclusive no this, we could not exclude this possible association, and therefore the present study was limited to case reports of antidiabetic medicines only, thereby eliminating the effect of the disease itself. Some studies however suggest that more severe diabetes itself is also associated with higher risk of infections [14, 22], although this is not supported by strong evidence. As disease severity is therefore possibly associated with both exposure and outcome, this can be a confounding factor. DPP-4 inhibitors are indicated as a second or third line therapy in combination with other oral antidiabetic drugs according to treatment guidelines in different parts of the world [23, 24]. Therefore, patients who are treated with DPP-4 inhibitors may in general be more severely ill in comparison to patients being treated with for example biguanides or SU-derivates. However, in the present study, the large majority of the case reports reported a DPP-4 inhibitor as the only antidiabetic drug, which indicates monotherapy with DPP-4 inhibitors. The question rises whether in the present study the patients treated with DPP-4 inhibitors monotherapy are indeed the more severely ill patients, as one antidiabetic drug is sufficient for these patients. In addition, for users of a combination of an oral antidiabetic and insulin or combination therapy of two antidiabetics, i.e. usually the more severely ill patients, we did not found an increased risk of infections. This is in line with the studies that did not found an association between diabetes mellitus and infection.

Besides infections in general, the association between diabetes and urinary tract infections (UTI) has also been described in literature [12, 14, 15, 22], although we did not find a significant increased reporting of ADRs for urinary tract infections and use of any of the antidiabetic drugs. Only for combination therapy of an oral antidiabetic and insulin, we found a slightly increased reporting for urinary tract infections. Channelling of this combination therapy towards the more severely ill diabetes patients, for which the use of insulin in combination with an oral antidiabetic drug is a marker [25], may provide a possible explanation of this finding. This is in line with studies suggesting that the severity of the disease may play a role in the occurrence of UTI [14, 22]. Unfortunately, the subset of VigiBase used in this study did not contain information on the severity of the underlying disease so the effect of this phenomenon in the present study remains unclear.

Post-marketing evaluation of safety concerns raised during the pre-registration phase of medicinal products is of importance for the assessment of the benefit-risk balance of drugs. This study adds to the knowledge of this specific safety issue for the DPP-4 inhibitors. The results of the study, using data reported to National Pharmacovigilance Centres, are in line with the findings from the clinical trial program that included a much more selected patient population. However, more research is needed to further evaluate the clinical and regulatory consequences of this finding such as severity of the infections.

As a result of the observed increased risk in randomised clinical trials, the Risk Management Plans for DPP-4 inhibitors also address a possible increased risk of infections. The definition

of the outcome ("infection") in the post-authorisation safety studies (PASS) that are being conducted as part of the RMP, is therefore of particular importance. Since our study points out that several types of infections (upper respiratory tract infections such as sinusitis and nasopharyngitis) are more frequently reported than others, the outcome should not be limited to infections in general, but also take specific types of infections into account. In addition, in the PASS, the non-serious infections seem to be neglected as all studies aim to investigate the risk of serious infections [1-3]. Although from a regulatory point of view the focus on serious infections is understandable, it can be argued that the impact of (recurrent) non-serious infections on the quality of life may be considerable.

In conclusion, the results of this study show that there is an increased reporting of infections for users of DPP-4 inhibitors compared to users of other antidiabetic drugs. However, the limitations of spontaneous reporting systems (e.g. underreporting, the "Weber"-effect, reporting bias) should be taken into account. Nevertheless, physicians and patients should remain vigilant on the occurrence of infections and continue the reporting of infections as possible adverse events. Although infections may be related to diabetes, a direct effect of the medication on the occurrence of infections should be considered.

REFERENCES

1. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Januvia®. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Scientific_Discussion/human/000722/WC500039057.pdf (last accessed: 15 December 2010).
2. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Galvus®. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Scientific_Discussion/human/000771/WC500020330.pdf (last accessed: 15 December 2010).
3. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Onglyza®. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/001039/WC500044319.pdf (last accessed: 15 December 2010).
4. Reinhold D, Biton A, Goihl A, Pieper S, Lendeckel U, Faust J, et al. Dual inhibition of dipeptidyl peptidase IV and aminopeptidase N suppresses inflammatory immune responses. Ann N Y Acad Sci 2007; 1110 (1): 402-409.
5. Ansorge S, Bank U, Heimburg A, Helmuth M, Koch G, Tadje J, et al. Recent insights into the role of dipeptidyl aminopeptidase IV (DPIV) and aminopeptidase N (APN) families in immune functions. Clin Chem Lab Med 2009; 47 (3): 253-261.
6. Thompson MA, Ohnuma K, Abe M, Morimoto C, Dang NH. CD26/dipeptidyl peptidase IV as a novel therapeutic target for cancer and immune disorders. Mini Rev Med Chem 2007; 7 (3): 253-273.
7. Williams-Herman D, Engel SS, Round E, Johnson J, Golm GT, Guo H, et al. Safety and tolerability of sitagliptin in clinical studies: a pooled analysis of data from 10,246 patients with type 2 diabetes. BMC Endocr Disord 2010; 10: 7.
8. Ligueros-Saylan M, Foley JE, Schweizer A, Couturier A, Kothny W. An assessment of adverse effects of vildagliptin versus comparators on the liver, the pancreas, the immune system, the skin and in patients with impaired renal function from a large pooled database of Phase II and III clinical trials. Diabetes Obes Metab 2010; 12 (6): 495-509.
9. European Commission. Volume 9A of the rules governing medicinal products in the European Union: guideline on pharmacovigilance for medicinal products for human use. Available at: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9a_09-2008.pdf (last accessed: 23 August 2010).
10. Duncan BB, Schmidt MI. The epidemiology of low-grade chronic systemic inflammation and type 2 diabetes. Diabetes Technol Ther 2006; 8 (1): 7-17.
11. Alexandraki K, Piperi C, Kalofoutis C, Singh J, Alaveras A, Kalofoutis A. Inflammatory process in type 2 diabetes: The role of cytokines. Ann N Y Acad Sci 2006; 1084 (1): 89-117.
12. Muller LM, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AI, et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis 2005; 41 (3): 281-288.
13. Bertoni AG, Saydah S, Brancati FL. Diabetes and the risk of infection-related mortality in the U.S. Diabetes Care 2001; 24 (6): 1044-1049.
14. Boyko EJ, Fihn SD, Scholes D, Chen CL, Normand EH, Yarbro P. Diabetes and the risk of acute urinary tract infection among postmenopausal women. Diabetes Care 2002; 25 (10): 1778-1783.

15. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care 2003; 26 (2): 510-513.

16. Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. N Engl J Med 1999; 341 (25): 1906-1912.

17. Rayfield EJ, Ault MJ, Keusch GT, Brothers MJ, Nechemias C, Smith H. Infection and diabetes: the case for glucose control. Am J Med 1982; 72 (3): 439-450.

18. Edwards IR, Olsson S. The WHO International Drug Monitoring Program In: In: Aronson JK, ed. Side effects of drugs, Annual 26 Amsterdam: Elsevier Science 2003: 548-557.

19. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001; 345 (15): 1098-1104.

20. Hamilton CD. Infectious complications of treatment with biologic agents. Curr Opin Rheumatol 2004; 16 (4): 393-398.

21. Weber JCP. Epidemiology of adverse reactions to nonsteroidal antiinflammatory drugs In: Advances in inflammation research. Vol. 6. New York: Raven Press, 1984: 1-7.

22. Boyko EJ, Fihn SD, Scholes D, Abraham L, Monsey B. Risk of urinary tract infection and asymptomatic bacteriuria among diabetic and nondiabetic postmenopausal women. Am J Epidemiol 2005; 161 (6): 557-564.

23. National Institue for Health and Clinical Excellence. Type 2 diabetes - Newer agents (update) 2008. NICE clinical guideline 87. Available at: http://www.gserve.nice.org.uk/nicemedia/pdf/CG87NICE-Guideline.pdf (last accessed: 20 December 2010).

24. Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract 2009; 15 (6): 540-559.

25. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999; 281 (21): 2005-2012.

Appendix 1: Infections for DPP-4 inhibitors (reported as lower level MedDRA term)

	Number of MedDRA terms of infection (n=242)
Upper respiratory tract infections	**171 (70.7%)**
Upper respiratory tract infection	90 (37.2%)
Nasopharyngitis	37 (15.3%)
Sinusitis	18 (7.4%)
Rhinitis	9 (3.7%)
Pharyngitis	8 (3.3%)
Laryngitis	4 (1.7%)
Acute tracheobronchitis	2 (0.8%)
Influenza	2 (0.8%)
Tracheitis	1 (0.4%)
Lower respiratory tract infections	**20 (8.3%)**
Pneumonia	12 (5.0%)
Bronchitis	7 (2.9%)
Lower respiratory tract infection	1 (0.4%)
Urinary tract infections	**7 (2.9%)**
Urinary tract infection	11 (4.5%)
Cystitis	1 (0.4%)
Pyelonephritis	1 (0.4%)
Other infections	**51 (21.1%)**
Respiratory tract infection NOS	9 (3.7%)
Sepsis	4 (1.7%)
Infection NOS	4 (1.7%)
Fungal infection	3 (1.2%)
Candidiasis	2 (0.8%)
Other infections*	28 (11.6%)

* All reported only once; MedDRA: Medical Dictonary for Regulatory Activities; NOS: Not otherwise specified

Chapter 2.3

Initiation of DPP-4 inhibitors and infection risk

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ABSTRACT

Introduction: To evaluate the baseline risk of infections for patients initiating DPP-4 inhibitors and to assess the impact of these medicines on the number of infection-episodes.

Methods: We performed an observational before-after study in the PHARMO Record Linkage System, containing pharmacy-dispensing data from a representative sample of the Dutch population (1998-2008). We included 156,220 incident users of one or more antidiabetic drugs. Cumulative incidences of infections were calculated, measured by treatment episodes for antibiotics in the three months before and after start of antidiabetic medication. Differences in treatment episodes for infections before and after the start of an antidiabetic drug, were expressed as relative risks (RR).

Results: 73,291 patients were identified who started with a biguanide, SU-derivate (n=44,788), thiazolidinediones (TZDs) (n=12,850), DPP-4 inhibitor (n=382) and/or insulin therapy (n=24,909). Patients initiating DPP-4 inhibitors had an increased risk of bacterial infections within three-months after initiation compared to a three-month period before (RR 1.58 (95% CI 1.07-2.34). In contrast, for starters of biguanides, SU-derivatives and TZDs, the risk of infection was statistically significant decreased. For drugs used in the treatment of systemic fungal infections, there was a statistically significant decrease in use of those drugs after start of any antidiabetic drug of approximately 50%, while for antiviral drugs no effect of start of any antidiabetic drug was found.

Discussion: The results of this study, in combination with the biologic plausibility may suggest a potential relation between DPP-4 inhibitors and infections. Further research is needed to evaluate the clinical and regulatory consequences of this finding.

INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a relatively new class of antidiabetic drugs, the first of which was introduced in 2007 [1, 2]. DPP-4 inhibitors inactivate incretin hormones (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)) which leads to improved glycaemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes [3]. Currently, three DPP-4 inhibitors have been registered in the EU (sitagliptin, vildagliptin, and saxagliptin) [1, 4, 5]. In addition to the effect on glucose homeostasis, DPP-4 influences the regulation of multiple T-cell functions, e.g. induction of TGF-β1 in activated T-cells and suppression of production of inflammatory cytokines by T-cells [6]. These effects have given rise to concerns regarding a possible increase in the occurrence of infections [7]. In addition, a disproportionality analysis using the spontaneous reporting database Vigibase maintained by the World Health Organization showed that infections were more frequently reported for DDP-4inhibitors compared to metformin [8].

Most treatment guidelines position DPP-4 inhibitors as second or third line therapy [9, 10]. As a result, patients starting DPP-4 inhibitors may be more severely ill in comparison to patients starting other antidiabetic drugs. Some studies have associated diabetes, especially not well-controlled diabetes, with an increased risk of infections [11-16], although there are still uncertainties whether a direct relation truly exists [17-19]. Thus, when studying the effect of DPP-4 inhibitors on the occurrence of infection using an observational study design, disease severity could be an important confounding or effect-modifying factor that should be taken into account.

In the present study, we compared treatment courses of antibiotic, antimycotic and antifungal drugs for systemic use as a measure of infection risk between patients initiating DPP-4 inhibitors and patients starting with other classes of diabetes drugs shortly before and after initiation of an antidiabetic drug.

METHODS

Setting

Data for this study were obtained from the PHARMO Record Linkage System (RLS) (http://www.pharmo.nl). The PHARMO RLS includes the demographic details and complete medication history of more than two million community-dwelling residents of more than twenty-five population-defined areas in the Netherlands from 1985 onwards, further linked to hospital admission records as well as several other health registries, including pathology, clinical laboratory findings and general practitioner data. Since virtually all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are virtually complete with regard to prescription drugs [20]. For this study, only drug

dispensing data were used. The computerised drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen, and the estimated duration of use. The duration of use of each dispensed drug is estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification [21].

Study population

All patients starting an antidiabetic drug in the period November 1998 to December 2008 were identified. Incident users of biguanides, sulfonylurea (SU) derivates, thiazolidinediones (TZDs), DPP-4 inhibitors, and insulins and analogues were included. For all patients, at least one year of medication history had to be available. Incident use was defined as not having a dispensing for the drug in the 12 months before. Multiple starts were allowed for a single patient. The date of first dispensing for any new antidiabetic drug was defined as the index date. For each patient, information on baseline characteristics was extracted from the database. This information included age, gender, number of concomitantly used antidiabetic drugs, years since first prescription for any type of antidiabetic drug and the use of concomitant medication (diuretics, beta blocking agents, ACE inhibitors, calcium channel blockers, angiotensin II antagonists, vitamin K antagonists, platelet aggregation inhibitors, statins, antidepressants, antipsychotics, benzodiazepines and NSAIDs).

Outcome assessment

The outcome of interest in this study was the occurrence of infections. Therefore, we identified all dispensings for antibiotics (ATC-code J01), antimycotic drugs (J02) and antiviral drugs (J05), all for systemic use. The duration of each dispensing was calculated by dividing the number of prescribed units by the dose regimen. For each type of anti-infective agent, we constructed treatment episodes. A treatment episode was defined as a series of subsequent dispensings, independent of switching to another drug within the same class or dosage regimen. A new treatment episode was assumed if an interval of 14 days or more occurred between the theoretical end date of drug use and the next dispensing date. We assessed the number of occurrences of infection within a three-month period before and after incident use of an antidiabetic drug by counting the number of treatment episodes within each period. Treatment courses were used because we were interested in new and recurrent infections, rather than in chronic use of these drugs (such as for infection prophylaxis).

Data analysis

We tested whether the number of infection episodes before start of the antidiabetic drug differed between the cohorts of patients using a Chi-Square test. Multivariate, unconditional logistic regression analysis was used to explore whether covariates such as age, gender,

duration of diabetes, and concomitant medication could explain observed differences in number of infection episodes before start between these cohorts.

To assess differences in treatment episodes for infection before and after the start of an antidiabetic, we calculated cumulative incidences (proportion of patients with at least one new treatment episode for an antibiotic, antimycotic, or antiviral drug) and relative risks with 95% confidence intervals. A sensitivity analysis was conducted to check how changing the risk window affected the results. Therefore, we analysed the number of infection episodes in different time windows, namely one month, three and six months before and after start of an antidiabetic drugs. Furthermore, we performed a stratified analysis to test whether the above-mentioned covariates were effect-modifying factors. All statistical analyses were carried out using SPSS 16.0 statistical software (SPSS Inc. Chicago, Illinois, USA) and Episheet by K. Rothman (version June 11, 2008).

RESULTS

We identified 382 patients who started with a DPP-4 inhibitor, 73,291 patients who started with biguanides, 44,788 patients starting a SU-derivate, 12,850 patients started to use a TZD, and 24,909 patients started insulin therapy. The baseline characteristics of the study population are shown in Table 1. Patients starting a DPP-4 inhibitor or insulin therapy were slightly younger compared to initiators of other antidiabetic drugs (ADDs) (Table 1). For all therapies, approximately half of the patients were females (n=79,777, 51.1%). Among initiators of DPP-4 inhibitors and TZDs, monotherapy was uncommon (0% for DPP-4 inhibitors and 1.4% for TZDs), while this was frequent among for initiators of biguanides (29.4%), SU-derivates (22.9%) and insulin therapy (14.8%). Time between the date of first prescription for ADDs and the index date was the longest for patients starting to use DPP-4 inhibitors (mean 5.3 years (sd 3.3)), while time since prescription for any ADD was shortest for SU-derivates (mean 0.6 (1.3)). Drugs for the treatment of cardiovascular disease (diuretics, beta blocking agents, ACE-inhibitors, calcium channel blockers, and angiotensin II antagonists) were used more frequently by patients starting a DPP-4 inhibitor compared to patients starting other antidiabetic treatment (Table 1).

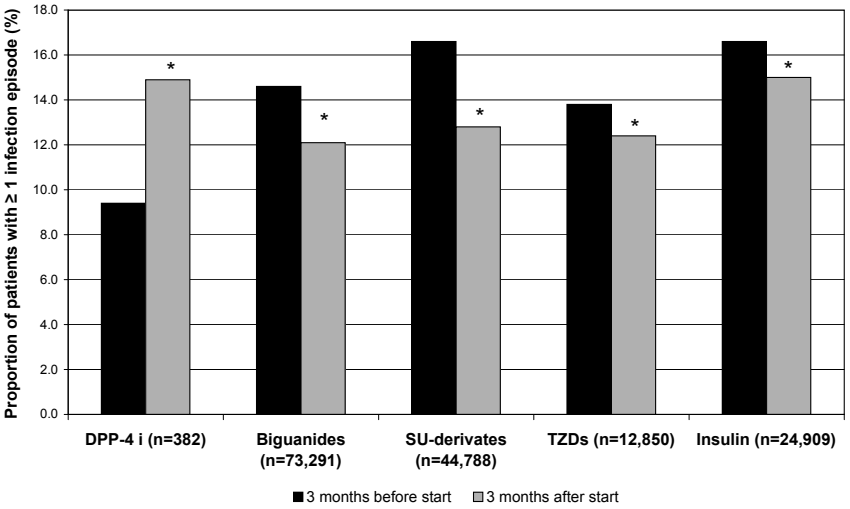
For bacterial infections, the cumulative incidence in the three months before the index date was lower for initiators of DPP-4 inhibitors (9.4%) than for starters of other antidiabetic drugs (biguanides 15.6%, SU-derivates 17.8%, TZDs 14.9% and insulin 17.7% ($p<0.01$)) (Figure 1). In the three months after start the cumulative incidence of antibiotic treatment courses was comparable for biguanides (12.1%, SU-derivates (12.8%) and TZDs (12.4%) and was higher for patients initiating DPP-4 inhibitors (14.9%) and insulin therapy (15.0%) (Figure 1). The relative risk of 1.58 (95% CI 1.07-2.34) indicates an increased risk of infections for patients starting a DPP-4 inhibitor while for starters of biguanides (RR 0.83 (95% CI .0.81-0.85)), SU-derivates (RR 0.77 (95% CI 0.75-0.80)), TZDs (RR 0.89 (95% CI 0.84-0.95)) and insulin (RR 0.90 (95% CI 0.87-0.94)), the relative

Table 1: Baseline characteristics of the study participants

Variable	DPP-4 i (n=382)	Biguanides (n=73,291)	SU-derivates (n=44,788)	TZDs (n=12,850)	Insulin (n=24,909)
Age (mean (sd))	61.8 (11.9)	63.3 (13.2)	64.0 (13.5)	63.0 (12.4)	61.1 (15.5)
Female gender	202 (52.9%)	37,111 (50.6%)	22,929 (51.2%)	6,732 (52.4%)	12,803 (51.4%)
Number of ADD used					
1	0 (0%)	21,519 (29.4%)	10,277 (22.9%)	182 (1.4%)	3,675 (14.8%)
2	41 (10.7%)	32,532 (44.4%)	22,053 (49.2%)	1,912 (14.9%)	3,456 (13.9%)
3	124 (32.5%)	15,671 (21.4%)	10,080 (22.5%)	6,155 (47.9%)	13,751 (55.2%)
≥ 4	217 (56.8%)	3,569 (4.9%)	2,378 (5.3%)	4,601 (35.8%)	4,027 (16.1%)
Years since first prescription for ADD (mean (sd))	5.3 (3.3)	1.3 (2.0)	0.6 (1.3)	3.3 (2.4)	2.9 (2.7)
Concomitant medication					
Diuretics	169 (44.2%)	24,631 (33.6%)	14,845 (33.1%)	4,263 (33.2%)	8,190 (32.9%)
Beta blocking agents	125 (32.7%)	21,908 (29.9%)	13,073 (29.2%)	3,709 (28.9%)	6,772 (27.2%)
ACE inhibitors	115 (30.1%)	16,245 (22.2%)	9,003 (20.1%)	3,479 (27.1%)	6,808 (27.3%)
Calcium channel blockers	73 (19.1%)	10,792 (14.7%)	6,319 (14.1%)	2,072 (16.1%)	3,878 (15.6%)
Angiotensin II antagonists	129 (33.8%)	9,194 (12.5%)	4,599 (10.3%)	2,288 (17.8%)	3,038 (12.2%)
Vitamin K antagonists	24 (6.3%)	4,997 (6.8%)	3,269 (7.3%)	765 (6.0%)	2,093 (8.4%)
Platelet aggregation inhibitors	110 (28.8%)	17,164 (23.4%)	10,058 (22.5%)	3,299 (25.7%)	6,243 (25.1%)
Statins	236 (61.8%)	22,790 (31.1%)	12,157 (27.1%)	5,585 (43.5%)	8,824 (35.4%)
Antidepressants	38 (9.9%)	6,146 (8.4%)	3,664 (8.2%)	1,041 (8.1%)	2,157 (8.7%)
Antipsychotics	10 (2.6%)	1,834 (2.5%)	1,190 (2.7%)	283 (2.2%)	675 (2.7%)
Benzodiazepines	72 (18.8%)	13,529 (18.5%)	9,251 (20.7%)	2,342 (18.2%)	4,835 (19.4%)
NSAIDs	77 (20.2%)	15,880 (21.7%)	9,998 (22.3%)	2,826 (22.0%)	4,851 (19.4%)

SU: sulfonylurea; TZDs: thiazolidinediones; DPP-4: dipeptidyl peptidase-4; ADD: antidiabetic drugs; ACE: angiotension converting enzyme; NSAID: nonsteroidal anti-inflammatory drug

Figure 1: Cumulative incidence (at least one treatment episode) for antibiotics (J01)



* Indicates a significant difference between the number treatment episodes of infections before and after start of the drug ($p<0.05$)

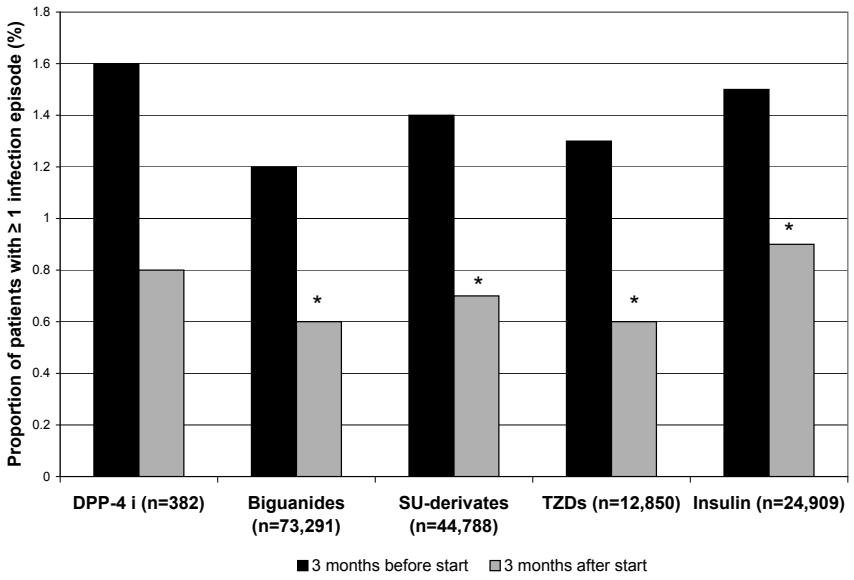
risk indicates a decreased risk of infections (Table 2). Furthermore, a stratified analysis indicated that patient or diabetes related characteristics were not effect-modifying factors (data not shown). For drugs used in the treatment of systemic fungal infections, there was a statistically significant decrease in use of those drugs after start of any antidiabetic drug of approximately 50% (Figure 2, Table 2), while for antiviral drugs the data did not indicate an effect of start of any antidiabetic drug (Figure 3, Table 2), although the absolute numbers were small.

Table 2: Relative risks with 95% confidence intervals for the prescription of antibiotics, antimycotic and antiviral drugs in the three months before and after start of antidiabetic drug

	DPP-4 i (n=382)	Biguanides (n=73,291)	SU-derivates (n=44,788)	TZDs (n=12,850)	Insulin (n=24,909)
Antibacterials (J01)*	1.58 (1.07-2.34)	0.83 (0.81-0.85)	0.77 (0.75-0.80)	0.89 (0.84-0.95)	0.90 (0.87-0.94)
Antimycotics (J02)*	0.50 (0.13-1.98)	0.50 (0.45-0.57)	0.49 (0.43-0.56)	0.48 (0.37-0.63)	0.59 (0.50-0.69)
Antivirals (J05)*	n/a	0.81 (0.65-1.02)	1.12 (0.88-1.43)	1.00 (0.61-1.64)	1.01 (0.74-1.39)
Any infection	1.49 (1.03-2.15)	0.81 (0.79-0.83)	0.76 (0.74-0.78)	0.87 (0.82-0.93)	0.90 (0.86-0.93)

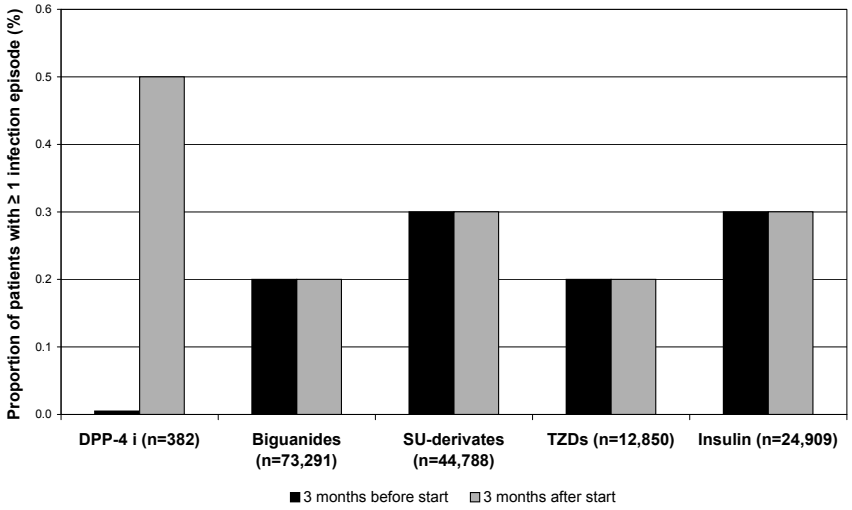
* For systemic use; SU: sulfonylurea; TZDs: thiazolidinediones; DPP-4: dipeptidyl peptidase-4

Figure 2: Cumulative incidence (at least one treatment episode) for antimycotic drugs (J02)



* Indicates a significant difference between the number treatment episodes of infections before and after start of the drug ($p<0.05$)

Figure 3: Cumulative incidence (at least one treatment episode) for antiviral drugs (J05)



* Indicates a significant difference between the number treatment episodes of infections before and after start of the drug ($p<0.05$)

DISCUSSION

In this study, we found that patients initiating DPP-4 inhibitors had a statistically significant increased risk of antibiotic courses as a measure for bacterial infections within 3-months after initiation compared to the three-month period before. In contrast, for starters of biguanides, SU-derivatives, thiazolidinediones, and insulins, the risk of infection decreased in the three months after start of the drug. For treatment with antimycotic drugs, the opposite was found: for all antidiabetic drugs the use of antimycotics decreased by approximately 50%.

Based on the results of the present study it may be hypothesised that the effect of DPP-4 inhibitors results in a slight imbalance of the immune system, causing increased numbers of common infections. This is supported by the results of the pivotal randomised clinical trials, where also increased numbers of common infections were reported, rather than an increase in the number of serious infections [1, 4, 5], and also by the results of a disproportionality analysis in the WHO Vigibase [8].

Strengths of this study are its population-based setting, the size of the study population and the method of data collection. The PHARMO RLS consists of a large and representative sample of Dutch residents, which allows us to study the infection risk in a daily clinical practice setting. In this study, all people initiating antidiabetic treatment were included. It is often suggested that the risk of infections increases with disease severity of diabetes, although this is not supported by strong evidence [17]. According to Dutch treatment guidelines for diabetes mellitus [22], DPP-4 inhibitors are not indicated as first-line therapy. It could therefore be hypothesised that

the use of DPP-4 inhibitors is channelled towards more severely ill patients. Indeed, we found that patients initiating therapy with DPP-4 inhibitors had a longer history of pharmacologically treated diabetes mellitus and used more frequently concomitant medication, including multiple antidiabetic drugs, compared to patients using other antidiabetic drugs. Nevertheless, the number of bacterial infection episodes in the period before initiating DPP-4 inhibitors was lower compared to the other ADDs. To find an explanation for this lower risk of infections in the three months before start for DPP-4 inhibitors in comparison to starters of other drugs, we performed several additional analyses. Multivariate, unconditional logistic regression modelling showed that none of the covariates in Table 1 was responsible for this observed lower infection risk (data not shown). We also considered that the risk window of three months was not adequate for our objective. Thus, we repeated the analyses for a six-month period and a one-month period before and after start. Although absolute numbers changed, the trend we found was in line with the results of the three-month analysis. In summary, we were not able to explain the statistically lower risk of infections for the starters of DPP-4 inhibitors in the three-month period before start compared to starters of other antidiabetic drugs. However, we do not feel that this was caused by the differences between the cohorts, because the before-after design of this study prevented this.

A limitation of our study is that by using a prescription database to define episodes of infections, the focus is on bacterial infections, as for common viral infections such as upper respiratory tract infections, no standard treatment is available. The antiviral drugs for systemic use that we analysed in this study are in general not indicated for the treatment of these common viral infections. Hence, this type of infection is not captured by the PHARMO RLS data. However, from pre-registration trials of DPP-4 inhibitors, it is known that especially upper respiratory tract infections, which are often viral in origin, occurred more frequently. Nonetheless, even when not taking into account the common viral infections as is done in this study, there is a large increase in the number of bacterial infection episodes following the start of DPP-4 inhibitors.

We also found a decrease of approximately 50% in use of antimycotic drugs for systemic use following the start of all antidiabetic drugs. It should be noted however, that we included only antimycotics for systemic use in this study. We were not able to identify recent literature on either fungal infection or systemic antimycotic therapy and diabetes mellitus. In addition, the antiviral drugs were also only included when indicated for systemic therapy. Therefore, we were not able to study the effect of antidiabetic drugs on the treatment of the common fungal infections as for example vulvovaginal candidiasis or fungal skin infections, or common viral infections.

In this study, we used dispensings for antibiotics, antiviral and antimycotic medicines as a measure for infection risks. However, we were not able to confirm the diagnoses with objective test methods (e.g. cell culturing, or microscopic examination). This may have affected our results, but it is not likely that this effect is different among the studied classes of antidiabetic drugs. Therefore, the effect of this non-differential misclassification will be limited. Additionally,

for the DPP-4 inhibitors, the Summaries of Product Characteristics contain information on infections. This could have led to differential monitoring of infections for DPP-4 inhibitors compared to other antidiabetic drugs. However, it can be questioned whether an increased risk of infections is indeed general knowledge among health care professionals.

In conclusion, we observed a significant increase in the number of treatment episodes for bacterial infections in patients starting DPP-4 inhibitors, but not in starters of any other antidiabetic drug. An association between DPP-4 inhibitors and occurrence of infections might therefore be likely. Further research is needed to evaluate the clinical and regulatory consequences of this finding.

REFERENCES

1. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Januvia®. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Scientific_Discussion/human/000722/WC500039057.pdf (last accessed: 15 December 2010).
2. Piya MK, Tahrani AA, Barnett AH. Emerging treatment options for type 2 diabetes. Br J Clin Pharmacol 2010; 70 (5): 631-644.
3. Thornberry NA, Gallwitz B. Mechanism of action of inhibitors of dipeptidyl-peptidase-4 (DPP-4). Best Pract Res Clin Endocrinol Metab 2009; 23 (4): 479-486.
4. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Galvus®. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Scientific_Discussion/human/000771/WC500020330.pdf (last accessed: 15 December 2010).
5. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Onglyza®. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/001039/WC500044319.pdf (last accessed: 15 December 2010).
6. Reinhold D, Biton A, Goihl A, Pieper S, Lendeckel U, Faust J, et al. Dual inhibition of dipeptidyl peptidase IV and aminopeptidase N suppresses inflammatory immune responses. Ann N Y Acad Sci 2007; 1110 (1): 402-409.
7. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA 2007; 298 (2): 194-206.
8. Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Meyboom RH, Egberts AC, Leufkens HG. Use of DPP-4 inhibitors and the reporting of infections: a disproportionality analysis in WHO Vigibase. Diabetes Care 2011; 34: 369-374.
9. National Institue for Health and Clinical Excellence. Type 2 diabetes - Newer agents (update) 2008. NICE clinical guideline 87. Available at: http://www.gserve.nice.org.uk/nicemedia/pdf/CG87NICEGuideline.pdf (last accessed: 20 December 2010).
10. Rodbard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract 2009; 15 (6): 540-559.
11. Muller LM, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AI, et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis 2005; 41 (3): 281-288.
12. Stapleton A. Urinary tract infections in patients with diabetes. Am J Med 2002; 113 (Suppl 1A): 80S-84S.
13. Bertoni AG, Saydah S, Brancati FL. Diabetes and the risk of infection-related mortality in the U.S. Diabetes Care 2001; 24 (6): 1044-1049.
14. Boyko EJ, Fihn SD, Scholes D, Chen CL, Normand EH, Yarbro P. Diabetes and the risk of acute urinary tract infection among postmenopausal women. Diabetes Care 2002; 25 (10): 1778-1783.
15. Boyko EJ, Fihn SD, Scholes D, Abraham L, Monsey B. Risk of urinary tract infection and asymptomatic bacteriuria among diabetic and nondiabetic postmenopausal women. Am J Epidemiol 2005; 161 (6): 557-564.

16. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care 2003; 26 (2): 510-513.

17. Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. N Engl J Med 1999; 341 (25): 1906-1912.

18. Wheat LJ. Infection and diabetes mellitus. Diabetes Care 1980; 3 (1): 187-197.

19. Thornton GF. Infections and diabetes. Med Clin North Am 1971; 55 (4): 931-938.

20. Buurma H, Bouvy ML, De Smet PA, Floor-Schreudering A, Leufkens HG, Egberts AC. Prevalence and determinants of pharmacy shopping behaviour. J Clin Pharm Ther 2008; 33 (1): 17-23.

21. WHO Collaborating Centre for Drug Statistics Methodology. Complete ATC index Available at: http://www.whocc.no/atcddd/ (last accessed: 15 December 2010).

22. Nederlands Huisartsen Genootschap Diabetes mellitus type 2 (M01). 2006. Available at: http://nhg.artsennet.nl/kenniscentrum/k_richtlijnen/k_nhgstandaarden/Samenvattingskaartje-NHGStandaard/M01_svk.htm (last accessed: 15 December 2010).

Chapter 2.4

Psychiatric and cardiovascular co-morbidities in patients with diabetes mellitus starting anti-obesity drugs

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ABSTRACT

Introduction: The aim of the study was to assess whether the baseline risk of psychiatric and cardiovascular disease in patients with diabetes mellitus differed between those starting to use anti-obesity drugs and those not starting to use these drugs.

Methods: A retrospective nested case–control study within the General Practice Research Database (1987–2002) was done. The cohort included all patients with diabetes mellitus (n=141,164). Information on patient characteristics (general, cardiovascular, and psychiatric characteristics) was extracted from the medical records. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Results: A total of 511 patients starting to use anti-obesity drugs (cases) and 3,065 controls were included in the study cohort. Starters were younger and more frequently female. Of the starters, 91.8% did not receive any dietary advice before starting treatment. Depression (in the year before index date) was associated with the use of anti-obesity drugs (OR 2.2 (95% CI 1.7-2.8)), as was anxiety (OR 1.6 (95% CI 1.1-2.4)). Of the cases, 25.2% had multiple cardiovascular risk factors (≥ 5) compared to 19.0% of the controls.

Discussion: The baseline risk for psychiatric disorders and cardiovascular disease was found to be higher in patients with diabetes mellitus starting to use anti-obesity drugs compared to patients with diabetes mellitus not starting such treatment.

INTRODUCTION

In June 2007, the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration stated that rimonabant does not demonstrate an acceptable benefit/risk profile [1]. This statement was largely based on the observed increased risk of neurological and psychiatric adverse effects. Subsequently, Sanofi-Aventis decided to withdraw the New Drug Application in the United States. In Europe, a review of the available data on psychiatric events by the European Medicines Agency resulted in new safety recommendations. These events attributed to the keen interest in the baseline risks of these and other types of adverse events in patients seeking pharmacological treatment for obesity. Therefore, the objective of this study was to assess whether the baseline risk of psychiatric and cardiovascular disease differs between patients with diabetes mellitus who start and those who do not start to use anti-obesity drugs.

METHODS

Data were collected from the General Practice Research Database, a computerized database containing medical records from general practitioners in the United Kingdom. These records contain information about patient's demographics, specific characteristics (e.g. weight, height), symptoms, diagnoses (using Oxford Medical Information System and Read codes), and information about hospital admissions and drug prescriptions (using British National Formulary (BNF) codes). Information is available for almost 4 million person-years originating from about 450 general practices throughout the United Kingdom [2]. The recorded information on drug exposure and diagnoses has been validated and proven to be of high quality [3, 4]. The study was approved by the Scientific and Ethical Advisory Group of the General Practice Research Database.

Between 1 June 1987 and 21 January 2002, all patients with diabetes mellitus (both type 1 and type 2) were included in the study cohort (n=141,164) [5, 6]. A retrospective nested case–control study was performed within this cohort. Starters (cases) were defined as patients with a first prescription for any anti-obesity drug (BNF-codes 04.05) within the study period. The date of first prescription for the anti-obesity drug was defined as the index date. Nonstarters (controls) did not use anti-obesity drugs before the index date. Within the same general practitioner practice, up to six controls were randomly sampled for each case from the study cohort, and they were assigned the same index date. Both starters and nonstarters were eligible for inclusion when they had at least one year of information available before the index date.

Information on characteristics of patient was extracted from the medical records. The following characteristics of patients were determined: number of cardiovascular risk factors at index date (risk factors include ≥ 45 years of age, male gender, smoker, type 2 diabetes,

hypercholesterolemia, high blood pressure, Body Mass Index (BMI) > 25 kg/m^2), in the year before index date prescriptions (antidepressants (BNF codes 04.03); anxiolytics (04.01.02), antipsychotics (04.02), all psychiatric medication (04)) or diagnoses related to psychiatric disorders (e.g. depression, anxiety, psychosis), prescriptions or diagnoses related to cardiovascular events (search terms angina pectoris, arrhythmias, cardiac arrhythmias, cardiovascular disease, cardiovascular event, coronary heart disease, heart failure, ischemic heart disease, myocardial infarction, stroke; BNF-codes 02.01–02.09, except 02.08.01: parenteral anticoagulants), diagnoses related to hypertension, and prescriptions (BNF-codes 02.12: lipid lowering drugs) or diagnoses related to dyslipidemia. In addition, information was collected on gender, BMI (at index date or based on most recent weight measurement and adult height measurement), smoking status (at index date), type of diabetes mellitus (based on both prescriptions (BNF-codes 06.01.01 (insulins) and 06.01.02 (oral antidiabetic drugs) and diagnoses), number of drugs prescribed at the index date, the number of previous dietary advices, and the total number of general practitioner visits in the year before the index date. Descriptive statistics were applied to examine and compare the characteristics of the patient population that started to use anti-obesity medication and those that did not. We provided univariate estimates for all associations, because the aim of this study was not whether such an association was causal in nature. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

RESULTS

In our study cohort, 511 starters of anti-obesity drugs (cases) and 3,065 nonstarters (controls) were identified. The anti-obesity drugs, which were used included mainly fluramines (72.2%) and orlistat (21.3%). The number of patients starting to use anti-obesity drugs varied over time and can be partly explained by publications concerning safety issues in medical literature (Figure 1). The starters were younger and more frequently female (Table 1). Of the starters, 79.1% had a BMI ≥ 27 kg/m^2, compared to 34.8% of the nonstarters. In addition, 91.8% of the starters did not receive any dietary advice before starting treatment, whereas 5.9% received dietary advice only once before starting treatment. Although the absolute numbers were small, the use of an anti-obesity drug was positively associated with receiving dietary advice.

Depression (in the year before index date) occurred more frequent among starters of anti-obesity drugs (OR 2.2 (95% CI 1.7-2.8)) as was anxiety (OR 1.6 (95% CI 1.1-2.4)) (Table 1). Of the starters, 19.4% had been prescribed antidepressants in the year before index date compared to 9.7% of the controls. Diagnosis of any psychiatric disorder and the use of any psychotropic medication were both more prevalent among starters. Cardiovascular drug use and diagnoses were slightly, but not significantly, more frequent among the starters. However, in starters of anti-obesity drugs, we observed in one out of four (25.2%) multiple cardiovascular risk factors (≥ 5) (e.g. hypertension, dyslipidaemia), compared to 19.0% in the controls (OR 1.7 (95% CI 1.3-2.3)).

Figure 1: Number of patients starting to use anti-obesity drugs over time

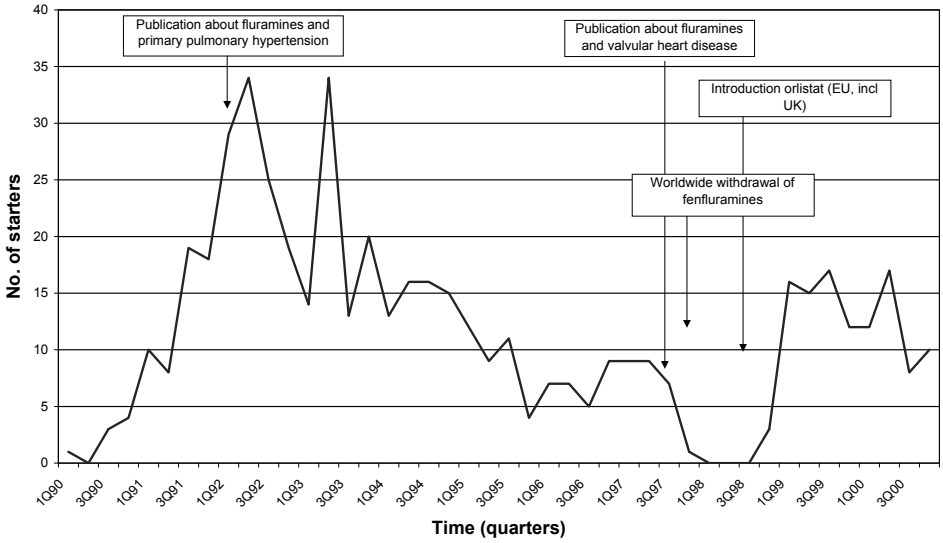

Table 1: Baseline characteristics of the study population

	Starters of AODs (n=511)	Patients not starting AOD (n=3,065)	OR (95% CI)
General characteristics			
Mean age (years) (sd)	53.5 (11.9) [a]	62.9 (15.4)	n/a
Female gender	316 (61.8%)	1,404 (45.8%)	1.9 (1.6-2.3)
Smoking status			
Never smoker	330 (64.6%)	1,855 (60.5%)	1.0 (reference)
Former smoker	61 (11.9%)	270 (8.8%)	1.3 (0.9-1.7)
Current smoker	37 (7.2%)	242 (7.9%)	0.9 (0.6-1.2)
Unknown	83 (16.2%)	698 (22.8%)	n/a
No. of GP visits*			
0 – 5	116 (22.7%)	1,156 (37.7%)	1.0 (reference)
6 – 11	169 (33.1%)	1,024 (33.4%)	1.6 (1.3-2.1)
≥ 12	226 (44.2%)	885 (28.9%)	2.5 (2.0-3.2)
No. of drugs at index date			
0 – 2	172 (33.7%)	1,140 (37.2%)	1.0 (reference)
3 – 4	162 (31.7%)	1,081 (35.3%)	0.9 (0.8-1.3)
≥ 5	177 (34.6%)	844 (27.5%)	1.4 (1.1-1.7)
Dietary advices*			
No	469 (91.8%)	2,935 (95.8%)	1.0 (reference)
Yes	42 (8.2%)	130 (4.2%)	2.0 (1.4-2.9)
Diabetes characteristics			
Diabetes type			
Type 1	27 (5.3%)	330 (10.8%)	1.0 (reference)
Type 2	431 (84.3%)	2,320 (75.7%)	2.3 (1.5-3.4)
Unknown	53 (10.4%)	415 (13.5%)	n/a

Table 1: Continued

	Starters of AODs (n=511)	Patients not starting AOD (n=3,065)	OR (95% CI)
BMI			
< 27 kg/m^2	12 (2.3%)	1,046 (34.1%)	1.0 (reference)
≥ 27 kg/m^2	404 (79.1%)	1,067 (34.8%)	33.0 (18.5-59.0)
Unknown	95 (18.6%)	952 (31.1%)	n/a
Psychiatric characteristics			
Diagnosis of anxiety			
No	494 (96.7%)	3,010 (98.2%)	1.0 (reference)
Yes	17 (3.3%)	55 (1.8%)	1.9 (1.1-3.3)
Use of anxiolytics			
No	482 (94.3%)	2,957 (96.5%)	1.0 (reference)
Yes	29 (5.7%)	108 (3.5%)	1.6 (1.1-2.5)
Diagnosis of depression			
No	477 (93.3%)	2,955 (96.4%)	1.0 (reference)
Yes	34 (6.7%)	110 (3.6%)	1.9 (1.3-2.8)
Use of antidepressants			
No	412 (80.6%)	2,768 (90.3%)	1.0 (reference)
Yes	99 (19.4%)	297 (9.7%)	2.2 (1.7-2.9)
Diagnosis of psychosis			
No	511 (100%)	3,063 (99.9%)	n/a
Yes	0 (0%)	2 (0.1%)	n/a
Use of antipsychotics			
No	502 (98.2%)	2,987 (97.5%)	1.0 (reference)
Yes	9 (1.8%)	78 (2.5%)	0.7 (0.3-1.4)
Diagnosis of any psychiatric disorders			
No	466 (91.2%)	2,903 (94.7%)	1.0 (reference)
Yes	45 (8.8%)	162 (5.2%)	1.7 (1.2-2.4)
Use of any psychotropic medication			
No	364 (71.2%)	2,485 (81.1%)	1.0 (reference)
Yes	147 (28.8%)	580 (18.9%)	1.7 (1.4-2.1)
Cardiovascular characteristics			
Dyslipidaemia[†]			
No	449 (87.9%)	2,835 (92.5%)	1.0 (reference)
Yes	62 (12.1%)	230 (7.5%)	1.7 (1.3-2.3)
Diagnosis of hypertension			
No	336 (65.8%)	1,788 (58.3%)	1.0 (reference)
Yes	175 (34.2%)	1,277 (41.7%)	1.4 (1.1-1.7)
Cardiovascular diagnosis			
No	417 (81.6%)	2,572 (83.9%)	1.0 (reference)
Yes	94 (18.4%)	493 (16.1%)	1.2 (0.9-1.5)
Cardiovascular drug use			
No	226 (44.2%)	1,502 (49.0%)	1.0 (reference)
Yes	285 (55.8%)	1,563 (51.0%)	1.2 (1.0-1.5)
Number of CV risk factors			
0 – 2	91 (17.8%)	707 (23.1%)	1.0 (reference)
3	123 (24.1%)	835 (27.2%)	1.1 (0.9-1.5)
4	168 (32.9%)	940 (30.7%)	1.4 (1.1-1.8)
≥ 5	129 (25.2%)	582 (19.0%)	1.7 (1.3-2.3)

AOD: anti-obesity drug; CI: confidence interval; sd: standard deviation; GP: general practitioner; n/a: not applicable; OR: odds ratio. [*] In the year before index data; [†] Based on both diagnoses and drug prescriptions

DISCUSSION

We found that patients with diabetes mellitus, who start to use anti-obesity drugs, were more frequently female and younger compared to the patients not starting to use anti-obesity drugs. They also had a higher BMI and were more likely to receive a dietary advice, although the absolute number of advices was very low. The baseline risk for psychiatric and cardiovascular disease was higher in starters of anti-obesity drugs. The same was found for the use of antidepressants.

It would have been very informative to present a variable, which can be used as a general psychiatric risk score (comparable to the Framingham risk score for cardiovascular disease), to use as a prediction model for psychiatric conditions. Unfortunately, no such general risk score for psychiatric disease is available. This might be due to the range of psychiatric disorders being very diverse, all with their own specific risk factors and indicators. In addition, it is known that underdiagnosis of psychiatric disorders is relatively common, which may lead to an underestimation of the psychiatric risk [7]. Alternatively, the possible use of various psychotropic medication classes for "off-label" indications in our study might overestimate the true prevalence of even the targeted psychiatric problems at baseline. However, we expect that the amount of "off-label" use of psychotropic medication is relatively small compared to the use according to the indication.

Within the study period (1987–2002), a number of safety issues with anti-obesity drugs occurred [8]. The amphetamine-like compounds (fenfluramine, dexfenfluramine) were withdrawn from the market because they were associated with valvular heart disease and primary hypertension [9, 10]. Our study period covers the use of the newer drugs only to a limited extent. Nevertheless, we do not expect that the characteristics of our patients differ from the patients currently using these drugs. We assume that the characteristics of these patients are comparable to the population eligible for the use of more recently introduced anti-obesity treatments associated with psychiatric events, such as rimonabant. The low number of dietary advices may partly be explained by underreporting in the General Practice Research Database, but reinforcement of non-pharmacological recommendations seems warranted [11].

In conclusion, the baseline risk for psychiatric and to a lesser extent cardiovascular disease is higher for patients with diabetes mellitus who start to use anti-obesity drugs compared to patients with diabetes mellitus who do not start to use anti-obesity drugs. Patients starting to use anti-obesity drugs seem to be more vulnerable especially to psychiatric morbidity. This might be independent of the anti-obesity drugs itself which may induce additional side effects. These findings urge us to be very careful in interpreting the benefits and risks of such anti-obesity drugs, both in terms of preventing possible exposure of drugs associated with psychiatric events in susceptible patients and in the evaluation of causality when a possible drug induced problem occurs.

REFERENCES

1. Food and Drug Administration. Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee meeting. 13 June 2007. Available at: http://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4306m1-final.pdf. (last accessed: 13 December 2010).
2. Wood L, Martinez C. The general practice research database: role in pharmacovigilance. Drug Saf 2004; 27 (12): 871–881.
3. Jick SS, Kaye JA, Vasilakis-Scaramozza C, Garcia Rodríguez, Ruigómez A, Meier CR, et al. Validity of the general practice research database. Pharmacotherapy 2003; 23 (5): 686–689.
4. Lawrenson R, Williams T, Farmer R. Clinical information for research; the use of general practice databases. J Public Health Med 1999; 21 (3): 299–304.
5. Verdel BM, Souverein PC, Egberts AC, Leufkens HG. Difference in risks of allergic reaction to sulfonamide drugs based on chemical structure. Ann Pharmacother 2006; 40 (6): 1040–1046.
6. Van de Garde EM, Hak E, Souverein PC, Hoes AW, van den Bosch JM, Leufkens HG. Statin treatment and reduced risk of pneumonia in patients with diabetes. Thorax 2006; 61 (11): 957–961.
7. Prince M, Patel V, Saxena S, Maj M, Maselko J, Philips MR, et al. No health without mental health. Lancet 2007; 370 (9590): 859–877.
8. Ioannides-Demos LL, Proietto J, Tonkin AM, McNeil JJ. Safety of drug therapies used for weight loss and treatment of obesity. Drug Saf 2006; 29 (4): 277–302.
9. Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med 1996; 335 (9): 609–616.
10. Jick H, Vasilakis C, Weinrauch LA, Meier CR, Jick SS, Derby LE. A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. N Engl J Med 1998; 339 (11): 719–724.
11. Anonymous. Obesity: weight loss without drugs: a balanced diet avoiding high-calorie foods, plus exercise. Prescrire Int 2007; 16 (90): 162–167.

Chapter 2.5

Dynamics in health care utilisation in patients prior to initiation of anti-obesity drug use

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ABSTRACT

Background: To assess the dynamics in health care utilisation prior to start of anti-obesity drugs (AODs).

Methods: In the IPCI database (1996-2008), all patients with first AOD-prescription (cases) were sampled to four controls (no use of AOD). Demographics and patterns in health care utilisation (HCU) were compared between cases and controls during the three years prior to start of AOD (index date (ID)) using unconditional logistic regression.

Results: 1,415 Cases (52 rimonabant, 746 orlistat, 512 sibutramine and 105 users of other AODs) and 5,660 control patients were included. In the 3 years before ID, cases were more likely to have ≥ 1 physician contact than controls (odds ratio (OR): 1.9 (95% CI 1.6-2.2)). The OR increased slightly towards the index date, and the same was found for the total number of prescriptions. The OR of ≥ 1 change in medication was 3.2 (95% CI 2.8-3.7).

Discussion: There is an increased HCU in patients starting AOD-therapy compared to patients not starting these drugs, and differences increase gradually over the 3-year period. Initiation of AODs is preceded by a gradual, and not a sudden sharp increase in HCU in the overall population and in substrata of patients with and without co-morbidity, regardless of gender.

INTRODUCTION

There are only few medicines that are registered in the EU for the treatment of obesity. For these drugs, little is known about the patients who are actually using these drugs and on what the decision to start therapy with an anti-obesity drug is based upon. Due to a combination of limited efficacy and the occurrence of adverse events, anti-obesity drugs are not widely used. Currently, orlistat is the only drug registered in Europe for the treatment of obesity. It is indicated for use in conjunction with lifestyle measures both as prescription medicine (Xenical®, 120 mg) as well as pharmacy-only drug not requiring a prescription (Alli®, 60 mg) [1]. Mainly due to the limited sustained efficacy, this product is not widely used. In the past, several anti-obesity drugs have been associated with severe adverse events. The fenfluramine-like drugs were taken out of the market due to severe cardiovascular adverse events [2], and in 2008 rimonabant (Acomplia®) was withdrawn because the benefits no longer outweighed the risks, a decision mainly driven by the increasing numbers of psychiatric adverse events reported post-marketing [3]. More recently, the marketing authorisation of sibutramine (Reductil®) was suspended in the European Union (EU) because data from the Sibutramine Cardiovascular OUtcomes Trial (SCOUT) showed an increased risk of serious, non-fatal cardiovascular events (e.g. stroke, myocardial infarction) compared to placebo [4].

In general, obese patients have a higher healthcare utilisation compared to normal-weight people [5-7]. This might partly be due to the fact that patients with obesity are at an increased risk of suffering from and developing other morbidities, such as cardiovascular disease [8, 9], arthritis, but also several types of cancer [10-12]. For psychiatric diseases the association is less straightforward but also points to an increased risk in obese patients [13-17]. Part of the obese population starts to use anti-obesity drugs and we hypothesise that anti-obesity drugs may be selectively prescribed to patients who do not respond optimally to other obesity-related therapies (such as treatment for cardiovascular or psychiatric disease), e.g. experience either ineffectiveness or adverse events. Our assumption is that anti-obesity drugs may thus be used as an alternative last line treatment for improvement of the cardiovascular profile and general (mental) well-being.

From a regulatory point of view, especially for weighing the benefit-risk ratio, it is important to have accurate knowledge on the context in which a medicine is used in terms of the patterns of drug use, concomitantly used medication and previous medical history of the patient population. This kind of information helps to place efficacy and occurrence of adverse events in the right perspective. There are, however, only very few studies which investigated the patient population using anti-obesity drugs. In a previous study [18], we therefore compared patients with a first prescription for an anti-obesity drug with patients without prescription for such a drug. This study showed that both cardiovascular and psychiatric co-morbidities were more prevalent among starters of anti-obesity drugs compared to non-starters [18].

Several studies have been published investigating the predictive value of changes in medication or health care utilisation on hospital admissions or specific diagnoses [19-21]. These studies found a sharp increase in medication changes or health care utilisation in the short period (1-3 months) prior to the studied event. The aim of the present study was to investigate general health care utilisation and especially the dynamics of health care utilisation that precede the start of anti-obesity drugs, in order to identify patterns of health care utilisation that may point at an early stage the chance that an anti-obesity drug is started. This will increase the knowledge on the context in which these medicines are used, which is of importance for assessment of benefit-risk profiles**.** In addition, this may further reconcile health care with the needs of individual patients.

METHODS

Setting

Data were collected from the Integrated Primary Care Information (IPCI) database, a computerized database containing electronic medical records from general practitioners (GPs) in the Netherlands. The database currently comprises data from more than 1.2 million patients. The database was set up in 1992 and is maintained by the Department of Medical Informatics of the Erasmus, University Medical Centre, Rotterdam, the Netherlands. In the Dutch health care system, almost all citizens are registered with a GP practice and the GP acts as the gatekeeper to and as the central receiver of information from secondary care. The medical record from each individual patient can therefore be assumed to contain all relevant medical information of that person. The records contain information about patient demographics (age, gender, patient identification, and GP registration information), diagnoses and symptoms, physical, laboratory and specialist finding, information about hospital admissions and drug prescriptions. The International Classification of Primary Care (ICPC) is used to register symptoms and diagnoses, although these can also be entered as free text. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the World Health Organization [22]. Summaries of hospital discharge letters or information from specialists are included as free text. The IPCI database complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmacoepidemiological research. Extended details about the database have been reported elsewhere [23]. The governance board of the IPCI project has approved the present study.

Study population

We performed a population-based, retrospective case-control study. The source population included all patients enlisted in the IPCI database in the period January 1996 to January 2008. Cases were all patients with a first prescription for one of the anti-obesity drugs (rimonabant

(ATC-code A08AX01), sibutramine (A08AA10), orlistat (A08AB01) and the amphetamine-like drugs fenfluramine (A08AA02), dexfenfluramine (A08AA04), and mazindol (A08AA05)) during the study period with absence of such drug use anytime earlier in the available medical history (at least three and a half years of information was available for each patient). All these products were authorised in the Netherlands in (parts of) the study period. No users of the recently introduced anti-obesity drug Alli® (orlistat 60 mg) were included, because this product has a pharmacy-only status and does not require a prescription.

The index date was defined as the date of the first prescription of the anti-obesity drug within the study period. For each patient with a first prescription of an anti-obesity drug, four control patients were randomly sampled from the same practice and were assigned the same index date. The control patients did not have a prescription for any anti-obesity drug in their available history or during the study period. No matching criteria were used. Cases and controls were only included if they were ≥18 years of age and if they had a minimum of three and a half years of information available prior to the index date and 6 months after the index date. This extensive follow-up time was needed for an accurate classification of the patients with regard to the dynamics in health care utilisation described below.

Patient characteristics

Information on general, cardiovascular and psychiatric patient characteristics was extracted from the medical records by electronic searches and manual validation, as described in more detail in a previous study [18]. The general characteristics that were identified were age at the index date and gender. The following cardiovascular morbidities in the year before the index date were defined: ischemic heart disease (including angina pectoris and myocardial infarction) (ICPC codes K74-76), hypertension (K85-87), heart failure (K77), dyslipidaemia (T93), stroke (K89-90), and arrhythmias (K78) and the presence of diabetes mellitus (defined as use of antidiabetic drugs (ATC-code A10A, A10B) or coded diagnoses (ICPC: T89, T90)). Insulin-dependent diabetes (type 1) was defined as a diagnosis of insulin-dependent diabetes mellitus and/or the use of insulin, without any prescription for an oral antidiabetic drug. Non-insulin-dependent diabetes mellitus (type 2) was defined as a diagnosis of non-insulin dependent diabetes mellitus and/or the use of oral antidiabetic drugs. Pharmacological untreated diabetes was classified as non-insulin dependent diabetes mellitus.

Information on cardiovascular medication with the ATC-codes C01-C10, B01AC was also extracted from the medical records. To characterise the psychiatric morbidities in the year before the index date, prescriptions and diagnoses related to psychiatric disorders from the medical records were extracted. We used the psychological codes P71 to P99 (excluding category P85 (mental retardation)), and the following ATC-codes: N05A (antipsychotics), N06AA (tricyclic antidepressants), N06AB (selective serotonin reuptake inhibitors), N05B (anxiolytics) and N05C (hypnotics).

Dynamics in health care utilisation

Definition of time periods

For each patient, 12 three-monthly time periods (0-3, 3-6, 6-9, 9-12, 12-15, 15-18, 18-21, 21-24, 24-27, 27-30, 30-33, 33-36 months before the index date) were defined and all variables were repeatedly assessed within these time periods. The length of the time periods was based on the maximum duration of a prescription, which is three months in the Netherlands.

Visits to the general practitioner and medical specialists

Within each time period in the three-year period before the index date, the number of visits to the general practitioner (GP) regardless of reason for the visit was assessed. Both visits by the patient to the practice and visits from the GP to the patient (day or night) were taken into account. Consults of the GP by telephone, and provision of routine repeat prescriptions were not counted. Within each time period in the three-year period before the index date, the number of visits to the general practitioner (GP) regardless of reason for the visit was assessed. In addition to visits to the GP, we also analysed the number of visits to the specialist within each time period. This was also assessed regardless of the reason for the visit. To extract information on specialist referrals, summaries of hospital discharge letters and information from specialists (available as free text) was used.

Number of prescriptions (all drugs)

The total number of drug prescriptions (all ATC codes) that were issued by each patient within each 3-month period before the index date was abstracted electronically from the medical records. Again, the length of the time periods was based on the maximum duration of a prescription, which is three months in the Netherlands.

New obesity-related diagnoses

Information on diagnoses was extracted from the medical records by electronic searches and manual validation. We focussed on co-morbidities that are related to obesity [24-26]: diabetes mellitus (ICPC-code: T90), respiratory disease (R78, R91, R96), musculoskeletal disease (L84, L88-L91), hypertension (K85), hypercholesterolemia (T93), coronary heart disease (K74, K75), depression (P76), anxiety (P74) and biliary tract disorders (D98). The date of occurrence of the first diagnosis of one of the above-mentioned diseases in a patient's medical record was considered to be the date of first diagnosis. The diagnosis was counted in the three-month period in which the first diagnosis fell.

Changes in obesity-related drug treatment

For the prescriptions we focussed on drug classes that are used for the diseases that are known to be associated with obesity [24-26], i.e. oral antidiabetics (ATC-code A10B), antihypertensives (C02, C03, C07, C08 and C09), antidepressants (N06A), antiplatelet therapy (B01), lipid modifying

drugs (C10), analgesics (N02, excluding N02C anti-migraine preparations), anti-inflammatory and anti-rheumatic products (M01) and drugs for treatment of gastrointestinal disorders (A02). For practical reasons, only formulations for systemic use were taken into account. Within the time periods that were defined for each patient, changes in the use of these drugs were recorded. Different variables were defined to describe medication changes. Initiation of a drug was defined as prescription of a drug that has not been used before (including addition of a drug for same indication, e.g. addition of rosiglitazone to metformin therapy), a drug was considered discontinued when there were no follow-up prescriptions recorded for at least 90 days after the theoretical end date of the last supply of that certain drug. Switch to another drug was defined as start of a drug within the same ATC-class (5 characters) while another drug from that same ATC-class was discontinued, within 28 days. Within each time period, drug use was defined based on the theoretical duration of each prescription, which was calculated by dividing the number of prescribed units by the prescribed number of units per day. Drugs that had a theoretical end date beyond the end of a certain time period were considered to be used in this time period.

Data analysis

Frequencies of visits to physicians (general practitioners and medical specialists), newly diagnosed obesity-related disease, and changes in obesity-related medication were calculated. Odds ratios with 95% confidence intervals were calculated to estimate the likelihood of cases (compared to controls) to experience one of the defined "health care utilisation" events. The odds ratio then indicates for example how much more likely a patient starting to use anti-obesity drugs is to contact a physician at least one time compared to patients not starting to use AODs. Odds ratios were adjusted for age, using unconditional logistic regression analysis.

As is known from literature, there is a difference in health care utilisation between men and women. Women tend to have a higher use of health care resources than men, independent of age [27, 28]. Overweight and obesity are related with several chronic diseases and are also related to an increased use of primary health care [6, 29]. To take these differences in health care utilisation into account, all analyses were stratified for gender and co-morbidities (as specified above).

RESULTS

A total of 1,415 patients with a first prescription of an anti-obesity drug and 5,660 patients who never used an anti-obesity drug before, were included in the study. Of the patients starting to use anti-obesity drugs, more than half (n=746, 52.7%) were prescribed orlistat, 521 patients (36.8%) were prescribed sibutramine, 52 patients (3.7%) were prescribed rimonabant and the amphetamine-like drugs were used by 7.4% of the patients (n=105). The mean age

at the index date was 45.1 years for starters and 47.7 years for non-starters. Patients starting to use anti-obesity drugs were more frequently female (77.2% versus 52.5%) and had more cardiovascular diseases (43.7% versus 27.1%) compared to patients not starting to use these drugs. Also psychiatric disease was more prevalent among starters compared to non-starters (19.7% versus 10.8%) (Table 1).

Table 1: Baseline characteristics of the study population

	Patients starting AOD (n=1,415); n (%)	**Patients not starting AOD (n=5,660); n (%)**
General characteristics		
Age; mean (sd)	45.1 (12.8)	47.7 (17.3)
Female gender	1,093 (77.2%)	2,971 (52.5%)
Anti-obesity drugs used		
Rimonabant	52 (3.7%)	n/a
Orlistat	746 (52.7%)	n/a
Sibutramine	512 (36.2%)	n/a
Amphetamine-like drugs	105 (7.4%)	n/a
Fenfluramine	96 (6.8%)	
Dexfenfluramine	2 (0.1)%	n/a
Mazindol	7 (0.5%)	n/a
Cardiovascular co-morbidities		
Diabetes mellitus	103 (7.3%)	175 (3.1%)
Type 1	9 (0.6%)	20 (0.4%)
Type 2	94 (6.6%)	152 (2.7%)
New cardiovascular diagnoses*	495 (35.0%)	1206 (21.3%)
Ischemic heart disease (including angina pectoris, myocardial infarction) (ICPC-codes K74-76)	11 (0.8%)	41 (0.7%)
Hypertension (K85-87)	396 (27.9%)	889 (15.7%)
Heart failure (K77)	7 (0.5%)	22 (0.4%)
Dyslipidaemia (T93)	210 (14.8%)	513 (9.1%)
Stroke (K89-90)	5 (0.4%)	25 (0.4%)
Arrhythmias (K78)	2 (0.1%)	12 (0.2%)
Cardiovascular drug use*	361 (25.5%)	807 (14.3%)
Cardiac therapy (ATC-code C01)	24 (1.7%)	107 (1.9%)
Beta-blockers (C07)	146 (10.3%)	313 (5.5%)
Diuretics (C03)	114 (8.1%)	196 (3.5%)
Agents acting on RAS-system (C09)	160 (11.3%)	302 (5.3%)
Lipid-modifying drugs (C10)	115 (8.1%)	249 (4.4%)
Calcium-channel blockers (C08)	49 (3.5%)	150 (2.7%)
Use of platelet aggregation inhibitors (B01AC)	59 (4.2%)	214 (3.8%)
Other cardiovascular drugs (C02, C04, C05)	14 (1.0%)	36 (0.6%)
Any cardiovascular diagnosis or drug use	619 (43.7%)	1,531 (27.0%)
Psychiatric co-morbidities		
Psychiatric diagnoses*	20 (1.4%)	36 (0.6%)
Depressive disorder (P76)	12 (0.8%)	21 (0.4%)
Anxiety disorder/anxiety state (P74)	4 (0.3%)	8 (0.1%)

Table 1: Continued

	Patients starting AOD (n=1,415); n (%)	Patients not starting AOD (n=5,660); n (%)
Other psychiatric disease (P71-73, P75, P76-84, P86-P99)	4 (0.3%)	9 (0.2%)
Psychiatric drug use*	279 (19.7%)	610 (10.8%)
Anti-psychotics (N05A)	7 (0.5%)	21 (0.4%)
Anxiolytics and hypnotics (N05B, N05C)	218 (15.4%)	205 (3.6%)
Anti-depressants (N06A)	117 (8.3%)	496 (8.8%)
Any psychiatric diagnosis or drug use	279 (19.7%)	613 (10.8%)
Cardiovascular and psychiatric co-morbidities combined		
Cardiovascular and/or psychiatric co-morbidities	765 (54.1%)	1,854 (32.8%)

* In the year before the index date

Overall, male and female starters contacted the GP more often in the three years before the index date than male and female non-starters (mean 23.6 contacts (standard deviation (sd): 24.3) vs. 9.0 (sd: 15.8) for males and 26.3 (sd: 25.3) vs. 13.6 (sd: 19.3) for females). The same pattern was found for specialist contacts; in the whole period under review male starters had an average of 3.2 (sd: 3.8) specialist referrals, while male non-starters were referred to the specialist 1.6 times (sd: 3.0). For females these numbers were 3.8 (sd: 4.6) and 2.3 (sd: 3.3) respectively. When combining visits to the GP and referrals to medical specialist, the average number of contacts increased more over the 3-year period before anti-obesity drug initiation for starters (both males and females) compared to non-starters (Figure 1a). The odds ratio of having at least one physician contact increased towards the index date, from OR 3.0 (95% CI 2.4-3.8) 33 to 36 months before start to OR 3.5 (95% CI 2.8-4.5) 0 to 3 months before start for males and from OR 1.9 (95% CI 1.7-2.2) to OR 2.7 (95% CI 2.3-3.2) for females (Table 2).

The number of issued prescriptions in the whole period was comparable for male and female patients starting to use anti-obesity drugs. Overall, starters received more drug prescriptions compared to non-starters; however, female non-starters had more prescriptions compared to the male non-starters (females 25.4 prescriptions (sd: 26.8 versus 16.8 (sd: 24.1), males 26.5 (sd: 29.3) versus 10.6 (sd: 20.2), female 25.4 (sd: 26.8) versus 16.8 (sd: 24.1)) (Figure 1b). The odds ratio for receiving at least one prescription for any drug compared to receiving no prescriptions per 3-month period are, per 3-month period, presented in Table 2. The odds ratios for males are increasing, while the ORs for females remained relatively stable (Table 2).

More new obesity-related diseases were diagnosed among patients starting to use anti-obesity drugs (mean 0.7 (sd: 0.9) versus 0.3 (sd: 0.7) for males and 0.6 (sd: 0.9) versus 0.4 (sd: 0.7) for females), compared to patients not starting to use anti-obesity drugs, but the odds ratio for having at least one newly diagnosed disease did not increase in the period under study (Table 2). The average number of medication changes in obesity-related drugs in the whole period was slightly higher in the whole period for cases than for controls, and there was also a difference in gender (female starters mean was 2.6 (sd: 2.7), and for female non-starters the

Figure 1a: Average number of general practitioner plus medical specialist contacts, stratified by gender

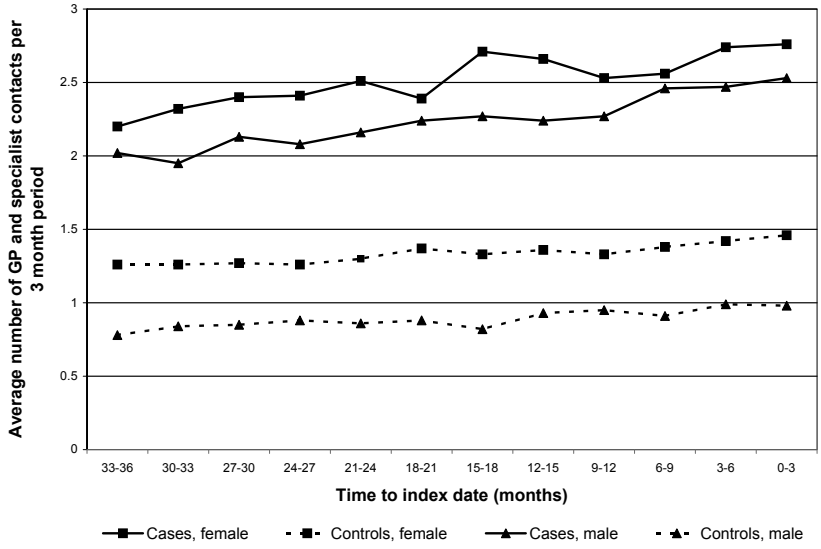


Figure 1b: Average number of prescriptions (all ATC-codes), stratified by gender

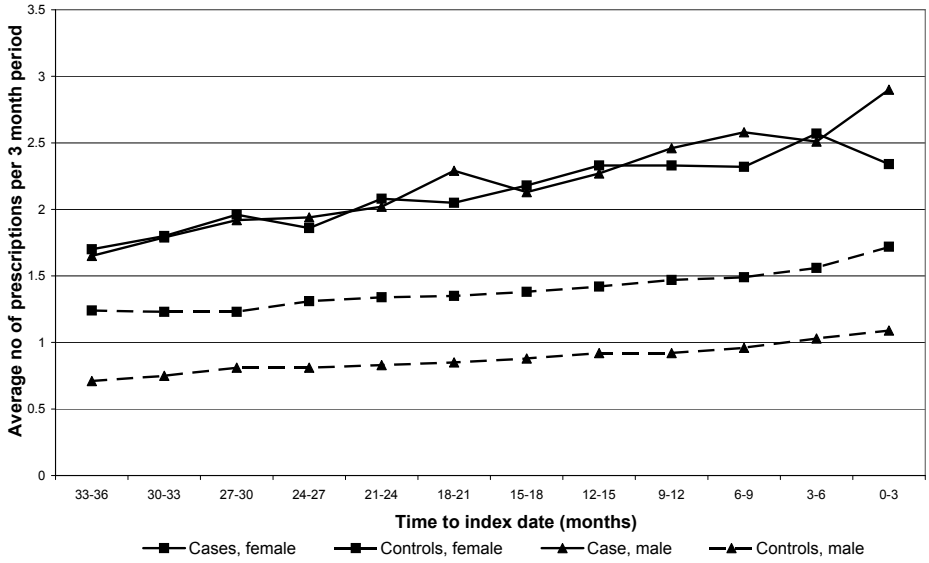


Table 2: Likelihood (expressed as odds ratios) of at least one "health care utilisation" event comparing patients starting to use anti-obesity drugs with patients not starting to use anti-obesity drugs, per 3 month period

Time before start of AOD* (months)	Visits to the GP and medical specialists (OR (95% CI)) †		Prescriptions (OR (95% CI)) ‡		New obesity-related diagnoses (OR (95% CI))§		Medication changes in obesity-related drugs (OR 5%CI)) #	
	Males	Females	Males	Females	Males	Females	Males	Females
36-33	3.0 (2.4-3.8)	1.9 (1.7-2.2)	2.5 (2.0-3.2)	1.8 (1.5-2.0)	2.9 (1.7-5.1)	1.3 (0.8-1.9)	2.0 (1.5-2.7)	1.9 (1.6-2.2)
33-30	2.4 (1.9-3.0)	2.1 (1.9-2.5)	2.5 (1.9-3.2)	1.7 (1.5-1.9)	2.7 (1.5-4.9)	1.9 (1.3-2.7)	1.4 (1.0-1.9)	1.8 (1.5-2.2)
30-27	2.4 (1.9-3.0)	2.0 (1.7-2.3)	2.3 (1.8-2.9)	1.9 (1.7-2.2)	3.5 (2.0-6.0)	2.1 (1.5-3.1)	2.3 (1.7-3.0)	2.0 (1.7-2.4)
27-24	2.8 (2.2-3.6)	2.2 (1.9-2.6)	2.9 (2.3-3.8)	1.6 (1.4-1.9)	2.4 (1.4-4.1)	2.3 (1.6-3.4)	1.9 (1.4-2.6)	1.8 (1.5-2.2)
24-21	2.9 (2.3-3.6)	2.1 (1.8-2.4)	2.8 (2.2-3.6)	2.0 (1.7-2.3)	2.5 (1.4-4.5)	2.9 (2.1-4.0)	1.7 (1.3-2.4)	2.4 (2.0-2.9)
21-18	2.8 (2.2-3.6)	2.2 (1.9-2.6)	3.1 (2.4-3.9)	2.0 (1.7-2.3)	2.9 (1.8-4.9)	1.5 (1.0-2.3)	2.9 (2.2-3.8)	2.6 (2.2-3.1)
18-15	3.3 (2.6-4.2)	2.4 (2.1-2.8)	3.5 (2.8-4.5)	2.3 (2.0-2.6)	2.7 (1.6-4.6)	1.9 (1.3-2.7)	2.8 (2.1-3.8)	2.0 (1.6-2.4)
15-12	3.2 (2.5-4.1)	2.1 (1.9-2.5)	3.2 (2.5-4.1)	2.1 (1.8-2.4)	1.7 (0.9-3.0)	1.8 (1.2-2.6)	2.1 (1.6-2.9)	2.1 (1.7-2.5)
12-9	2.7 (2.2-3.5)	2.2 (1.9-2.6)	3.1 (2.4-3.9)	2.1 (1.8-2.4)	1.9 (1.1-3.5)	1.8 (1.2-2.6)	1.4 (1.0-1.9)	2.1 (1.7-2.5)
9-6	3.2 (2.5-4.1)	2.4 (2.1-2.8)	4.1 (3.2-5.4)	2.2 (1.9-2.6)	2.3 (1.4-3.9)	1.4 (1.0-2.0)	1.8 (1.3-2.5)	2.5 (2.1-3.0)
6-3	3.2 (2.5-4.1)	2.3 (2.0-2.7)	3.0 (2.4-3.9)	2.1 (1.8-2.5)	2.2 (1.3-3.7)	2.4 (1.7-3.4)	2.2 (1.6-2.9)	2.6 (2.2-3.1)
3-0	3.5 (2.8-4.5)	2.7 (2.3-3.2)	4.3 (3.2-5.5)	2.1 (1.8-2.5)	1.9 (1.1-3.3)	1.3 (0.9-1.8)	2.0 (1.4-2.8)	2.0 (1.6-4.5)

*AOD=anti-obesity drugs; †: OR of at least one visits to physician compared to no visits to physician; ‡ OR of at least one prescription compared to no prescriptions; § OR of at least one new obesity-related diagnose compared to no new diagnoses; # OR of at least one medication change compared to no changes in medication.

Figure 2a: Average number of general practitioner plus medical specialist contacts, stratified by co-morbidity

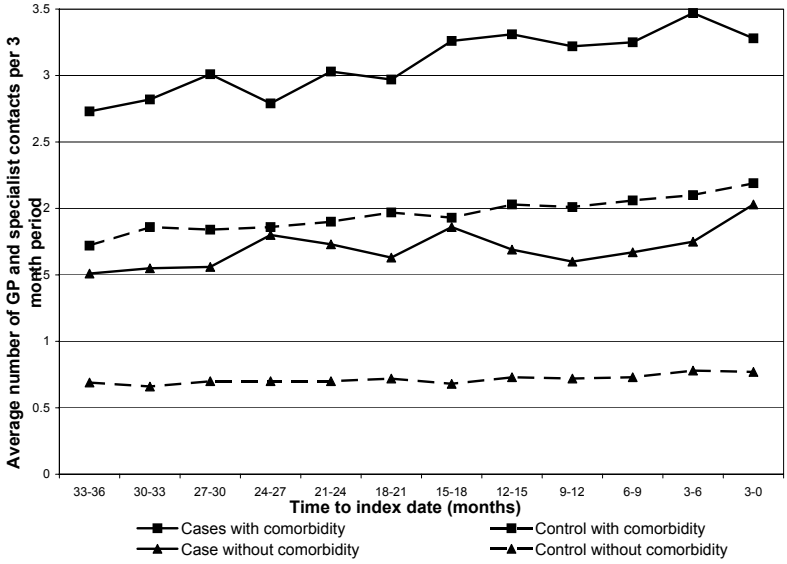
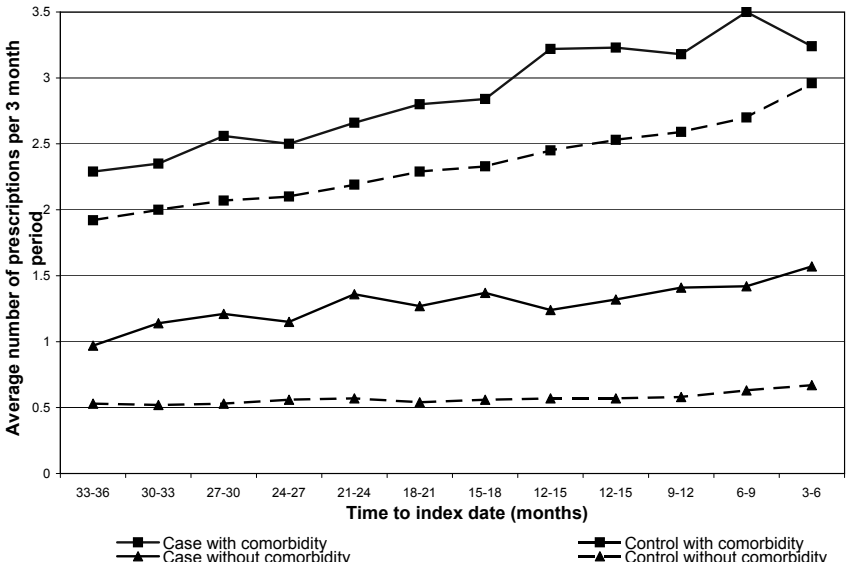


Figure 2b: Average number of prescriptions (all ATC-codes), stratified by co-morbidity



mean was 1.5 (sd: 2.7); for males this was 2.5 (sd: 2.3) and 1.3 (sd: 2.4) respectively). For both males and females, the OR of having at least one change in obesity-related medication was relatively stable over the whole 3-year period (Table 2). Stratification for baseline co-morbidities (cardiovascular and/or psychiatric) showed that the resource use was higher for patients with co-morbidity and that in both groups the pattern was the same, a gradual increase in visits (especially in those with co-morbidity) and absence of a sharp increase shortly before the index date (Figures 2a and 2b).

DISCUSSION

The main finding of this study is that the difference in physician contacts (either GP or medical specialist) and the total number of issued prescriptions for both males and females increases gradually over the whole 3-year period but no specific point in time before AOD initiation could be identified where differences between cases and controls began to appear.

We investigated whether changes in medication and increased health care utilisation precede the start of anti-obesity drugs. Although we found large differences between cases and controls with regard to all studied variables, which is in line with our previous work [18], we were not able to detect a specific point in time where these differences started to appear. This makes it difficult to identify patients who will start to use an anti-obesity drug at an early stage.

Previous studies already indicated that AODs are selectively prescribed to patients with multiple obesity-related co-morbidities. This study also indicated increased numbers of prescriptions for these co-morbidities [18, 30]. In several other fields of medicine it was shown that severity of disease and health care utilisation are closely connected [31, 32]. We were however not able to confirm the hypothesis of a sharp increase in physician contacts and prescriptions in the period shortly before start of an AOD.

Other studies investigating medication changes prior to hospital admissions found a large increase of medication changes [19, 20], and several studies reported an increase of changes in health care utilisation prior to a certain diagnoses [21], all in the relatively short period of 1-3 months before the event of interest. In our study we found a slight increase for two variables (physician contacts and number of issued prescriptions) towards the index date, but no sharp increase in the period closest to the index date was found.

The strength of this study is the population-based character, which makes it possible to study the complete medical record of the patients in daily clinical practice. This allows extrapolation of the results to other users of anti-obesity drugs. However, our study also has several limitations. Firstly, none of the anti-obesity drugs in the Netherlands is being reimbursed by health insurances [33-35], which may have introduced selection bias. However, if this were true we would have expected that the non-starters would suffer from more co-morbidities compared to the starters, since people from higher socioeconomic classes, who can afford

the anti-obesity drugs, are known to have a better health in general, and thus less health care utilisation, than people from lower socioeconomic classes [6, 36]. Secondly, we do not know if other obesity treatments (e.g. lifestyle interventions, non-prescription dietary supplements) are being used by patients. Some patients who are considered controls in this study, may therefore actually use obesity treatment other than anti-obesity drugs on prescription. However, dietary advice is not frequently reported in the medical records of both cases and controls (manual search, data not shown) and additionally several studies, all conducted in the US, showed that the number of non-prescription dietary supplements is relatively small. Assuming that this is the same for the Netherlands, we expect that the lack of information on other treatments for obesity does not change our results. In this study, we did not take hospitalisation as such into account. Nonetheless, the variable "general practitioner plus medical specialist contacts" includes information on both outpatient visits to medical specialists as well as hospital stays, as obtained from discharge letters.

This study adds to the knowledge on patient characteristics and health care utilisation in patients starting to use anti-obesity drugs. As there is a growing interest in management of obesity, with several new anti-obesity drugs currently under development by the pharmaceutical industry, knowledge on this specific patient population is of importance during the design of, and patient selection for clinical trials. Post-marketing information is needed for an adequate assessment of the efficacy and safety of these drugs in the real world population in addition to information on the context in which a medicine is used (e.g. patterns of drug use, concomitantly used medication, medical history). Recently regulatory decision-making regarding two anti-obesity drugs, rimonabant and sibutramine showed the importance of accurate knowledge on patient populations. For rimonabant, patients that were included in the rimonabant clinical trials pre-marketing differed substantially from the real-world population, which led to increased post-marketing reporting of psychiatric adverse events [3]. More recently the market authorisation of sibutramine was suspended in the European Union based on the results of the Sibutramine Cardiovascular OUtcomes Trial (SCOUT), investigating long-term effects in elderly women with cardiovascular risk factors [37]. However, the use of sibutramine was contraindicated in these patients. In addition, in the SCOUT-study long-term use (three years) was studied, while in the Summary of Product Characteristics (SPC) the use of sibutramine is limited to a maximum of one year. One of our previous studies showed that the large majority of the patients is only using anti-obesity drugs for a very limited period of time [18]. The validity of extrapolation of the results of the SCOUT-study to daily clinical practice is therefore doubtful.

To our knowledge this is the first study investigating changes in health care utilisation and medication changes prior to the start of lifestyle drugs. We conclude that there is an increased utilisation of health care resources in patients starting AOD-therapy compared to patients not starting these drugs, and the difference increases gradually over the whole 3-year period. However, no specific point in time before AOD initiation could be identified where differences

between cases and controls began to appear. This suggests that AODs are selectively prescribed to patients with a higher burden of obesity-related co-morbidities, but that initiation of AODs is not preceded by a sudden, sharp increase in health care utilisation.

REFERENCES

1. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Xenical® - Initial marketing authorisation details. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000154/WC500058424.pdf (last accessed: 11 December 2010).
2. Jick H, Vasilakis C, Weinrauch LA, Meier CR, Jick SS, Derby LE. A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. N Engl J Med 1998; 339 (11): 719-724.
3. Committee for Medicinal Products for Human Use (CHMP). The European Medicines Agency recommends suspension of the marketing authorisation of Acomplia. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/acomplia/53777708en.pdf (last accessed: 11 December 2010).
4. Committee for Medicinal Products for Human Use (CHMP). European Medicines Agency recommends suspension of marketing authorisations for sibutramine. Available at: http://www.ema.europa.eu/pdfs/human/referral/sibutramine/3940810en.pdf (last accessed: 09 December 2010).
5. Arterburn DE, Maciejewski ML, Tsevat J. Impact of morbid obesity on medical expenditures in adults. Int J Obes (Lond) 2005; 29 (3): 334-339.
6. Van Dijk L, Otters HB, Schuit AJ. Moderately overweight and obese patients in general practice: a population based survey. BMC Fam Pract 2006; 7: 43.
7. Finkelstein EA, Fiebelkorn IC, Wang G. State-level estimates of annual medical expenditures attributable to obesity. Obes Res 2004; 12 (1): 18-24.
8. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol 2009; 53 (21): 1925-1932.
9. Kwok S, McElduff P, Ashton DW, Lowe GD, Wood D, Humphries SE, et al. Indices of obesity and cardiovascular risk factors in British women. Obes Facts 2008; 1 (4): 190-195.
10. McMillan DC, Sattar N, Lean M, McArdle CS. Obesity and cancer. BMJ 2006; 333 (7578): 1109-1111.
11. Vigneri P, Frasca F, Sciacca L, Frittitta L, Vigneri R. Obesity and cancer. Nutr Metab Cardiovasc Dis 2006; 16 (1): 1-7.
12. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. JAMA 2007; 298 (17): 2028-2037.
13. Carpiniello B, Pinna F, Pillai G, Nonnoi V, Pisano E, Corrias S, et al. Psychiatric comorbidity and quality of life in obese patients. Results from a case-control study. Int J Psychiatry Med 2009; 39 (1): 63-78.
14. Carpiniello B, Pinna F, Pillai G, Nonnoi V, Pisano E, Corrias S, et al. Obesity and psychopathology. A study of psychiatric comorbidity among patients attending a specialist obesity unit. Epidemiol Psichiatr Soc 2009; 18 (2): 119-127.
15. Dixon JB, Dixon ME, O'Brien PE. Depression in association with severe obesity: changes with weight loss. Arch Intern Med 2003; 163 (17): 2058-2065.
16. Dong C, Sanchez LE, Price RA. Relationship of obesity to depression: a family-based study. Int J Obes Relat Metab Disord 2004; 28 (6): 790-795.
17. Annesi JJ. Relations of mood with body mass index changes in severely obese women enrolled in a supported physical activity treatment. Obes Facts 2008; 1 (2): 88-92.

18. Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Leufkens HG, Egberts AC, Sturkenboom MC. Cardiovascular and psychiatric risk profile and patterns of use in patients starting anti-obesity drugs. Pharmacoepidemiol Drug Saf 2009; 18 (7): 631-638.

19. Handoko KB, Zwart-van Rijkom JE, Hermens WA, Souverein PC, Egberts TC. Changes in medication associated with epilepsy-related hospitalisation: a case-crossover study. Pharmacoepidemiol Drug Saf 2007; 16 (2): 189-196.

20. Stuffken R, Heerdink ER, de Koning FH, Souverein PC, Egberts AC. Association between hospitalization and discontinuity of medication therapy used in the community setting in the Netherlands. Ann Pharmacother 2008; 42 (7): 933-939.

21. Van Soest EM, Dieleman JP, Sturkenboom MC, Siersema PD, Kuipers EJ. Gastro-oesophageal reflux, medical resource utilization and upper gastrointestinal endoscopy in patients at risk of oesophageal adenocarcinoma. Aliment Pharmacol Ther 2008; 28 (1): 137-143.

22. WHO Collaborating Centre for Drug Statistics Methodology. Complete ATC index. Available at: http://www.whocc.no/atcddd/ (last accessed: 03 December 2010).

23. Van der Lei J, Duisterhout JS, Westerhof HP, van der Does E, Cromme PV, Boon WM, et al. The introduction of computer-based patient records in the Netherlands. Ann Intern Med 1993; 119 (10): 1036-1041.

24. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA 1999; 282 (16): 1523-1529.

25. Molenaar EA, Numans ME, van Ameijden EJ, Grobbee DE. [Considerable comorbidity in overweight adults: results from the Utrecht Health Project]. Ned Tijdschr Geneeskd 2008; 152 (45): 2457-2463.

26. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 2003; 289 (1): 76-79.

27. Song J, Chang RW, Manheim LM, Dunlop DD. Gender differences across race/ethnicity in use of health care among Medicare-aged Americans. J Womens Health (Larchmt) 2006; 15 (10): 1205-1213.

28. Gerritsen AA, Deville WL. Gender differences in health and health care utilisation in various ethnic groups in the Netherlands: a cross-sectional study. BMC Public Health 2009; 9: 109.

29. Saez M, Saurina C, Coenders G, Gonzalez-Raya S. Use of primary health care services according to the different degrees of obesity in the Girona Health Region, Spain. Health Econ 2006; 15 (2): 173-193.

30. Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Leufkens HG, Egberts AC. Psychiatric and cardiovascular co-morbidities in patients with diabetes mellitus starting anti-obesity drug Obesity (Silver Spring) 2008; 16 (10): 2331-2335.

31. Jansson SA, Andersson F, Borg S, Ericsson A, Jonsson E, Lundback B. Costs of COPD in Sweden according to disease severity. Chest 2002; 122 (6): 1994-2002.

32. Formiga F, Fort I, Robles MJ, Riu S, Sabartes O, Barranco E, et al. Comorbidity and clinical features in elderly patients with dementia: differences according to dementia severity. J Nutr Health Aging 2009; 13 (5): 423-427.

33. Dutch Health Care Insurance Board.Advice on the reimbursement status of Acomplia® in the Netherlands. Available at: http://www.cvz.nl/resources/cfh0709%20rimonabant-Acomplia%20rapport_tcm28-22818.pdf (last accessed: 03 December 2010).

34. Dutch Health Care Insurance Board.Advice on the reimbursement status of Reductil® in the Netherlands. Available at: http://www.cvz.nl/resources/cfh0203%20verzamel%20rapport_tcm28-20548.pdf (last accessed: 03 December 2010).

35. Dutch Health Care Insurance Board. Advice on the reimbursement status of Xenical® in the Netherlands. Available at: http://www.cvz.nl/resources/cfh0411%20orlistat-Xenical%20rapport_tcm28-19504.pdf (last accessed: 03 December 2010).

36. Mackenbach JP, Stirbu I, Roskam AJ, Schaap MM, Menvielle G, Leinsalu M, et al. Socioeconomic inequalities in health in 22 European countries. N Engl J Med 2008; 358 (23): 2468-2481.

37. James WPT, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J of Med 2010; 363 (10): 905-917.

Chapter 2.6

Cardiovascular and psychiatric risk profile and patterns of use in patients starting anti-obesity drugs

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ABSTRACT

Introduction: Real-life experience with anti-obesity drugs has shown that psychiatric and cardiovascular diseases may be reported as adverse drug reactions. For adequate risk assessment of these drugs, knowledge on baseline risks of patients starting anti-obesity drugs and insight in patterns of use is needed. The aim was to assess whether baseline characteristics of patients starting anti-obesity drugs differ from those not being prescribed these drugs, and to study patterns of anti-obesity drug use.

Methods: A population-based cohort study was conducted in the IPCI database (1995-2007). The index cohort comprised all persons who started an anti-obesity drug. The reference cohort comprised up to six randomly sampled patients from the same GP practice with same index date. Baseline characteristics were assessed for both cohorts. The index cohort was followed for one year to study patterns of drug use. Unconditional logistic regression was used to calculate crude odds ratios and 95% confidence intervals.

Results: The index and reference cohort comprised 1,471 and 8,736 persons, respectively. Both cardiovascular and psychiatric co-morbidities were more prevalent among starters compared to non-starters. 77.7% of the patients stopped using anti-obesity drugs within 90 days. Users of amphetamine-like drugs differed from patients using orlistat or sibutramine, whereas users of orlistat and sibutramine were highly comparable.

Discussion: The increased prevalence of co-morbidities constitutes a baseline risk which may translate in higher occurrence of psychiatric and cardiovascular diseases during use of anti-obesity drugs, independent of the drugs. The limited period of use might reduce possible cardiovascular benefits of weight reduction induced by these drugs.

INTRODUCTION

Overweight and obesity are associated with an increased risk for other morbidities including diabetes mellitus, heart disease, and certain cancers [1, 2], and the prevalence of obesity is increasing. Lifestyle interventions (increased physical activity and adequate management of diet) are effective, but have low adherence rates. This gives way to the treatment of obesity with medicines [3].

During the past decades different classes of anti-obesity drugs have been introduced, and several of those drugs have been associated with serious adverse events. The amphetamine-like drugs fenfluramine and dexfenfluramine were associated with valvular heart disease and pulmonary hypertension, and have been withdrawn from the market in 1997 [4-6]. Mazindol was suspected for its safety in cardiac patients, and sibutramine has also been associated with cardiovascular adverse effects [7]. The adverse effects of orlistat are virtually limited to the gastrointestinal tract because of its low systemic absorption. Orlistat has not been associated with serious adverse effects,

In 2007, the Food and Drug Administration's (FDA) Endocrinologic and Metabolic Drugs Advisory Committee concluded that rimonabant, the first cannabinoid receptor antagonist, did not demonstrate an acceptable benefit-risk profile [8] and Sanofi-Aventis decided to withdraw the New Drug Application in the US [9]. In the European Union (EU) rimonabant was approved in 2006 and recently, in October 2008 the marketing authorisation for rimonabant across the EU was suspended because the benefits of rimonabant no longer outweigh its risks. The most recently published clinical trial for rimonabant, the Stradivarius-study [10], reported unexpected high numbers of psychiatric adverse events, both in the rimonabant-group and in the placebo-group (43.4% vs. 28.4%, $p<0.001$) while the expected cardiovascular benefits were not confirmed in this study.

These events contributed to the keen interest in the identification of baseline risks of these and other types of adverse events in patients seeking pharmacological treatment for obesity, since the real life patient population using these drugs might already be more vulnerable at baseline towards developing these adverse events, even more than the population in clinical trials as new drugs are often channelled to the patients most in need in real life. This might affect the benefit-risk assessment, which is evaluated continuously post-marketing. In order to assess whether the cardiovascular and psychiatric risk profile differs between patients who start and those who do not start to use anti-obesity drugs, or differs between the different anti-obesity drugs, we compared baseline characteristics between users of different anti-obesity drugs and non-users.

It is known that the benefit-risk balance may be affected by the duration of drug use as this is related to the effectiveness of the drug. In the case of anti-obesity drugs, the cardiovascular benefits are expected only after long-term use, whereas the adverse effects may occur already after short-term use. The second objective of our study was to describe the pattern of use of the anti-obesity drugs and to describe a possible relation between the risk profile at baseline and the duration of use of anti-obesity drugs.

Objective

The aim of this study was to assess whether baseline characteristics - especially psychiatric and cardiovascular co-morbidities - of patients starting anti-obesity drugs differ from those not using these drugs, and to study patterns of anti-obesity drug use.

METHODS

Setting

Data were collected from the Integrated Primary Care Information (IPCI) database, a computerised database containing electronic medical records from general practitioners (GPs) in the Netherlands. The database currently comprises data from more than 600,000 patients from more than 150 GPs in the Netherlands. The database was set up in 1992 and is maintained by the Department of Medical Informatics of the Erasmus MC, University Medical Centre, Rotterdam, the Netherlands. In the Dutch health care system, almost all citizens are registered with a single GP practitioner and the GP acts as the gatekeeper to and as the central receiver of information from secondary care. The medical record from each individual patient can therefore be assumed to contain all relevant medical information on that person. The records contain information about patient demographics (age, gender, patient identification and GP registration information), diagnoses and symptoms (the International Classification of Primary Care (ICPC) is used to register symptoms and diagnoses, although these can also be entered as free text), physical, laboratory and specialist findings, information about hospital admissions and drug prescriptions. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the World Health Organization [11]. Summaries of hospital discharge letters or information from specialists are included as free text. The IPCI database complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmacoepidemiological research. Extended details about the database have been reported elsewhere [12, 13]. The Scientific and Ethical Advisory Board of the IPCI project has approved the present study.

Study population

We performed a population-based, retrospective follow-up study. The source population included all patients in the IPCI database in the period January 1995 to January 2007 who had at least one year of valid database information (registered for at least one year). From the source population all patients with a first prescription for any anti-obesity drug within the study period were identified.

The anti-obesity cohort comprised all patients who started with a first prescription for one of the anti-obesity drugs (sibutramine (ATC-code A08AA10), orlistat (A08AB01) and the amphetamine-like drugs fenfluramine (A08AA02), dexfenfluramine (A08AA04), and mazindol

(A08AA05)), during the study period and absence of such drug use anytime earlier in the available historic data. No rimonabant users were included because this product was launched in the Netherlands in September 2007.

The index date was defined as the date of the first prescription for that specific anti-obesity drug within the study period. For each patient in the index drug cohort, six reference patients were randomly sampled from the same practice and assigned the same index date. No matching criteria were used. The reference patients did not have a prescription for any anti-obesity drug in their available history. Patients were excluded from the cohorts if they had less than 1 year of valid database history prior to the index date. This was necessary to be able to describe the patients' medical history.

Cardiovascular and psychiatric risk profile of patients

Information on general, cardiovascular and psychiatric patient characteristics was extracted from the medical records by electronic searches and manual validation. The general characteristics that were identified were age at the index date and gender. The following cardiovascular morbidities in the year before the index date were defined: presence of diabetes mellitus (defined as use of antidiabetic drugs (ATC-code: A10A, A10B) or coded diagnoses (ICPC-code: T89, T90)). Insulin-dependent diabetes was defined as a diagnosis of insulin-dependent diabetes mellitus and/or the use of insulin, without any prescription for an oral antidiabetic drug. Non-insulin-dependent diabetes mellitus was defined as a diagnosis of non-insulin dependent diabetes mellitus and/or the use of oral antidiabetic drugs. Pharmacological untreated diabetes was classified as non-insulin dependent diabetes mellitus. In addition, prescriptions and diagnoses related to cardiovascular disease in the year before the index date were extracted (ICPC codes K74-78, K85-87, K89, K90, T93; ATC-codes C01-C10, B01AC). To characterise the psychiatric morbidities in the year before the index date, prescriptions and diagnoses related to psychiatric disorders from the medical records were extracted. Therefore, we used the psychological ICPC-codes P71 to P99, excluding category P85 (mental retardation), and the following ATC-codes: N05A (antipsychotics), N06AA (tricyclic antidepressants), N06AB (selective serotonin reuptake inhibitors), N05B (anxiolytics) and N05C (hypnotics). The before mentioned cardiovascular and psychiatric characteristics were combined to evaluate the number of patients who are suffering from both co-morbidities.

Patterns of anti-obesity drug use

In the Netherlands, the duration for a first prescription is often only 14 days to avoid wasting in patients that do not tolerate the drug. The theoretical duration of a prescription was calculated by dividing the number of prescribed units by the dose regimen. The duration of use was defined as the total number of days for which the drug was prescribed during the year following the index date. Switching between the different anti-obesity drugs was allowed.

Data analysis

To compare starters of anti-obesity drugs with non-starters of these drugs with regard to general, cardiovascular and psychiatric characteristics, odds ratios with 95% confidence intervals were calculated using unconditional logistic regression analysis. Univariate estimates for all associations were provided because no causal relation was studied. Cardiovascular and psychiatric characteristics were compared between starters and non-starters together, and within the drug cohort also between starters of different anti-obesity drugs.

Within the cohort of anti-obesity drug users, duration of use was described in the first year after starting. The anti-obesity drugs fenfluramine, dexfenfluramine and mazindol, were categorised as amphetamine-like drugs. Cox proportional hazard model was used to estimate the risk of stopping anti-obesity drug use in the year following the index date.

RESULTS

The drug cohort comprised 1,471 persons who started with an anti-obesity drug between January 1995 and January 2007, and these were matched to 8,736 reference patients. The anti-obesity drugs that were mainly prescribed were orlistat (n=926, 63.0%) and sibutramine (n=240, 16.3%) (Table 1). The amphetamine-like drugs (n=305, 20.7%) included fenfluramine (n=85), dexfenfluramine (n=136), and mazindol (n=84). Starters were slightly younger (45.3 vs. 47.0 years) and were more frequently females (76.3 vs. 51.4%). The type of anti-obesity drug and the incidence of patients starting to use anti-obesity drugs varied over time (Figure 1).

Table 1: Characteristics of the study population

Variable	Patients starting anti-obesity drugs (n=1,471); n (%)	Patients not starting anti-obesity drugs (n=8,736); n (%)
General characteristics		
Age; mean (sd)	45.3 (12.5)	47.0 (17.6)
18 – 34 years	305 (20.7%)	2,492 (28.5%)
35 – 54 years	809 (55.0%)	3,504 (40.1%)
≥ 55 years	357 (24.3%)	2,740 (31.4%)
Female gender	1,123 (76.3%)	4,490 (51.4%)
Anti-obesity drug use		
Orlistat	926 (63.0%)	n/a
Sibutramine	240 (16.3%)	n/a
Amphetamine-like drugs	305 (20.7%)	n/a
Dexfenfluramine	136 (9.2%)	n/a
Fenfluramine	85 (5.8%)	n/a
Mazindol	84 (5.7%)	n/a

Table 1: Continued

Variable	Patients starting anti-obesity drugs (n=1,471); n (%)	Patients not starting anti-obesity drugs (n=8,736); n (%)
Cardiovascular co-morbidities		
Diabetes mellitus	103 (7.0%)	315 (3.6%)
Type 1	10 (0.7%)	48 (0.5%)
Type 2	93 (6.3%)	267 (3.1%)
Cardiovascular diagnoses	423 (28.8%)	1,464 (16.8%)
Ischemic heart disease (including angina pectoris, myocardial infarction)	35 (2.4%)	158 (1.8%)
Hypertension	389 (26.4%)	1,261 (14.4%)
Heart failure	10 (0.7%)	34 (0.4%)
Dyslipidaemia	52 (3.5%)	197 (2.3%)
Stroke	3 (0.2%)	25 (0.3%)
Arrhythmias	6 (0.4%)	40 (0.5%)
Cardiovascular drug use	487 (33.1%)	1,533 (17.5%)
Cardiac therapy (C01)	41 (2.8%)	261 (3.0%)
Beta-blockers (C07)	202 (13.7%)	634 (7.3%)
Diuretics (C03)	186 (12.6%)	468 (5.4%)
Agents acting on RAS-system (C09)	163 (11.1%)	527 (6.0%)
Lipid-modifying drugs (C10)	113 (7.7%)	326 (3.7%)
Calcium-channel blockers (C08)	72 (4.9%)	305 (3.5%)
Use of platelet aggregation inhibitors (B01AC)	71 (4.8%)	410 (4.7%)
Other cardiovascular drugs (C02, C04, C05)	57 (3.9%)	209 (2.4%)
Any cardiovascular diagnosis or drug use	605 (41.1%)	2,060 (23.6%)
Psychiatric co-morbidities		
Psychiatric diagnoses	73 (5.0%)	174 (2.0%)
Depressive disorder	42 (2.9%)	96 (1.1%)
Anxiety disorder/anxiety state	11 (0.7%)	37 (0.4%)
Other psychiatric disease	21 (1.4 %)	49 (0.6%)
Psychiatric drug use	426 (29.0%)	1,323 (15.1%)
Antipsychotics (N05A)	21 (1.4%)	52 (0.6%)
Anxiolytics and hypnotics (N05B, N05C)	337 (22.9%)	1,125 (12.9%)
Antidepressants (N06A)	47 (3.2%)	104 (1.2%)
Any psychiatric diagnosis or drug use	434 (29.5%)	1,360 (15.6%)
Cardiovascular and psychiatric co-morbidities combined		
Cardiovascular and psychiatric co-morbidities	828 (56.3%)	2,837 (32.5%)

Overall, a difference was found in cardiovascular characteristics in the year before the index date between the starters and non-starters (Table 2). Diabetes mellitus was more prevalent among the starters (OR 2.0 (95% CI 1.6-2.5)). In addition, hypertension was twice as prevalent among starters (OR 2.1 (95% CI 1.9-2.4)) while the prevalence of ischemic heart disease, heart failure and dyslipidaemia did not significantly differ between starters and non-starters. Starters did use more cardiovascular drugs compared to non-starters (OR 2.3 (95% CI 2.1-2.6)). Also psychiatric co-morbidities were more prevalent among patients starting anti-obesity drugs compared to non-starters (OR 2.5 (95% CI 2.2-2.9)). Users of amphetamine-like drugs

Figure 1: Incidence of anti-obesity drug use

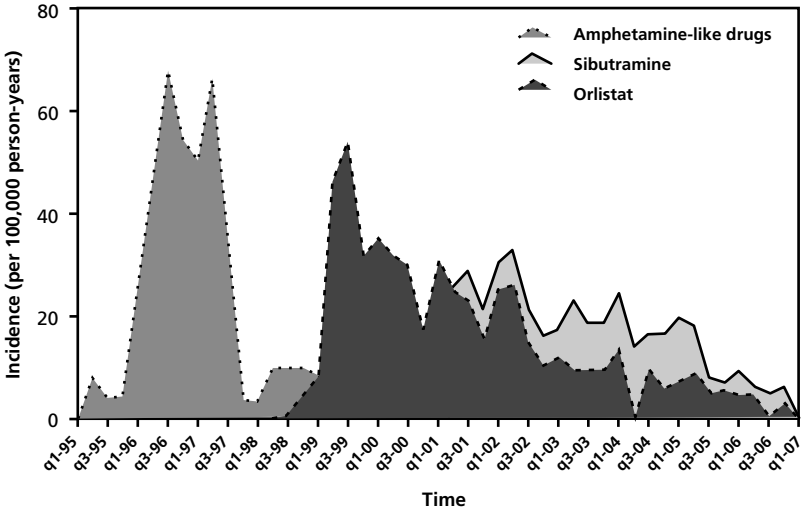

Table 2: Differences in characteristics between starters and non-starters of different anti-obesity drugs

	Overall (n=1,471) OR (95% CI)	Orlistat (n=926) OR (95% CI)	Sibutramine (n=240) OR (95% CI)	Amphetamine-like drugs (n=305) OR (95% CI)
General characteristics				
Age				
18 – 34 years	Reference	Reference	Reference	Reference
35 – 54 years	1.9 (0.6-2.2)	2.3 (1.9-2.8)	1.2 (0.9-1.7)	1.6 (1.2-2.1)
≥ 55 years	1.1 (0.9-1.3)	1.4 (1.1-1.7)	0.8 (0.5-1.1)	0.4 (0.5-1.0)
Female gender	3.1 (2.7-3.5)	2.6 (2.2-3.0)	2.5 (1.9-3.4)	7.4 (5.1-10.6)
Cardiovascular co-morbidities				
Diabetes mellitus	2.0 (1.6-2.5)	2.2 (1.7-2.9)	2.6 (1.6-4.2)	0.5 (0.2-1.4)
Any cardiovascular diagnoses	2.0 (1.8-2.3)	2.3 (1.9-2.6)	2.0 (1.5-2.8)	1.2 (0.9-1.7)
Any cardiovascular drug use	2.3 (2.1-2.6)	2.7 (2.3-3.2)	2.1 (1.5-2.8)	1.4 (1.1-1.9)
Any cardiovascular diagnosis or drug use	2.3 (2.0-2.5)	2.7 (2.3-3.0)	2.1 (1.6-2.8)	1.4 (1.1-1.9)
Psychiatric co-morbidities				
Any psychiatric diagnoses	2.6 (1.9-3.4)	2.3 (1.6-3.3)	2.5 (1.2-5.0)	3.4 (2.0-5.7)
Any psychiatric drug use	2.6 (2.2-2.9)	2.7 (2.2-3.1)	2.7 (1.9-3.8)	2.3 (1.7-3.1)
Any psychiatric diagnosis or drug use	2.5 (2.2-2.9)	2.6 (2.2-3.1)	2.4 (1.7-3.4)	2.3 (1.8-3.2)
Cardiovascular and psychiatric co-morbidities combined				
Cardiovascular and psychiatric co-morbidities	2.7 (2.4-3.0)	3.1 (2.7-3.6)	2.3 (1.8-3.1)	1.9 (1.5-2.4)

significantly differed from patients using orlistat or sibutramine, with regard to gender and prevalence of diabetes mellitus. Users of orlistat and sibutramine were highly comparable with regard to general characteristics and all co-morbidities studied.

The majority of the starters (n=800 (54.4%)) was prescribed an anti-obesity drug only once and 3% of the patients switched to another anti-obesity drug within the first year. The duration of use did not differ between patients with different baseline risk profiles (Figure 2). No association was found between patient characteristics and the risk of stopping anti-obesity therapy (Table 3).

Figure 2: Number of patients stopping to use anti-obesity drugs in the year after the index date

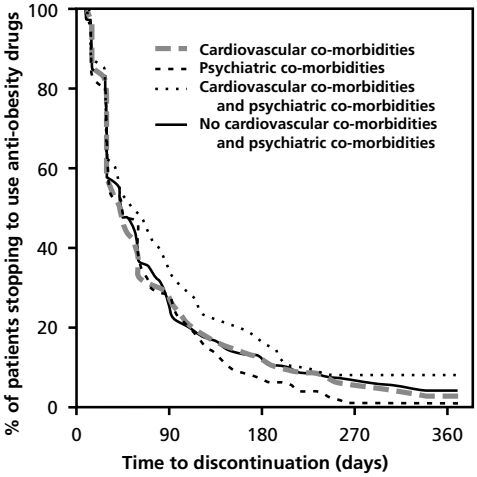

Table 3: Association between characteristics at or before start of anti-obesity drugs and risk of stopping therapy

	Hazard rate	95% CI
General characteristics		
Age		
18 – 34 years	Reference	Reference
35 – 54 years	1.04	0.91-1.19
≥ 55 years	0.85	0.73-1.00
Female gender	1.03	0.94-1.21
Cardiovascular co-morbidities		
Diabetes mellitus	1.26	1.02-1.56
Any cardiovascular diagnoses	1.00	0.88-1.13
Any cardiovascular drug use	1.02	0.89-1.17
Any cardiovascular diagnosis or drug use	1.02	0.90-1.14
Psychiatric co-morbidities		
Any psychiatric diagnoses	1.07	0.79-1.45
Any psychiatric drug use	0.99	0.88-1.11
Any psychiatric diagnosis or drug use	1.02	0.91-1.15
Cardiovascular and psychiatric co-morbidities combined		
Cardiovascular and psychiatric co-morbidities	0.89	0.80-0.99

CI: confidence interval

DISCUSSION

We found that patients who started to use an anti-obesity drug suffered from more co-morbidities, both psychiatric and cardiovascular, compared to people not starting to use anti-obesity drugs. The majority of the starters (n=800 (54.4%)) received only a single prescription for an anti-obesity drug, and 77.7% of the patients stopped using anti-obesity drugs within 90 days. Users of amphetamine-like drugs differed significantly from patients using orlistat or sibutramine, with regard to gender and prevalence of diabetes mellitus, whereas users of orlistat and sibutramine were highly comparable with regard to all co-morbidities. No association was found between patient characteristics and the risk of stopping anti-obesity therapy.

In our previous study, we found that the patients suffering from diabetes mellitus who started to use anti-obesity drugs (mainly orlistat and amphetamine-like drugs) were also suffering from more cardiovascular (odds ratio (OR) 1.2 (95% CI 1.0-1.5)) and psychiatric (OR 1.7 (95% CI 1.4-2.1)) co-morbidities [14]. In the present study, we showed that in a general population, and in a more recent time period, cardiovascular and psychiatric co-morbidities seemed to be even more prevalent among patients starting to use these drugs. No significant difference was found with regard to a history of cardiovascular disease between the start of sibutramine compared to orlistat, while we expected that patients with a cardiovascular history would have fewer prescriptions for sibutramine, because this drug is associated with cardiovascular adverse events. We did find a difference between orlistat/sibutramine and the amphetamine-like drugs with regard to prevalence of any cardiovascular diagnoses or drug use and prevalence of diabetes mellitus. A possible explanation is the increasing attention for obesity during the last decade, which might lead to prescribing anti-obesity drugs as part of the treatment of cardiovascular disease and the metabolic syndrome.

The increased prevalence of cardiovascular and psychiatric co-morbidities may partly be explained by channelling of anti-obesity drugs. With regard to cardiovascular co-morbidities, anti-obesity drugs might be prescribed to patients that are difficult-to-treat. In such cases, reduction of weight to (further) improve the cardiovascular risk profile can be initiated by the prescription of an anti-obesity drug. In addition, psychiatric co-morbidities such as depression are related to obesity whereby the start of an anti-obesity drug might be influenced by the psychiatric status of an obese person [15, 16] and may be used as an alternative treatment to improve the mental status of those patients.

In addition, we have found that anti-obesity drugs were used for a relatively short period of time, and the majority of the patients received only a single prescription in the year following the index date. We were not able to assess reasons for early stopping, but there might be at least two possible explanations. Firstly, adverse events, a lack of effect or a combination of both, may be the reason for patients to stop early after initiating therapy. However, if this were true, one might expect higher numbers of patients switching to other anti-obesity drugs. In our study, neither general patient characteristics nor a history of cardiovascular and/or psychiatric disease

did predict early stopping. Secondly, the anti-obesity drugs might be used as a short-term therapy to increase weight loss, thereby stimulating the patient to continue with life-style interventions more easily. When we compare the duration of use in this study to the UK Prescription-Event-Monitoring Study on orlistat and sibutramine [17], we found that the duration of use in our study did not match the rates reported in the PEM-study (77.7% stopped within 3 months in our study compared to 30.3% of the users of orlistat and 41.8% of the users of sibutramine in the PEM-study). The non-reimbursement status of the anti-obesity drugs in the Netherlands may have added to the short duration of use in our study compared to the PEM-study, as has been shown before for other drugs [18-19]. Especially for the anti-obesity drugs, information on the duration of use is needed for the assessment of the benefit-risk balance. One of the major advantages of these drugs should be that the beneficial effect on cardiovascular profile of the patients leads to decreased cardiovascular disease risk, but this would only be achieved in patients using these drugs for a long-term instead of short-term use. In our study we found that the large majority of the patients uses anti-obesity drugs only for a short period of time. This might have a negative impact on the cardiovascular benefit of these drugs.

In our study, we were able to obtain adequate data on medical history for all patients in the study population. The IPCI-database covers a representative sample of the Dutch population, and there is extensive information available on drug use and diagnoses. Nevertheless, our study also has several limitations. Firstly, we have only taken into account anti-obesity drugs, which were available on prescription. We expect that many people suffering from obesity may use drugs and herbals that are available without prescriptions. We were not able to include this information in our study. Blanck et al. reported that 15.2% of American adults (women 20.6%, men 9.7%) had ever used a weight loss supplement without prescription and 8.7% reported past year use of these supplements (women 11.3%, men 6.0%) [20]. Secondly, as we mentioned before, none of the anti-obesity drugs in the Netherlands were being reimbursed by health insurances. This may have introduced a selection bias because the people with a prescription for an anti-obesity drug may be of a higher socio-economic status than the control patients. However, if this were true, we would have expected that the non-starters would suffer from more co-morbidities compared to the starters, because people from higher socioeconomic classes are known to have a generally better health compared to people from lower socioeconomic classes [21].

The results of our study may have important implications. The increasing prevalence of obesity will give way to increasing importance of pharmacological interventions in the treatment of obesity. Knowledge of baseline characteristics of patients starting to use a drug is important to be able to design and conduct randomised clinical trials that will give valuable information on the efficacy and safety in the pre-registration phase of any new drug in the right population. In the post-marketing phase, this information is needed to be able to adequately assess adverse events and to optimise drug prescription, thereby minimising the risk of adverse events and increasing patient adherence.

We will illustrate this with the rimonabant case. Increased prevalence's for both depression and anxiety compared to placebo were found in the four Rimonabant In Obesity (RIO) studies [22-25], although absolute numbers were low. In those studies all patients with a history of psychiatric disease were excluded. The Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK) reported in January 2008 that already 876 psychiatric reactions (44% of all 1,971 reported reactions in the UK) were spontaneously reported since the introduction of rimonabant in the UK [26]. Furthermore, in the recently published Stradivarius-study [10], the absolute risks are higher compared to the RIO-studies. This, together with the large numbers of spontaneous reports, indicated a possible public health issue. In addition, the results of the Stradivarius-trial were disappointing with regard to the expected cardiovascular benefits. This led to the conclusion of European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) that the benefits of rimonabant no longer outweigh its risks, and the recommendation of suspending the marketing authorisation across the EU [27]. Among our starters, 29.5% had any psychiatric diagnosis or drug use, which is similar to the percentage of concomitant antidepressant use (30%) showed in a paper by the FDA [28]. This case illustrates that knowledge about the real-life users population, often obtained during post-marketing research, is important when designing randomised clinical trials and needs more attention already in the pre-marketing phase of a drug. Post-marketing data can be of value here.

In conclusion, patients starting to use anti-obesity drugs have more often a prior history of psychiatric and cardiovascular morbidities. This constitutes a baseline risk, which in itself may translate in higher occurrence of psychiatric and cardiovascular diseases during use of anti-obesity drugs, independent of the drugs. The duration of anti-obesity drug use is limited, which might reduce the possible cardiovascular benefits of weight reduction induced by these drugs. Knowledge of both baseline characteristics and duration of use are important for interpretation of benefit- risk balance of anti-obesity drugs.

REFERENCES

1. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003; 348 (17): 1625-1638.
2. Bergstrom A, Pisani P, Tenet V, Wolk A, Adami HO. Overweight as an avoidable cause of cancer in Europe. Int J Cancer 2001; 91 (3): 421-430.
3. Grundy SM. Drug therapy of the metabolic syndrome: minimizing the emerging crisis in polypharmacy. Nat Rev Drug Discov 2006; 5 (4): 295-309.
4. Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med 1996; 335 (9): 609-616.
5. Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 1997; 337 (9): 581-588.
6. Jick H, Vasilakis C, Weinrauch LA, Meier CR, Jick SS, Derby LE. A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. N Engl J Med 1998; 339 (11): 719-724.
7. Ioannides-Demos LL, Proietto J, Tonkin AM, McNeil JJ. Safety of drug therapies used for weight loss and treatment of obesity. Drug Saf 2006; 29 (4): 277-302.
8. Anonymous. Diet drug Acomplia / Zimulti dealt blow as FDA Panel says keep it off U.S. market. Available at: http://www.acompliareport.com/News/news-061807.htm (last accessed: 13 January 2009).
9. Sanofi-Aventis. Press-release Sanofi-Aventis. Available at: http://www.sanofi-aventis.com/press/ppc_17004.asp#3 (last accessed: 17 June 2008).
10. Nissen SE, Nicholls SJ, Wolski K, Rodes-Cabau J, Cannon CP, Deanfield JE, et al. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. JAMA 2008; 299 (13): 1547-1560.
11. WHO Collaborating Centre for Drug Statistics Methodology. Complete ATC index. Available at: http://www.whocc.no/atcddd/ (last accessed: 03 August 2009).
12. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, et al. Post-marketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med 1999; 38 (4-5): 339-344.
13. Van der Lei J, Duisterhout JS, Westerhof HP, van der Does E, Cromme PV, Boon WM, et al. The introduction of computer-based patient records in the Netherlands. Ann Intern Med 1993; 119 (10): 1036-1041.
14. Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Leufkens HG, Egberts AC. Psychiatric and cardiovascular co-morbidities in patients with diabetes mellitus starting anti-obesity drug Obesity (Silver Spring) 2008; 16 (10): 2331-2335.
15. Dixon JB, Dixon ME, O'Brien PE. Depression in association with severe obesity: changes with weight loss. Arch Intern Med 2003; 163 (17): 2058-2065.
16. Onyike CU, Crum RM, Lee HB, Lyketsos CG, Eaton WW. Is obesity associated with major depression? Results from the third National Health and Nutrition Examination Survey. Am J Epidemiol 2003; 158 (12): 1139-1147.
17. Perrio MJ, Wilton LV, Shakir SA. The safety profiles of orlistat and sibutramine: results of prescription-event monitoring studies in England. Obesity (Silver Spring) 2007; 15 (11): 2712-2722.

18. Bouvy ML, Egberts TC. Consequences of a change in reimbursement status on prescription patterns. Eur J Clin Pharmacol 2000; 56 (6-7): 511-512.

19. Stolk P, Schneeweiss S, Leufkens HGM, Heerdink ER. Impact analysis of the discontinuation of reimbursement: the case of oral contraceptives. Contraception 2008; 75 (5): 399-404.

20. Blanck HM, Serdula MK, Gillespie C, Galuska DA, Sharpe PA, Conway JM, et al. Use of nonprescription dietary supplements for weight loss is common among Americans. J Am Diet Assoc 2007; 107 (3): 441-447.

21. Mackenbach JP, Stirbu I, Roskam AJ, Schaap MM, Menvielle G, Leinsalu M, et al. Socioeconomic inequalities in health in 22 European countries. N Engl J Med 2008; 358 (23): 2468-2481.

22. Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet 2006; 368 (9548): 1660-1672.

23. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J, Group ftR-NAS. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA 2006; 295 (7): 761-775.

24. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet 2005; 365 (9468): 1389-1397.

25. Despres JP, Golay A, Sjostrom L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med 2005; 353 (20): 2121-2134.

26. Anonymous. Rimonabant: European suspension of marketing authorisation. Drug Safety Update 2008; 1 (10): 2-4.

27. Committee for Medicinal Products for Human Use. The European Medicines Agency recommends suspension of the marketing authorisation of Acomplia. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/acomplia/53777708en.pdf (last accessed: 24 August 2010).

28. FDA. Briefing Document - Zimulti (rimonabant) Tablets, 20 mg Sanofi Aventis Advisory Committee. 2007. http://www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4306b1-fda-backgrounder.pdf (last accessed: 20 December 2010).

Chapter 2.7

Reasons for and time to discontinuation of rimonabant therapy

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ABSTRACT

Objective: To explore relations between patient characteristics and reasons for and time to discontinuation of rimonabant therapy, focussing on psychiatric events, because these were the main safety concern for rimonabant.

Methods: A Modified Prescription-Event-Monitoring (M-PEM) study was conducted for rimonabant. Descriptive statistics were used to describe the patient population. Rate ratios (RRs) with 95% confidence intervals (95% CI) were calculated to explore associations between patient characteristics and selected categories of reasons for stopping (RfS). Median times to discontinuation were compared using a Mann-Whitney-U test.

Results: The cohort comprised 10,011 users of rimonabant, of which three were excluded because of missing age or gender. A total of 7,204 patients (72.0%) stopped using rimonabant (median observation time 323 days, IQR: 279-371 days). In addition, patients with a history of psychiatric illness were at an increased risk of early discontinuation of rimonabant therapy for all reasons, but most pronounced due to psychiatric events (RR 1.79 (95% CI 1.54-2.09)). In contrast, the rates of discontinuation due to lack of effectiveness, any clinical events and psychiatric events in patients with cardiovascular disease, type 2 diabetes mellitus, dyslipidaemia or hypertension tended to be lower (not all being significant) than those without. For patients who discontinued treatment due to lack of effectiveness, the median time to stop was significantly shorter for patients with a history of psychiatric conditions, compared to patients without a history of psychiatric conditions (86 vs. 97 days, p=0.03). For patients discontinuing treatment due to psychiatric events, the difference in median time to stop was also 11 days (64 vs. 75 days, p=0.38), although not statistically significant different. For patients stopping due to any clinical event the median time to stop were comparable for patients with and without a history of psychiatric conditions (61 vs. 63 days, p=0.90).

Conclusions: In this study reasons for and time to discontinuation were associated with patient characteristics. Patients discontinued treatment because of psychiatric events before the beneficial effects could develop, thereby negatively affecting the benefit-risk profile of rimonabant. Although in June 2008 the marketing authorisation for rimonabant was suspended, this type of information can be used for the identification and characterisation of early discontinuers and ultimately may add to further improvement of adherence to therapy and thus to optimalisation of treatment benefits and drug safety.

INTRODUCTION

Rimonabant (Acomplia®, Sanofi-Aventis) was launched in the United Kingdom (UK) in June 2006. It was the first (and until December 2010 the only) licensed antagonist of the cannabinoid-1 receptor, indicated for the treatment of obesity (body mass index (BMI) ≥ 30 kg/m^2) or overweight patients (BMI > 27 kg/m^2) with associated risk factor(s) such as type 2 diabetes or dyslipidaemia as an adjunct to diet and exercise [1].

The endocannabinoid system is involved in regulation of energy homeostasis [2]. In the brain, the cannabinoid-1 receptor is also involved in the regulation of cognition and mood functions, implying that it might be connected to the regulation of mood, anxiety, and depression [3]. In the pivotal clinical trial program, rimonabant was associated with depressed mood, depressive disorders, and anxiety. Consequently, psychiatric adverse events were identified as an important safety issue in the Risk Management Plan that needed further attention [4], and risk minimisation strategies were part of the initial marketing registration. Although the relative risk of psychiatric adverse events seemed to be comparable before and after registration, the absolute risks of psychiatric adverse events were considerably higher post-marketing possibly because of the higher baseline risk for psychiatric adverse events in the real world population compared to the clinical trial population [5]. Therefore, contraindications for major depression and use of antidepressants were added post-marketing to the Summary of Product Characteristics (SPC). Additionally, the SPC was updated with warnings concerning a history of depressive disorders and the need to monitor for the emergence of depressive symptoms or mood alterations. In October 2008, the Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits no longer outweighed the risks for rimonabant and the marketing authorisation was suspended [6].

Persistence, or continuation of drug use, refers to continued therapy for a defined period. In different fields of medicine, non-persistence has been associated with an increased risk of adverse health outcomes [7-9]. Early discontinuation may occur if patients suffer from an asymptomatic disease, if they do not experience direct beneficial treatment effects, when patients experience adverse drug reactions [10] or do not accept treatment [11]. This has for example been observed in the treatment of asthma/COPD [12], hypercholesterolemia [13], hypertension [14] and depression [15]. Early discontinuation will have a negative influence on a drug's benefit-risk profile if discontinuation occurs earlier in time than positive treatment effects. In a previous study our group from Utrecht found that anti-obesity drugs were used only for a short period of time; 77.7% discontinued treatment within 90 days [16]. We also found that patients initiating anti-obesity therapy often have a history of psychiatric disease [16, 17], a known risk factor for non-persistence [13, 14]. Links between patient characteristics and treatment discontinuation have not been established before in the field of obesity.

The aim of the study was to explore possible relations between patient characteristics and reasons for discontinuation in a general practice population. In addition, we aimed to assess time

to discontinuation in relation to patient characteristics and reasons for stopping. The focus of the study is on psychiatric clinical events, because these were the main area of concern for rimonabant.

METHODS

Study setting

An observational cohort study was conducted in England, using a modified technique of Prescription-Event-Monitoring (PEM) called M-PEM. The method of PEM has been described previously in more detail [18]. In brief, patients were identified from dispensed National Health Service prescriptions for rimonabant issued by General Practitioners (GPs) in England between June 2006 and October 2008 and information was supplied in confidence to the Drug Safety Research Unit (DSRU) by National Health Service Prescription Services (NHSRxS). Hospital prescriptions were not included in this study. At least six months after the initial prescription, M-PEM questionnaires were sent to prescribing GPs requesting additional data on exposure and information on any events[1] that had occurred since starting rimonabant (outcome data) *without* causality assessments. Per patient, the follow-up time was determined based on the information on exposure that was provided by the GP.

All reported events were entered into the DSRU database using the DSRU event dictionary, which has a hierarchical structure arranged by System Organ Class (SOC). The terminology used by the GP (doctor summary term) is grouped under a "lower-level" term (LLT), which is subsequently grouped under a broader, "higher-level" term (HLT), which is then linked to the respective SOC. An event was coded as a suspected Adverse Drug Reaction (ADR) if the GP specified on the M-PEM questionnaire that the event was attributable to the drug. All returned M-PEM questionnaires were reviewed by a DSRU research fellow. The M- PEM questionnaire also asked the doctor to record the reason why the drug was stopped if, in fact, it was stopped. These reasons may be clinical and non-clinical reasons; they may be recorded as events related to the indication (not necessarily adverse), adverse events, suspected adverse drug reactions, events related to effectiveness (or lack of effectiveness) or events related to other prescribing decisions. This is very informative because data is gathered on those reasons, which the doctor and/or the patient considers serious or sufficiently troublesome to stop the medication.

Study population

All patients for whom the GP returned a valid M-PEM questionnaire in the period June 2006-June 2008 were included in the present study. Information on age and gender had to be available

1 Definition of an event in Prescription-Event Monitoring: *"any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter into the patient's notes"*

for each patient. For each patient, information on baseline characteristics was extracted from the database. This information consisted of patient demographics (year of birth, gender of the patient), and aspects of drug utilization such as dates of starting and stopping therapy, and the reason for discontinuing therapy if treatment was stopped. In addition, the patient's body mass index (BMI), weight, and smoking status both immediately prior to starting rimonabant and since starting rimonabant were collected. Patients were excluded when no information was present on age and/or gender. In addition, information on previous medical history was collected. The questionnaires addressed a history of type 2 diabetes, dyslipidaemia, hypertension, and cardiovascular disease. Because these are all chronic diseases, it was highly likely that the diseases were still active co-morbidities during rimonabant therapy. Additionally, GP were asked to provide information on existing psychiatric disease, by indicating whether patients experienced a major or minor depressive episode, anxiety and/or insomnia requiring treatment or referral in the six months before rimonabant was started.

Study endpoints

The primary outcome of this study was reason for discontinuation of the use of rimonabant. A patient was considered to have discontinued using rimonabant when the question "Has rimonabant been stopped" was answered with "YES". Time to discontinuation was calculated based upon the date of first prescription and stop date. For this retrospective analysis, reasons for discontinuation of interest were categorised as follows:

(1) Discontinuation due to *any* clinical event with the following subgroup:

(1a) Discontinuation due to psychiatric events (all events in the System Organ Class "Psychiatric Disorders");

(2) Discontinuation due to lack of effectiveness (e.g. reason for stopping "Not effective", and "Weight gain");

(3) Discontinuation due to target weight loss reached (as a proxy for effectiveness);

(4) Other events reported as reason for stopping, such as "No further request", "Hospital referrals" and "Patient request".

Those patients recorded as having stopped, but for whom no reason was specified were included in a fifth group "No reason for discontinuation specified". In Appendix 1, examples are given of terms that are included in the categories for reason for stopping.

Data analysis

Descriptive statistics were used to present the data on the baseline characteristics of the cohort and frequency of events reported within each category of reason for stopping. The following determinants were analysed in relation to the categories of discontinuation (any clinical events, sub-group of psychiatric events; and lack of effectiveness): age, gender, BMI (< 35 kg/m^2 versus ≥ 35 kg/m^2, which is class II obesity according to the World Health Organization, www.who.int), smoking status, previous use of anti-obesity drugs, and history of psychiatric and cardiovascular

disease. In addition, we analysed a history of type 2 diabetes, dyslipidaemia, and hypertension as determinants of discontinuation. Rate ratios (RRs) with 95% confidence intervals based on incidence rates were calculated to explore associations between patient characteristics and treatment discontinuation for all patients for whom stopping was reported on the M-PEM questionnaires. The categories of "target weight loss reached", "other" and " no reason specified" were not analysed further because of small numbers (target weight loss reached) or because of lack of specificity in terminology ("other events" as reason for stopping and "no reason specified") for which in-dept analysis would not add to the aim of the study.

Within the cohort of rimonabant users, duration of use was examined for the first year after starting (index date) of rimonabant therapy, in relation to the categories of discontinuation of interest (see above). Cumulative hazard plots were constructed to depict the risk of stopping rimonabant therapy in the year following the index date. In addition, stratum specific median times to discontinuation and the interquartile ranges (IQR) were calculated and compared using a Mann-Whitney-U-test, between subgroups of patients defined by the presence or absence of a history of psychiatric disease, presence or absence of cardiovascular disease and for BMI (< 35 kg/m^2 versus ≥ 35 kg/m^2). All statistical analyses were carried out using SPSS 16.0 statistical software (SPSS Inc. Chicago, Illinois, USA).

RESULTS

The rimonabant M-PEM cohort consisted of 10,011 patients. Three patients were excluded from this analysis because no information on age or gender was available. Therefore, 10,008 patients were included in the analyses. Mean age of the patients was 50.5 (standard deviation (sd) 12.8), with eight patients (0.08%) younger than 18 years (Table 1). The majority of the patients were female (n=6,742, 67.4%). Mean BMI was 39.8 (sd 7.6) kg/m^2. A total of 6,305 patients (63.0%) reported that they had used other anti-obesity drugs before. In the six months before starting rimonabant, 15.1% (n=1,516) reported psychiatric disease. These consisted of major depressive episode (n=232, 15.3%), minor depressive episode (n=1,039, 68.5%), anxiety (n=396, 26.1%), and insomnia (n=281, 18.5%). A history of cardiovascular disease was reported in 1,326 patients (13.2%), type 2 diabetes mellitus in 39.2% (n=3,922), and dyslipidaemia in 36.0% (n=3,603) of patients. Hypertension was reported in 45.2% (n=4,520) of the patients.

Of the 10,008 patients in this analysis, 2,804 (28.0%) were reported to be taking rimonabant continuously during observation and 7,207 (72.0%) patients had discontinued rimonabant therapy (median observation time 323 days, IQR: 279-371 days), as indicated on the initial study questionnaire, which was sent at least six months after the initial rimonabant prescription for each individual (Table 2). For 20.0% (n=1,441) of the patients discontinuing rimonabant therapy, no reason for stopping was provided by the GP. Of the patients who discontinued treatment, and for whom a reason for discontinuation was specified, the most frequently reported reason

Table 1: Characteristics of the study cohort

Characteristics	Number of patients (n=10,008)
General patient characteristics	
Age (mean (sd))	50.5 (12.8)
Female gender	6,742 (67.4%)
BMI (mean (sd))	39.8 (7.6)
BMI missing	777 (7.8%)
Smoking status	
Current smoker	1,334 (13.3%)
Former smoker	3,216 (32.1%)
Never smoked/non-smoker	4,585 (45.8%)
Not known/unspecified	873 (8.7%)
Previous use of one or more AODs	6,305 (63.0%)
Orlistat	5,522 (87.6%)*
Sibutramine	2,493 (39.5%)*
Other	136 (2.2%)*
Medical history	
One or more psychiatric conditions†,‡	1,516 (15.1%)
Major depressive episode‡	232 (15.3%)§
Minor depressive episode‡	1,039 (68.5%)§
Anxiety‡	396 (26.1%)§
Insomnia‡	281 (18.5%)§
Convulsions/seizure‡	21 (0.2%)
Cardiovascular disease	1,326 (13.2%)
Type 2 diabetes mellitus	3,922 (39.2%)
Dyslipidaemia	3,603 (36.0%)
Hypertension	4,520 (45.2%)

BMI: body mass index (kg/m^2); AOD: anti-obesity drug; * % of past anti-obesity drug users; † At least one of the following events: major depressive episode, minor depressive episode, symptoms of anxiety or insomnia requiring treatment or referral; ‡ In the 6 months before start; § % of patients with a history of one or more psychiatric conditions

Table 2: (Dis-) continuation of rimonabant use and reasons for stopping

	Number of patients (n=10,008)
Patients stopped treatment	7,204 (72.0%)
No reason specified	1,441 (20.0%)
1 reason for stopping	4,653 (64.6%)*
2 reasons for stopping	891 (12.4%)*
≥ 3 reasons for stopping	219 (3.0%)*
Stopping due to any clinical events†,‡	1,896 (26.3%)
Stopping due to psychiatric events†	935 (13.0%)
Stopping due to lack of effectiveness†	2,480 (34.4%)
Target weight loss reached†	215 (3.0%)
No reason specified†	1,441 (20.0%)
Stopping due to other reasons†,§	1,773 (24.6%)

* % of the patients stopping † At least one; ‡ E.g. Nausea, diarrhoea, depression; § E.g. No further request, patient request, non-compliance

for stopping was lack of effectiveness (n=2,480, 34.4% of the patients who stopped). For 26.3% of patients (n=1,896), the reason was reported to be related to a clinical event; with psychiatric events reported in 13.0% (n=935) of the patients who stopped. The majority of patients who stopped (64.6%, n=4,653) reported one reason for stopping (Table 2).

The rate of discontinuation for all categories of stopping was significantly higher for female patients than males, in patients with a past history of other anti-obesity drug use than without such a history, and in patients with a past history of psychiatric disease than no history (Table 3). In addition, the highest RR estimate for stopping due to psychiatric events was observed in patients with a history of psychiatric disease compared to patients without such a history (RR 1.79 (95% CI 1.54-2.09)) compared to patients without such a history. Similarly, this subset of patients had higher rates of discontinuation due to any clinical event (RR 1.32 (95% CI 1.17-1.48)) and due to lack of effectiveness (RR 1.13 (95% CI 1.02-1.26)) (Table 3). In contrast, the rates of discontinuation due to lack of effectiveness, any clinical or psychiatric events in patients with cardiovascular disease, type 2 diabetes mellitus, dyslipidaemia or hypertension tended to be lower (not all being significant) than those without (Table 3).

In Figure 1-3, the cumulative hazard of stopping rimonabant therapy is presented for the selected reason for stopping categories of interest, stratified by the presence of a history of psychiatric disease. After 90 days, 18.3% of the patients with a history of psychiatric conditions and 15.2% of the patients without a history of psychiatric conditions had stopped treatment due to lack of effectiveness. For any clinical event, this was 17.9% and 14.3%, respectively, and for stopping due to psychiatric events, 10.6% of the patients with and 6.1% of the patients without a history of psychiatric conditions had stopped treatment with rimonabant.

For patients who discontinued treatment due to lack of effectiveness, the median time to stop was 86 days (IQR: 48-158 days) for patients with a history of psychiatric conditions, and 97 days (IQR: 54-173 days) (p=0.03) for patients without a history of psychiatric conditions. For patients discontinuing treatment due to any clinical events the median times to stop were 61 days (IQR: 28-120 days) and 63 days (IQR: 28-118 days) (p=0.90), for patients with and without a history of psychiatric conditions, respectively. For patients who discontinued treatment due to psychiatric events, the median time to stop was 64 days (IQR: 28-141 days) for patients with a history of psychiatric conditions, and 75 days (IQR: 30-136 days) (p=0.38) for patients without a history of psychiatric conditions. Finally, we analysed the time to discontinuation stratified by history of cardiovascular disease and BMI, and no differences were found (data not shown).

Table 3: Rates and crude rate ratios of reasons for discontinuation, by patient characteristics

		Lack of effectiveness			Any clinical event			Psychiatric event		
	Patient days	# Events	Rate*	RR (95% CI)	# events	Rate*	RR (95% CI)	# events	Rate*	RR (95% CI)
Age										
< 40 yrs	280,055	518	1.85	1.18 (1.07-1.30)	378	1.35	1.11 (0.99-1.24)	204	0.73	1.24 (1.07-1.45)
≥ 40 yrs	1,248,922	1,962	1.57	1	1,518	1.22	1	731	0.59	1
Gender										
Female	987,151	1,668	1.69	1.13 (1.04-1.23)	1,335	1.35	1.31 (1.18-1.44)	649	0.66	1.25 (1.08-1.43)
Male	541,826	812	1.50	1	561	1.04	1	286	0.53	1
BMI										
< 35kg/m^2	345,555	593	1.72	1.05 (0.96-1.15)	448	1.30	1.05 (0.94-1.17)	218	0.63	1.04 (0.90-1.22)
≥ 35kg/m^2	1,064,109	1,738	1.63	1	1,312	1.23	1	643	0.60	1
Current smoker										
Yes	200,082	312	1.56	0.96 (0.85-1.08)	219	1.09	0.87 (0.75-1.00)	101	0.50	0.80 (0.65-0.99)
No	1,328,895	2,168	1.63	1	1,677	1.26	1	834	0.63	1
Previous use of AOD										
Yes	931,138	1,742	1.87	1.49 (1.36-1.63)	1,257	1.35	1.27 (1.14-1.40)	638	0.69	1.39 (1.21-1.61)
No	510,867	643	1.26	1	545	1.07	1	251	0.49	1
Psychiatric disease†										
Yes	219,302	394	1.80	1.13 (1.02-1.26)	341	1.56	1.32 (1.17-1.48)	215	0.98	1.79 (1.54-2.09)
No	1,310,675	2,086	1.59	1	1,555	1.19	1	720	0.55	1
Cardiovascular disease										
Yes	222,728	304	1.36	0.80 (0.71-0.90)	269	1.21	0.96 (0.85-1.10)	128	0.57	0.92 (0.77-1.11)
No	121,599	2,079	1.71	1	1,518	1.25	1	754	0.62	1
Type 2 diabetes mellitus										
Yes	683,916	905	1.32	0.69 (0.64-0.75)	742	1.08	0.79 (0.72-0.86)	363	0.53	0.77 (0.68-0.88)
No	789,305	1,504	1.91	1	1,090	1.38	1	542	0.69	1
Dyslipidaemia										
Yes	599,246	884	1.48	0.83 (0.76-0.90)	724	1.21	0.94 (0.85-1.03)	350	0.58	0.91 (0.80-1.05)
No	780,638	1,385	1.77	1	1,006	1.29	1	500	0.64	1
Hypertension										
Yes	746,895	1,122	1.50	0.84 (0.77-0.91)	914	1.22	0.97 (0.89-1.07)	436	0.58	0.92 (0.80-1.05)
No	713,202	1,277	1.79	1	898	1.26	1	454	0.64	1

* Per 1,000 patient days; † Major/minor depressive episode, anxiety and insomnia; RR: rate ratio; BMI: body mass index; AOD: anti-obesity drug

Figure 1: Cumulative hazard plot for patients stopping rimonabant therapy due to lack of effectiveness, stratified according to a history of psychiatric disease. The vertical line indicates the 90 days juncture.

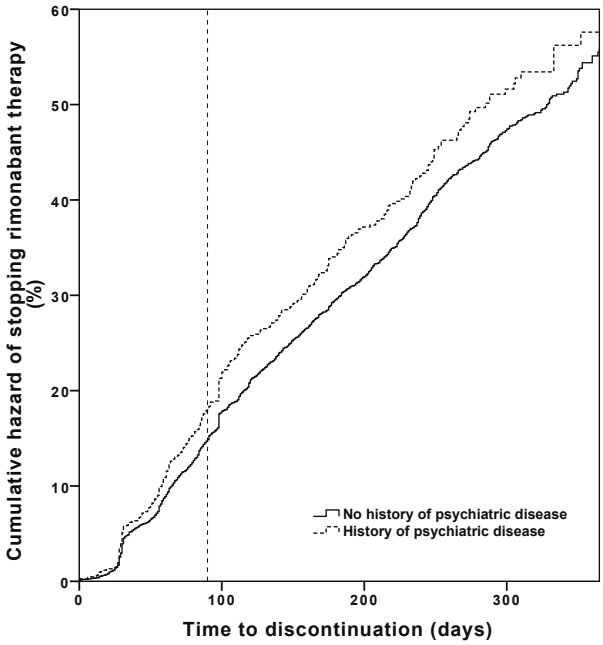


Figure 2: Cumulative hazard plot for patients stopping rimonabant therapy due to any clinical event, stratified according to a history of psychiatric disease. The vertical line indicates the 90 days juncture.

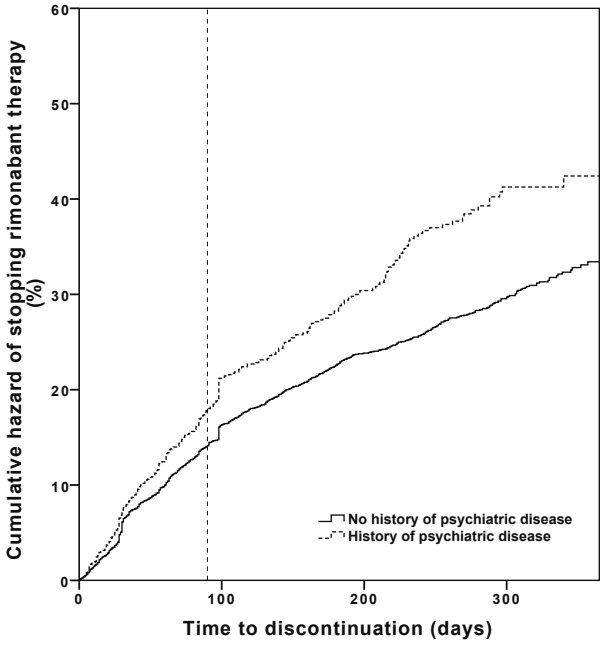
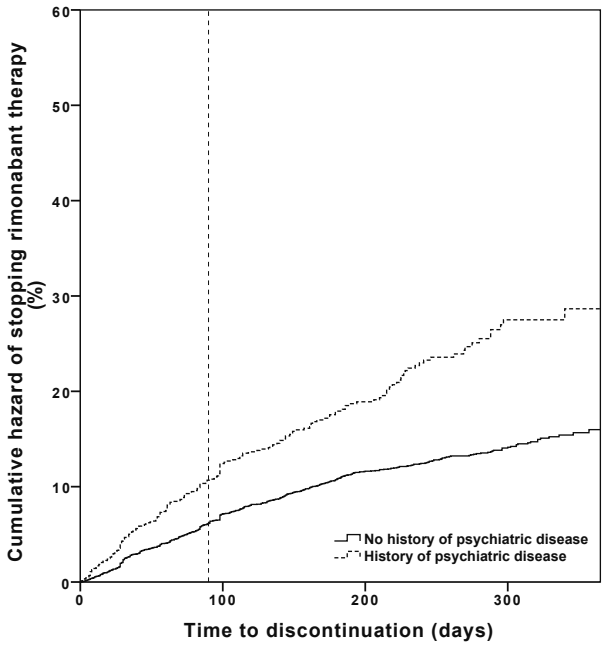


Figure 3: Cumulative hazard plot for patients stopping rimonabant therapy due to psychiatric events, stratified according to a history of psychiatric disease. The vertical line indicates the 90 days juncture.



DISCUSSION

We found that for almost three quarters (72.0%) of patients using rimonabant, GPs reported discontinuation of therapy (median observation time 323 days, IQR: 279-371 days). For patients who discontinued treatment due to lack of effectiveness or due to psychiatric events the median time to stop was 11 days shorter for patients with a history of psychiatric conditions, compared to patients without a history of psychiatric conditions. The median times to stop for patients discontinuing treatment due to any clinical event were comparable for patients with and without a history of psychiatric conditions. Patients with a history of psychiatric illness were at increased risk of early discontinuation of rimonabant therapy for all reasons, but more pronounced due to psychiatric events. In contrast, patients with cardiovascular disease, type 2 diabetes mellitus, dyslipidaemia or hypertension tended to be at a lower risk of discontinuation than those without.

The finding that overall 72.0% of patients discontinued rimonabant therapy is in line with our previous finding [16]. This high percentage of discontinuation can be explained, at least partly, by the fact that a contra-indication for use in patients with major depression or ongoing treatment with antidepressants was added to the SPC and consequently, GPs may have decided to stop therapy with rimonabant. Therefore, GPs may have stopped treatment in those

patients where any signs of depression or other psychiatric disease were evident, and especially in patients with a history of psychiatric disease.

We did find differences between time to discontinuation and the different reasons for stopping. Discontinuation due to lack of effectiveness in patients with and without a history of psychiatric disease differed 11 days (86 vs. 97 days; p=0.03). For patients who stopped due to any clinical event the difference was only 2 days (61 vs. 63 days; p=0.90) and in patients who stopped due to psychiatric events the difference in median time to stop was 11 days (64 vs. 75 days; p=0.38). Although the difference for patients stopping due to psychiatric events was not statistically significant different for patients with and without a psychiatric history, it was comparable with stopping due to lack of effectiveness in absolute terms. This is an important finding since this might have an effect on the benefit-risk profile: discontinuation occurred before the beneficial effects could occur.

Patients with a history of cardiovascular disease discontinued treatment less frequently compared to patients without such a history. This might be due to the fact that these patients are more familiar with chronic medication use. Another possible explanation might be that they are more aware of the importance of weight loss. In contrast, this was not the case in patients with a history of psychiatric disease, although their treatment also requires long-term therapy. In other studies, psychiatric disease was found to be an important risk factor for poor treatment compliance [19-22] and this may have led to early discontinuation of rimonabant therapy. However, this may not be the only case. As discussed before, rimonabant is an antagonist of the cannabinoid-1 (CB-1) receptor. In the brain, the CB-1 receptor is involved in the regulation of cognition and mood functions, implying that it is connected to regulation of mood, anxiety, and depression. After rimonabant came to the market in the EU, the number of patients reporting psychiatric adverse events increased compared to the numbers reported in the clinical trial program [5]. This can be explained by the fact that in the clinical trial program, patients with a psychiatric history were excluded while in the post-marketing setting rimonabant was also used by patient with such a history [5]. In these patients, the use of rimonabant may have exacerbated the development of psychiatric events. The subsequent update of the SPC in August 2007 [23], to include a contraindication for use in patients with ongoing major depression or antidepressant therapy, might have contributed to increased discontinuation of rimonabant therapy.

Because the ultimate goal for patients with overweight and obesity is to obtain a long-lasting decrease in weight, the persistence of anti-obesity medicines should be increased, thereby positively influencing the drug's benefit-risk profile. However, none of the anti-obesity drugs were indicated for achieving these ultimate long-term treatment goals, but all of these medicines were indicated for short-term treatment. Nevertheless, a long-lasting decrease in weight will lead to a reduction of the morbidity and mortality associated with excess weight in general, caused by the development of concomitant diseases, predominantly cardiovascular disease [24], type 2 diabetes [25] and certain types of cancer [26]. Therefore, persistent use of anti-obesity drugs leading to a long-term maintained weight loss is necessary to obtain

full benefits. Several studies have been conducted analysing different interventions aimed at improving treatment persistence, and although the results were not uniform, combination of different strategies seemed to be the most promising approach [27-30]. Thus such a combination of interventions, consisting of providing more detailed information, behavioural therapies, manual follow-up, and supportive care will be necessary for all anti-obesity drugs to cause maintained weight loss [28]. Also more effective anti-obesity drugs are required, there are none at the moment. The information on associations between patient characteristics in relation to treatment discontinuation as we presented in this study may add to the early identification of patients at risk of early discontinuation and ultimately may add to further improvement of persistence to therapy. Consequently, improved persistence may lead to shifting the benefit-risk balance of medicines towards a more favourable direction.

Strengths and limitations of studies using the Prescription-Event-Monitoring methodology have already been described before [31]. Through targeted questionnaires, detailed information was collected on the safety issues that were already identified during the pre-registration phase of rimonabant. Consequently, as the PEM-studies reflect the use of products in daily clinical practice rather than in the highly controlled setting of the randomised clinical trials, safety issues could be studied in daily clinical practice.

A limitation of the present study may be the response rate. Of the rimonabant M-PEM questionnaires sent (n=21,535), 11,207 (52.0%) were returned. The current median response rates for M-PEM studies is 64% so the response for the rimonabant M-PEM is lower compared to other M-PEM studies completed by the DSRU. The median response rate for standard PEM studies is 50%, which is comparable to the response in the present M-PEM study and to GP postal surveys [32]. This study did not assess the impact of non-response bias. Secondly, a general limitation is that underreporting of events might have affected the study results. However, Martin et al. showed that the level of underreporting for PEM-studies is at least comparable to that of spontaneous reporting systems to detect ADRs (e.g. UK yellow card system) [33]. Therefore, we do believe that the results of this study add important information to the knowledge of the use of rimonabant. Finally, PEM does not include hospital prescriptions (unless continued by the general practitioner). This will, however, only have had a limited effect on our results as it is likely that rimonabant is mainly prescribed by general practitioners.

In conclusion, patient characteristics were associated with reasons for and time to discontinuation. Patients discontinued treatment because of psychiatric events before the beneficial effects could develop, thereby negatively affecting the benefit-risk profile of rimonabant. Although in June 2008 the marketing authorisation for rimonabant was suspended, this type of information can be used for the identification and characterisation of early discontinuers and ultimately may add to further improvement of adherence to therapy and thus to optimalisation of treatment benefits and drug safety.

REFERENCES

1. Summary of Product Characteristics: Acomplia. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000666/WC500021287.pdf (last accessed: 20 December 2010).
2. Pavon FJ, Bilbao A, Hernandez-Folgado L, Cippitelli A, Jagerovic N, Abellan G et al. Antiobesity effects of the novel in vivo neutral cannabinoid receptor antagonist 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-3-hexyl-1H-1,2,4-triazole - LH 21. Neuropharmacology 2006; 51 (2): 358-366.
3. Parolaro D, Realini N, Vigano D, Guidali C, Rubino T. The endocannabinoid system and psychiatric disorders. Exp Neurol 2010; 224 (1): 3-14.
4. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Acomplia®. Available at: http://www.emea.europa.eu/humandocs/Humans/EPAR/acomplia/acomplia.htm (last accessed: 03 August 2010).
5. Rumsfeld JS, Nallamothu BK. The hope and fear of rimonabant. JAMA 2008; 299 (13): 1601-1602.
6. Committee for Medicinal Products for Human Use (CHMP). The European Medicines Agency recommends suspension of the marketing authorisation of Acomplia. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/acomplia/53777708en.pdf (last accessed: 24 August 2010).
7. Hershman DL, Shao T, Kushi LH, Buono D, Tsai WY, Fehrenbacher L et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat 2010; E-published ahead of print.
8. Ho PM, Peterson ED, Wang L, Magid DJ, Fihn SD, Larsen GC, et al. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. JAMA 2008; 299 (5): 532-539.
9. Hiligsmann M, Rabenda V, Gathon HJ, Ethgen O, Reginster JY. Potential clinical and economic impact of nonadherence with osteoporosis medications. Calcif Tissue Int 2010; 86 (3): 202-210.
10. Hugenholtz GW, Heerdink ER, Meijer WE, Stolker JJ, Egberts AC, Nolen WA. Reasons for switching between antipsychotics in daily clinical practice. Pharmacopsychiatry 2005; 38 (3): 122-124.
11. Van Geffen EC, van der Wal SW, van Hulten R, de Groot MC, Egberts AC, Heerdink ER. Evaluation of patients' experiences with antidepressants reported by means of a medicine reporting system. Eur J Clin Pharmacol 2007; 63 (12): 1193-1199.
12. Breekveldt-Postma NS, Gerrits CM, Lammers JW, Raaijmakers JA, Herings RM. Persistence with inhaled corticosteroid therapy in daily practice. Respir Med 2004; 98 (8): 752-759.
13. Mantel-Teeuwisse AK, Goettsch WG, Klungel OH, de Boer A, Herings RM. Long term persistence with statin treatment in daily medical practice. Heart 2004; 90 (9): 1065-1066.
14. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Rate and determinants of 10-year persistence with antihypertensive drugs. J Hypertens 2005; 23 (11): 2101-2107.
15. Van Geffen EC, van Hulten R, Bouvy ML, Egberts AC, Heerdink ER. Characteristics and reasons associated with nonacceptance of selective serotonin-reuptake inhibitor treatment. Ann Pharmacother 2008; 42 (2): 218-225.
16. Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Leufkens HG, Egberts AC, Sturkenboom MC. Cardiovascular and psychiatric risk profile and patterns of use in patients starting anti-obesity drugs. Pharmacoepidemiol Drug Saf 2009; 18 (7): 631-638.

17. Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Leufkens HG, Egberts AC. Psychiatric and cardiovascular co-morbidities in patients with diabetes mellitus starting anti-obesity drug Obesity (Silver Spring) 2008; 16 (10): 2331-2335.

18. Shakir S, Prescription-event monitoring, in Pharmacoepidemiology, B. Strom, Editor. 2005, John Wiley & Sons Ltd: Chichester. p. 203-216.

19. Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ et al. Depression and diabetes treatment nonadherence: a meta-analysis. Diabetes Care 2008; 31 (12): 2398-2403.

20. Valenstein M, Blow FC, Copeland LA, McCarthy JF, Zeber JE, Gillon L et al. Poor antipsychotic adherence among patients with schizophrenia: medication and patient factors. Schizophr Bull 2004; 30 (2): 255-264.

21. Zygmunt A, Olfson M, Boyer CA, Mechanic D. Interventions to improve medication adherence in schizophrenia. Am J Psychiatry 2002; 159 (10): 1653-1664.

22. Nose M, Barbui C, Gray R, Tansella M. Clinical interventions for treatment non-adherence in psychosis: meta-analysis. Br J Psychiatry 2003; 183: 197-206.

23. Committee for Medicinal Products for Human Use (CHMP)Acomplia: Procedural steps taken and scientific information after authorisation. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-Procedural_steps_taken_and_scientific_information_after_authorisation/human/000666/WC500021286.pdf (last accessed: 12 December 2010).

24. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol 2009; 53 (21): 1925-1932.

25. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006; 444 (7121): 840-846.

26. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology 2007; 132 (6): 2208-2225.

27. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Effectiveness of interventions by community pharmacists to improve patient adherence to chronic medication: a systematic review. Ann Pharmacother 2005; 39 (2): 319-328.

28. Nietert PJ, Tilley BC, Zhao W, Edwards PF, Wessell AM, Mauldin PD et al. Two pharmacy interventions to improve refill persistence for chronic disease medications: a randomized, controlled trial. Med Care 2009; 47 (1): 32-40.

29. Machado M, Bajcar J, Guzzo GC, Einarson TR. Sensitivity of patient outcomes to pharmacist interventions. Part I: systematic review and meta-analysis in diabetes management. Ann Pharmacother 2007; 41 (10): 1569-1582.

30. Machado M, Bajcar J, Guzzo GC, Einarson TR. Sensitivity of patient outcomes to pharmacist interventions. Part II: Systematic review and meta-analysis in hypertension management. Ann Pharmacother 2007; 41 (11): 1770-1781.

31. Shakir S, Prescription-event monitoring, in Pharmacovigilance, Mann RD, and Andrews EB, Editors. 2007, John Wiley & Sons Ltd: Chichester, UK. p. 307-316.

32. McAvoy BR, Kaner EF. General practice postal surveys: a questionnaire too far? BMJ 1996; 313 (7059): 732-733.

33. Martin RM, Kapoor KV, Wilton LV, Mann RD. Underreporting of suspected adverse drug reactions to newly marketed ("black triangle") drugs in general practice: observational study. BMJ 1998; 317 (7151): 119-120.

Appendix 1: Examples of terms that are included in the categories for reason for stopping.

1. Discontinuation due to *any* clinical event
Depression
Anxiety
Arrthymia
Hypertension
Headache
Dizziness
Urinary tract infection
Nausea
1a. Discontinuation due to psychiatric events
Depression
Mood change
Mood swings
Anxiety
Aggression
Panic attack
Contraindication antidepressants
Suicide, suicide attempt, drug overdose
2. Discontinuation due to lack of effectiveness
Not effective
Weight gain
3. Discontinuation due to target weight loss reached
Weight loss
4. Other events reported as reason for stopping
No further request
Withdrawn from the market
Road traffic accident
Marital
Non-compliance
Patient request
Polypharmacy
Inappropriate treatment

Chapter 2.8

Effect of the prescription status on the orlistat user population: prescription-only versus pharmacy-only

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ABSTRACT

Introduction: Since 2007, two strengths of orlistat are available, 120 mg (Xenical®, only available on prescription) and 60 mg (Alli®, available without prescription, pharmacy-only in the Netherlands). Because the benefit-risk profile, at least partly, dependent on the patient population in which medicines are being used, information on the populations using the two strengths of orlistat is of importance. The aim of this study was to investigate whether patients using the pharmacy-only formulation Alli® and the prescription-only formulation Xenical® are different regarding general and disease-related patient characteristics.

Methods: A retrospective cohort study was conducted in 35 community pharmacies in the Netherlands; all patients who had obtained orlistat (Alli® or Xenical®) between 20 January 2009 and August 2010 were identified. Information on patient characteristics and disease history were obtained from questionnaires; information on medicine use was obtained from the pharmacy systems. Categorical variables were compared using a Chi-Square test; for continuous variables an independent samples student t-test was used.

Results: In total, 605 patients using orlistat were identified; 504 were users of Alli® and 101 were users of Xenical®. Cardiovascular drugs, anti-thrombotic agents, and medication for the treatment of psychiatric disease were significantly more frequently used by patients using Xenical® than by patients using Alli® ($p<0.05$). However, all medicines were more frequently used by both orlistat formulations users compared to the usage in the general Dutch population, except anti-thrombotic agents and antibacterials for systemic use.

Conclusion: The results of this study imply that orlistat users are less healthy than the general population, while users of the prescription-only formulation are even less healthy than the patients who obtained orlistat in the pharmacy-only formulation. This information is important for an adequate assessment of the benefit-risk profile from a regulatory point of view and confirms that the more severely diseased patients use orlistat under supervision of a physician, while the pharmacy-only formulation is used by healthier patients. This illustrates that information from observational studies is valuable for benefit-risk evaluations.

INTRODUCTION

Currently, orlistat is the only drug licensed for the treatment of overweight in the European Union [1]. Orlistat was first registered in the EU in 1998 [2], and since 2007 two strengths are available: 120 mg (brand name: Xenical®) [2], which is available only on prescription (POM), and 60 mg (brand name: Alli®), which is available without a prescription [3, 4]. According to the European Public Assessment Report for Alli®, the decision to make orlistat 60 mg available without a prescription was in particular based on the safety profile; milder adverse drugs reactions were reported for the 60 mg dosage than for the already existing 120 mg dosage, which can be explained by the dose-dependency of the occurrence of adverse drug reactions [4]. In the Netherlands, Alli® is available without a prescription in pharmacies only (PhO) and the pharmacist is expected to assess whether patients are eligible for the use of Alli® and to perform pharmacovigilance through the use of a structured questionnaire [4].

Orlistat is a locally acting anti-obesity drug, which exerts its action through specific and long-term inhibition of gastrointestinal lipases. The inactivated lipases are thus unavailable for the hydrolysis of dietary fat, leading to a decreased absorption of fat and an increased excretion of faecal fat [5]. The adverse drug reactions that are reported for orlistat are mainly related to the mechanism of action of orlistat and are predominantly gastrointestinal in nature, e.g. fatty stool, increased defecation, and diarrhoea [6, 7].

Our previous studies indicated that patient populations using anti-obesity drugs are less healthy and used more drugs (other than those for the treatment of obesity) compared to the general population [8, 9]. These differences in the context in which these medicines are being used may influence the benefit-risk balance of these products. Now that there are two different channels to obtain orlistat, it might be postulated that there are differences in patient populations using Alli® and Xenical®.

It is hypothesised that the patients who start to use the pharmacy-only formulation would in general be healthier compared to the patients being prescribed orlistat by their phsysician. The benefit-risk profile of orlistat is therefore, at least partly, dependent on the patient population in which these two different formulations are being used. The broader context in which medicines, in this case two strengths of the same active component orlistat, are being used is of importance for the assessment of the benefit-risk profile, which may differ between the two products.

The aim of the present study was to investigate whether the patients using the pharmacy-only formulation of orlistat (Alli®) and the prescription-only formulation (Xenical®) are different in terms of general and disease-related patient characteristics. Therefore, we compared sociodemographic characteristics, co-morbidities, and concomitantly used medication between users of these two products. In addition, we looked at treatment outcomes, e.g. adverse drug reactions, and effectiveness.

METHODS

Setting

Data for this study were obtained through UPPER - Pharmacy Practice Research and Education Network of Utrecht University, the Netherlands. This network consists of approximately 900 community pharmacies, who participate in research and traineeships for pharmacy students of the Department of Pharmaceutical Sciences of Utrecht University on a regular basis. In the period May to August 2010, 35 pharmacy students conducted their final traineeship in 35 community pharmacies of the UPPER network and were invited to participate in the study. Of these, 33 pharmacies participated in the study. The participating pharmacies were located in a diverse range of urban and rural town settings. All pharmacies were equipped with an electronic information and administration system. The Institutional Review Board of UPPER reviewed and approved this study.

Patients and data collection

All patients aged 18 years and older, who had obtained orlistat (either Alli® or Xenical®) in the period since introduction of Alli® in the Netherlands (20 January 2009) until August 2010, were identified in the electronic pharmacy systems.

The pharmacists were asked to send a letter inviting all patients to whom orlistat had been dispensed, to participate in a telephone interview. This letter included general information on the study and was sent to all eligible patients. Pharmacy students contacted the patients for a telephone interview. The patients could refuse to participate in the interview at two occasions: firstly after having received the invitation letter and secondly at the start of the telephone interview. The interviews were guided by a structured questionnaire, which was pretested before the start of the study. All telephone interviews were performed by the students. Topics addressed included length and weight at time of start and stop (or in case the patient was still on treatment, the weight at the interview date), duration of use, occurrence of adverse events, previous history of obesity treatment, concomitantly used medication (both prescription and over-the-counter medication), medical history, and also information on living situation, smoking status and level of education. Education was divided in three categories: low (none, primary school), middle (secondary school) and high (college/university). The length of the interviews varied between 10 and 20 minutes.

Additionally, information was extracted on the medicines recorded in the pharmacy system since October 2008 (three months before the introduction of Alli® in the Netherlands), including over-the-counter medicines if registered. Since virtually all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are virtually complete with regard to prescription drugs [10]. The pharmacy records were obtained independently of the participation of patients in the telephone interview.

All data obtained during the study were anonymised before they were sent to the investigators.

Data analysis

To analyse whether patients using the two orlistat formulations with different prescription status were different, sociodemographic data (age, gender, body mass index, education, living situation, country of birth and smoking status), information regarding obesity and its treatment (trigger to start orlistat, previous use of anti-obesity drugs, time since first use) and self-reported disease history as obtained in the telephone interviews were compared. All categorical variables were compared using a Chi-Square test. Continuous variables were compared using an independent samples student t-test.

Additionally, the pharmacy records were used to analyse whether the use of co-medication (based on the first three characters of the Anatomical Therapeutic Chemical (ATC) classification system) differed between Alli® and Xenical® users by conducting a Chi-Square test. Thereby, the focus was on the drugs that were reported as commonly used among overweight patients [11]. In addition, a comparison was made between the use of co-medication in the study population and medication use in the general Dutch population, based on the data from the Statistics Netherlands (www.cbs.nl) and the Drug Information System of the Health Care Insurance Board (www.gipdatabank.nl).

Furthermore, an analysis on the outcomes of the two strengths of orlistat was conducted. These outcomes were the occurrence of adverse drug reactions and change in body mass index (BMI). For the categorical variable (occurrence in adverse drug reactions), relative risks with 95% confidence intervals were calculated. For the continuous variable, change in BMI, an independent samples student t-test was used.

Finally, to explore possible bias in the selection of patients participating in the interview, responders and non-responders were compared for age and gender by calculating relative risks with 95% confidence intervals. The statistical analyses were carried out using SPSS 16.0 statistical software (SPSS Inc. Chicago, Illinois, USA).

RESULTS

A total of 605 patients were identified who used orlistat during the study period. In the analysis of the telephone interview, 156 patients that used the pharmacy-only formulation (PhO) Alli® and 52 patients that used the prescription-only formulation (POM) Xenical® were included (Figure 1). The overall response rate for the telephone interview was 31.0% for Alli® and 51.5% for Xenical® (p=0.03). The mean body mass index for the patients using the two formulations was comparable: Xenical®: 34.9 (standard deviation (sd) 4.9) kg/m^2 and Alli®: mean 32.9 (sd 5.0) kg/m^2. When looking at the BMI categories, patients using the POM formulation had more often a BMI ≥ 35 kg/m^2 compared to patients using the PhO formulation. Users of Xenical® seemed lower educated (30.8% versus 18.6% reported low education), were more often living without

a partner (38.5% vs. 25.6%) and were less frequently reporting the Netherlands as country of birth (85.3% versus 75.0%) (all non-significant) (Table 1).

When looking at the variables related to obesity and its treatment, patients using the prescription-only formulation reported more frequently that health care professionals triggered them to start orlistat therapy in comparison to patients using the pharmacy-only formulation (67.3% versus 5.8%, p<0.001). On the contrary, patients using the POM formulation reported less frequently that internet, (1.9% versus 5.1%, p<0.001) and other media (11.5% versus 64.1%, p<0.001) triggered them to start orlistat therapy in comparison to patients using the PhO formulation. Patients were using Xenical® for a significantly longer period that the patients using Alli®: mean time since first use for Xenical® was 352.2 days (sd 659.4) and for Alli® 60.6 days (sd 72.3) (Table 1).

For disease history, the number of patients reporting no co-morbidities was higher for patients using the pharmacy-only formulation than for the prescription-only formulation (32.1% versus 21.2%, p<0.001). The same trend was found for one co-morbidity (25.0% vs. 23.1%, p=0.01) and for two co-morbidities (21.8% vs. 13.5%, p=0.001). For three or more co-morbidities the opposite was found: 42.3% of the patients using the POM formulation reported three co-morbidities or more versus 21.1% of the patients using the PhO formulation (p=0.606). When looking into the specific diseases that were reported by the patients, only rheumatoid arthritis was significantly more frequently reported by patients using Xenical® compared to patients using Alli® (205% versus 50.0%, p=0.04). Although for the other co-morbidities no statistically significant differences were found between users of the two formulations, the prevalences of self-reported co-morbidities were higher for Xenical® than for Alli® (diabetes mellitus (17.3% and 12.8%), hypertension (38.5% and 32.7%), heart failure (5.8% and 4.5%),

Figure 1: Selection and response of the study participants

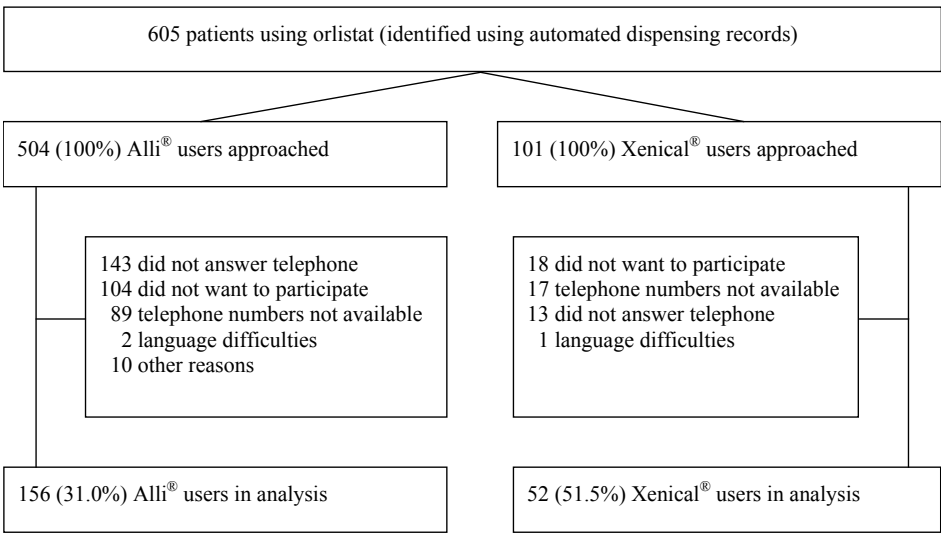


Table 1: Characteristics of users of the two orlistat formulations who participated in the telephone interview

	Alli® (PhO) (n=156), n (%)	**Xenical® (POM) (n=52), n (%)**
Sociodemographic variables		
Female gender	126 (80.8%)	42 (80.8%)
Age (years)		
18-30	10 (6.4%)	0 (0%)
31-45	42 (26.9%)	14 (26.9%)
46-60	57 (36.5%)	22 (42.3%)
> 60	47 (30.1%)	16 (30.8%)
BMI (mean (sd))	32.9 (5.0)	34.9 (4.9)
20-25 kg/m^2	1 (0.6%)	1 (1.9%)
25-30 kg/m^2	35 (22.4%)	6 (11.5%) *
30-35 kg/m^2	48 (30.8%)	12 (23.1%) *
≥ 35 kg/m^2	30 (19.2%)	20 (38.5%) *
Missing	42 (26.9%)	13 (25.0%)
Education		
High	53 (34.0%)	17 (32.7%)
Middle	71 (45.5%)	18 (34.6%)
Low	29 (18.6%)	16 (30.8%)
Living situation		
Partner	114 (73.1%)	32 (61.5%)
No partner	40 (25.6%)	20 (38.5%)
Country of birth		
The Netherlands	133 (85.3%)	39 (75.0%)
Suriname	8 (5.1%)	3 (5.8%)
Other	15 (9.6%)	10 (19.2%)
Smoking status		
Current smoker	32 (20.5%)	14 (26.9%)
Former smoker	63 (40.4%)	20 (38.5%)
Never smoker	61 (39.1%)	18 (34.6%)
Obesity and treatment		
Who or what triggered you to start orlistat?		
Health care professional	9 (5.8%)	35 (67.3%)*
Family, friends	29 (18.6%)	9 (17.3%)*
Internet	8 (5.1%)	1 (1.9%)*
Other media†	100 (64.1%)	6 (11.5%)*
Advertisement	7 (4.5%)	1 (1.9%)*
Other‡	3 (1.9%)	0 (0%)*
Previous use of anti-obesity drug		
No	137 (87.8%)	40 (76.9%)
Yes	19 (12.2%)	12 (23.1%)
Xenical®	3 (1.9%)	0 (0%)
Reductil®	2 (1.3%)	3 (5.8%)
Acomplia®	2 (1.3%)	0 (0%)
Other	12 (12.2%)	9 (17.3%)
Time since first orlistat use (mean (days) (sd))	60.6 (72.3)	352.2 (659.4)*
Number of concomitantly used medication		
0-4	112 (71.8%)	32 (61.5%)
5-9	42 (26.9%)	17 (32.7%)
10-14	2 (1.3%)	3 (5.8%)

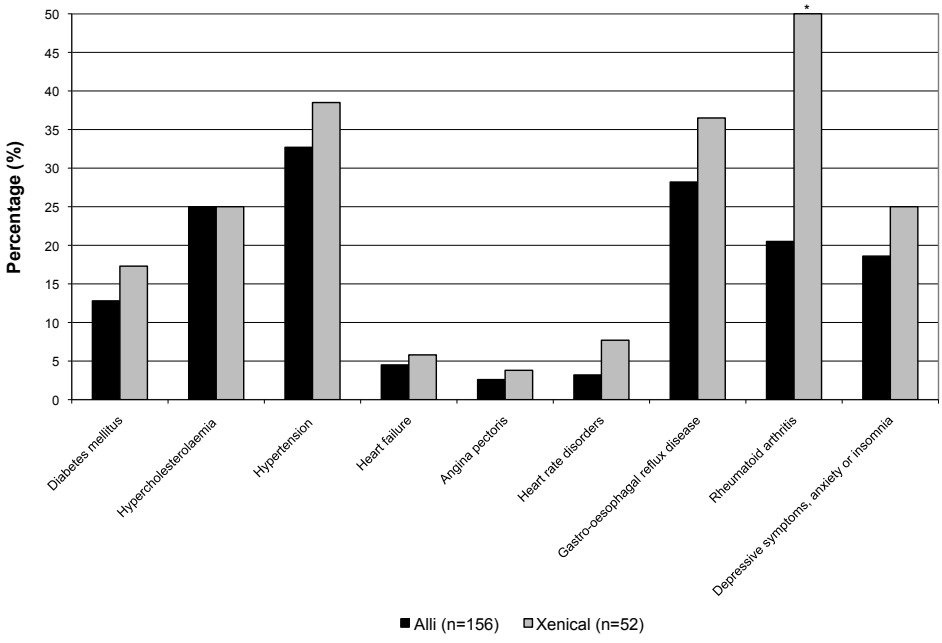
PhO: pharmacy-only; POM: Prescription-only medicine; BMI: body mass index; * indicates a significant difference ($p<0.05$); † Newspaper, television, radio, magazine; ‡ E.g. sport school, fair, participant in trial

angina pectoris (3.8% and 2.6%), gastro-oesophageal reflux disease (36.5% and 28.2%), and depressive symptoms (25.0 and 18.6%)) (Figure 2).

The analysis of the pharmacy records (including all patients who used orlistat, regardless of participation in the telephone interview) showed that 71.8% of the patients using the PhO formulation used 0 to 4 other medicines concomitantly, versus 61.5% for the patients using the POM formulation (p=0.010). The percentage of 5-9 and 10-14 concomitantly used medicines was higher for users of Xenical® than for patients using Alli® (5-9 concomitant medication: 32.7% versus 26.9% (p=0.143); 10-14 concomitant medication: 5.8% versus 1.3% (p<0.001))). Several groups of medicines were more frequently used by patients using the POM formulation than by patients using the PhO formulation. This concerned the antidiabetic agents, anti-thrombotic agents, diuretics, beta-blocking agents, agents acting on the renin-angiotensin system, antibacterials for systemic use, anti-inflammatory and antirheumatic drugs, analgesics, psycholeptics, psychoanaleptics, and drugs for obstructive airway diseases. For both orlistat formulations, all concomitantly used medicines were considerably more frequently used compared to the usage in the general Dutch population, except anti-thrombotic agents and antibacterials for systemic use for which a small difference was found (Figure 3).

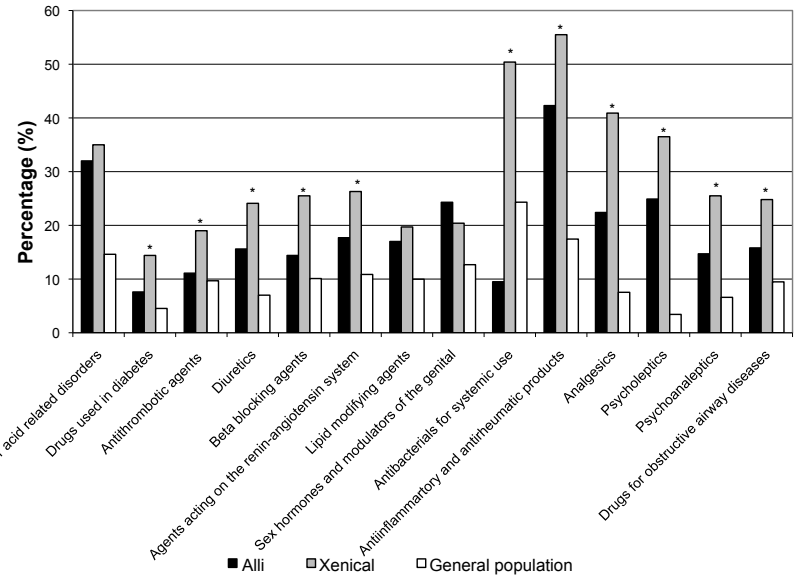
Additionally, the analysis on safety related outcomes indicated no significant differences between the two formulations regarding the reporting of adverse drug reactions: all adverse events including increased defecation (RR 0.83 (95% CI 0.39-1.78)) for PhO versus POM, flatus

Figure 2: Self-reported co-morbidities



* Indicates a significant difference (p<0.05) between the two formulations; no statistical comparison for general population is provided.

Figure 3: Co-medication in patients using the two orlistat formulations and of the general Dutch population



* Indicates a significant difference ($p<0.05$) between the two formulations; no statistical comparison for general population is provided.

with discharge (RR 0.77 (95% CI 0.39-1.50)), fatty oily stool (RR 0.76 (95% CI 0.44-1.31)), faecal incontinence (RR 0.33 (95% CI 0.05-2.31)) and soft and liquid stools (RR 0.83 (95% CI 0.43-1.62)) were equally reported by patients using the two formulations. When looking at effectiveness, the change in body mass index for Xenical® (mean BMI change -1.28 (sd 1.92) kg/m) was borderline significantly larger than the change in BMI for users of Alli® (mean BMI change -0.90 (sd 1.49), p=0.05) kg/m^2). Finally, the responder-non-responder analysis did not show differences regarding age and gender (data not shown).

DISCUSSION

In this study, we found that patients using the prescription-only formulation of orlistat and the pharmacy-only formulation were comparable for gender and mean BMI at start of the medication, but differed on sociodemographic characteristics such as education and living situation, co-morbidities and concomitant medication use. Cardiovascular drugs, anti-thrombotic agents, and medication for the treatment of psychiatric disease were significantly more frequently used by patients using the prescription-only formulation than by patients using the pharmacy-only formulation. Compared to the Dutch population, medicine use was higher in both groups (except for anti-thrombotic agents and antibacterials for systemic use.

These results confirm the outcomes of two prior studies on the patient characteristics of anti-obesity drug users. Previously, we found in two databases, namely the UK General Practice Research Database (GPRD) [9] and the Dutch Integrated Primary Care Information (IPCI) [8] (both comprising data from general practitioners (GPs)), that patients who were being prescribed anti-obesity drugs more often had a history of psychiatric and cardiovascular disease. In the present study, we found that cardiovascular and psychiatric drugs were more frequently dispensed to patients being prescribed orlistat by physicians than to patients who obtained orlistat without prescription, but that the difference with the general population was even larger.

The same trend was found diseases that were self-reported by the participants; except for hypercholesterolaemia all diseases were more frequently reported for Xenical® users than for Alli® users. These findings suggest that users of the prescription-only formulation of orlistat were less healthy than users of the pharmacy-only formulation, while users of both orlistat-containing products were less healthy than the general population. This confirms the hypothesis that users of the 60 mg dosage form are healthier than the users of the 120 mg dosage and therefore is an important finding from a regulatory point of view. The difference in availability regulated through the different legal status of the products led to patient populations that are not comparable. This knowledge is of importance for the benefit-risk profile of the two products. Although Alli® is available without prescription through the pharmacy, patients are generally consulted on BMI, co-morbid conditions and concomitant medication. Only if the pharmacist or pharmacy assistant judges the patient to be eligible for non-prescription Alli®, this medicine will be dispensed. In other cases, the patient will be referred to a GP or may not be eligible for anti-obesity medication at all. Our findings show that this system of pharmacy-only retailing effectively channels patients to the appropriate anti-obesity medication.

Several studies have investigated the use of dietary supplements [12-14]. In one of these studies, self-reported diseases were analysed, and the authors found that 19% of stimulant users in the survey said they had been told they had high blood pressure, heart disease, or diabetes. This proportion of patients is considerably lower than reported in our study, which might be explained by the fact that the dietary supplements that were studied by Blanck et al. were generally available. Thus, they may be obtained outside the health care setting by relatively healthy patients. The present study shows that the formulation that can be obtained without prescription was used by patients that were relatively healthier than users of the formulation that was prescribed by a physician, although these patients were more diseased compared to the general Dutch population or users of dietary supplements as described above. The fact that Alli® can only be obtained in pharmacies in the Netherlands will have contributed to this observation.

In the EU, benefit-risk evaluations are performed for the majority of the products on the level of the active ingredient, although benefit-risk analyses may also be conducted according to the indication. As an extreme example, sildenafil is indicated for treatment of erectile dysfunction (Viagra®) [15] but also for pulmonary arterial hypertension (Revatio®) [16], which is

a rare disease. Assessment of benefits and risks is clearly different for these two indications. In addition to performing benefit-risk assessments according to indications, differences in patient populations using the same active ingredient but in different strengths or with different legal prescription status, should also be taken into account. This requires that benefit-risk profiles of medicines should not only be determined by the data from (pre-) clinical research, but also from post-marketing observational studies because the patient populations between studies conducted in controlled environments differ substantially from the patients using these medicines in daily practice [17-19]. Consequently, information on the wider context in which medicines are being used is increasingly important.

The dose of Alli® is half of the dose of Xenical® and consequently it was expected that the effects on BMI would be less for Alli® than for Xenical®. Nevertheless, the difference in BMI was only borderline significant and of limited clinical relevance, and the efficacy of the two products can thus be considered comparable. As stated before, the adverse drug reactions are a direct consequence of the working mechanism of orlistat and it is therefore assumed that these are dose-dependent [7]. However, in this study, no differences were found regarding the self-reported occurrence of adverse drug reactions. This may be explained by the large difference in the time since first use, which was much longer for Xenical® than for Alli®. This may have affected the results, because the patients using Xenical® could have more difficulties with remembering the adverse drug reactions that occurred following start. It may also have caused that the patients who benefitted most and experienced less adverse drug reactions are still using Xenical®, while the patients with less treatment effects and more adverse drug reactions, discontinued therapy with Xenical®. Nevertheless, this does not explain the finding that the efficacy of both products is only slightly different.

Strength of this study is the use of both information from telephone interviews and the prescription data extracted from the pharmacy records. The telephone interviews provided information that was not available in pharmacy data, such as for example, data on disease history, smoking status, and experience of adverse drug reactions. Furthermore, patients were asked to provide their body length and weight at the moment of start and stop (or in cases the patient was still on treatment, the weight at the interview date) of orlistat. This type of information is poorly available in other databases used for observational research. However, it should be noted that these data are self-reported and were collected retrospectively, which might have introduced bias to the study [20]. In addition to the telephone interviews, which provided us with self-reported patient data, we used the pharmacy records to analyse the use of medication. As all pharmacies in the Netherlands have automated dispensing records available and because the majority of patients are registered with only one community pharmacy (independent of prescriber), these records are virtually complete [10]. When comparing the data on medications that were dispensed, with the self-reported disease history, we found no large differences. Therefore, the data that were self-reported by the patients were considered reliable.

A limitation of the study is that the number of patients that participated in the study was relatively low. Therefore, we could not establish statistically significant differences between the two orlistat formulations in some cases where percentages seemed to differ between the two groups. Nevertheless, as far as we were aware, no other studies have been published comparing users of the two dosage forms and thus we believe that this study is a first step in further analysing these two patient groups.

In conclusion, we found that patients using the prescription-only formulation of orlistat were sicker than users of the pharmacy-only formulation, whereas their BMI was comparable at initiation of the medication. This information is important for an adequate assessment of the benefit-risk profile from a regulatory point of view and illustrates that information from observational studies is valuable for benefit-risk evaluations.

REFERENCES

1. Williams G. Withdrawal of sibutramine in Europe. BMJ 2010; 340: c824.
2. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Xenical® - Initial marketing authorisation details. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000154/WC500058424.pdf (last accessed: 11 November 2010).
3. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Alli® - Initial marketing authorisation documents. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000854/WC500024117.pdf (last accessed: 11 November 2010).
4. Committee for Medicinal Products for Human Use (CHMP). European Medicines Agency. European Medicines Agency recommends first switch from prescription-only to non-prescription for a centrally authorised medicine. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500014828.pdf (last accessed: 12 November 2010).
5. Li M, Cheung BM. Pharmacotherapy for obesity. Br J Clin Pharmacol 2009; 68 (6): 804-810.
6. Perrio MJ, Wilton LV, Shakir SA. The safety profiles of orlistat and sibutramine: results of prescription-event monitoring studies in England. Obesity (Silver Spring) 2007; 15 (11): 2712-2722.
7. Summary of Product Characteristics: Xenical®. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000154/human_med_001158.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125 (last accessed: 19 December 2010).
8. Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Leufkens HG, Egberts AC, Sturkenboom MC. Cardiovascular and psychiatric risk profile and patterns of use in patients starting anti-obesity drugs. Pharmacoepidemiol Drug Saf 2009; 18 (7): 631-638.
9. Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Leufkens HG, Egberts AC. Psychiatric and cardiovascular co-morbidities in patients with diabetes mellitus starting anti-obesity drug Obesity (Silver Spring) 2008; 16 (10): 2331-2335.
10. Buurma H, Bouvy ML, De Smet PA, Floor-Schreudering A, Leufkens HG, Egberts AC. Prevalence and determinants of pharmacy shopping behaviour. J Clin Pharm Ther 2008; 33 (1): 17-23.
11. Milder IE, Klungel OH, Mantel-Teeuwisse AK, Verschuren WM, Bemelmans WJ. Relation between body mass index, physical inactivity and use of prescription drugs: the Doetinchem Cohort Study. Int J Obes (Lond) 2010; 34 (6): 1060-1069.
12. Blanck HM, Serdula MK, Gillespie C, Galuska DA, Sharpe PA, Conway JM et al. Use of nonprescription dietary supplements for weight loss is common among Americans. J Am Diet Assoc 2007; 107 (3): 441-447.
13. Blanck HM, Khan LK, Serdula MK. Use of nonprescription weight loss products: results from a multistate survey. JAMA 2001; 286 (8): 930-935.
14. Pillitteri JL, Shiffman S, Rohay JM, Harkins AM, Burton SL, Wadden TA. Use of dietary supplements for weight loss in the United States: results of a national survey. Obesity (Silver Spring) 2008; 16 (4): 790-796.
15. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Viagra® - Initial marketing authorisation details. Available at: http://www.ema.europa.eu/

docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000202/WC500049826.pdf (last accessed: 11 November 2010).

16. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Revatio® - Initial marketing authorisation details. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000638/WC500055837.pdf (last accessed: 11 November 2010).
17. Leufkens HGM, Urquhart J. Variability in patterns of drug usage. J Pharm Pharmacol 1994; 46 (Suppl 1): 433-437.
18. Tlusta E, Handoko KB, Majoie M, Egberts TC, Vlcek J, Heerdink ER. Clinical relevance of patients with epilepsy included in clinical trials. Epilepsia 2008; 49 (8): 1479-1480.
19. Wieringa NF, Vos R, van der Werf GT, van der Veen WJ, de Graeff PA. Co-morbidity of 'clinical trial' versus 'real-world' patients using cardiovascular drugs. Pharmacoepidemiol Drug Saf 2000; 9 (7): 569-579.
20. Novick G. Is there a bias against telephone interviews in qualitative research? Res Nurs Health 2008; 31 (4): 391-398.

Chapter 3

General discussion

INTRODUCTION

From the first results of the toxicity studies in animals to the reporting of adverse drug reactions when a drug is being used in daily practice; safety issues arise at different stages of drug development. Also the knowledge on the beneficial effects of drugs evolves during the drug life cycle, from efficacy tested under ideal circumstances to effectiveness in the circumstances of the daily health care practice [1].

During the last two decades, several drugs have been withdrawn from the market because their benefit risk balance changed during their life cycle. Well-known examples are Vioxx® (rofecoxib) and Avandia® (rosiglitazone), but also three anti-obesity drugs were withdrawn (Table 1) during this period. These recent cases of drug withdrawals have shown the importance of continuous benefit-risk assessment in the life cycle of medicines. Fenfluramine and dexfenfluramine were withdrawn from the market 24 years after approval. In 1997, the New England Journal of Medicine published a case series describing 24 women using fenfluramine-phentermine who were all diagnosed with heart valve abnormalities [2], which was the first report of this serious adverse drug event. Subsequently, a population-based study confirmed the association between the use of fenfluramine and dexfenfluramine and heart valve disorders, especially when these drugs were used for four months or more [3]. Following the withdrawal of these drugs from the market, a commentary was published in the Journal of the American Medical Association advocating for a continuous benefit-risk evaluation for marketed drugs [4].

The withdrawal of (dex)fenfluramine was triggered by the reporting of spontaneous cases, in the case of sibutramine the decision was based on the results of a large post-marketing randomised clinical trial, which was a requirement from the competent authorities. For sibutramine, cardiovascular adverse effects such as tachycardia and increased blood pressure were already known from the pre-approval studies, and use of sibutramine was therefore contraindicated in patients with a history of cardiovascular disease or uncontrolled hypertension. The large clinical trial called Sibutramine Cardiovascular OUtcomes Trial (SCOUT) was conducted on request of the regulatory authorities to assess the long-term effects of sibutramine such as incidence of cardiovascular outcomes in obese and overweight in high risk patients [5]. The study showed a small but statistically significant increased risk of non-fatal myocardial infarction and stroke, which finally led to the decision to withdraw sibutramine from the market [6].

The third anti-obesity drug that was withdrawn from the market was Acomplia®, containing rimonabant. The pharmacological mechanisms of action probably leading to psychiatric adverse events were already known from (pre-) clinical research. The pre-approval clinical studies excluded patients with a history of psychiatric disease, which resulted in an inadequate reflection of the patient population using these drugs after marketing. Consequently, it only became clear after registration what the magnitude of the spontaneous reporting of psychiatric adverse drug reactions was in the real world population, which tended to be more prone towards the development of psychiatric adverse drug reactions than the pre-approval

Table 1: Overview of three examples of anti-obesity drugs that have been withdrawn from the market:

	Fenfluramine-Phentermine	Rimonabant	Sibutramine
General			
Safety issue	Valvular heart disease	Psychiatric ADRs	Unbeneficial cardiac profile
Withdrawal decision based on	Spontaneous reports (case series in NEJM)	(High number of) spontaneous reports through active surveillance	One randomised clinical trial (SCOUT-study)
Predictability of safety issue	No pharmacological explanation	Risk seen in pivotal RCTs, pharmacological explanation	Hypertension and increased heart rate known ADRs. Long-term effects unknown
Available data from literature and studies			
Effect size	Rare but very serious.	RR ≈ 2, both pre- and post-marketing. Large differences in absolute numbers as a result of differences in baseline risk	RR of 1.2 enough to suspend
Patient characteristics	No history of cardiac disease in patients reporting valve problems: no increased susceptibility for ADR in patients with relevant medical history	Patients with relevant medical history (psychiatric disease) were excluded from RCTs	Due to contraindications in SPC, patients in SCOUT-trial were not eligible for treatment with sibutramine according to registered indication
Measurement of outcome	Diagnosis itself clearly made by echocardiography	Complex outcome measurement methods and definitions for diagnosis of psychiatric disease differs largely between trials	Cardiac disease was primary outcome in SCOUT-study
Post-marketing			
Use in daily clinical practice	Short-term use indicated, effect seen after long-term use	Short-term use indicated, AEs seen within short period from start	Indicated for short-term use, effects seen after long-term use in RCT
Risk minimisation measures	No risk minimisation	Risk minimization (SPC, DHPC) did not led to a decrease number of reports	SPC: contraindication for patients with cardiac disease. No additional risk minimization

ADR: adverse drug reaction; NEJM: New England Journal of Medicine; SCOUT: Sibutramine Cardiovascular OUtcomes Trial; RCT: randomised clinical trial; RR: relative risk; SPC: Summary of product characteristics; DHPC: direct health care professional communication

clinical trial population. Hence, the absolute risks of psychiatric adverse events were considerably higher post-marketing as a result of the higher baseline risk of psychiatric disease in the post-marketing setting compared to the clinical trial population, whereas the relative risk of psychiatric adverse events was approximately two for the reporting of psychiatric adverse events both before and after registration [7].

For both sibutramine and rimonabant, an increased risk of adverse events was reported in populations that were either contraindicated or excluded from the clinical trial program. Nevertheless, given the indication of both medicines, it could have been expected that the medicines would be used in these populations with both an increased baseline risk of cardiovascular and

psychiatric events. Thus, the different context in which these medicines were used in daily practice affected the benefit-risk profile negatively.

In this thesis, we focussed on the importance of the context in which medicines are being used for benefit-risk evaluations. In this general discussion, we will discuss three aspects that should be taken into account during these assessments, namely:

- Influence of patient characteristics;
- Influence of duration of use and usage patterns;
- Influence of the regulated availability of medicines.

In addition, we will discuss the position of different study designs in the life cycle of medicines and consider the implications of the studies in this thesis for both regulatory authorities and the pharmaceutical industry. Finally, we will give recommendations for future research.

TOWARDS FURTHER OPTIMALISATION OF BENEFIT-RISK ASSESSMENT

Influence of patient characteristics

The knowledge on characteristics of patients using medicines is important in the assessment of benefit-risk profiles. For psychiatry, the relevance of the differences in patients that are included in randomised clinical trials and the patients using medicines in daily practice has been described previously [8-10]. For example, Goedhard et al. assessed the comparability of patients in psychiatric long-stay wards with patients in trials investigating maintenance therapy for whom aggression is an ongoing problem. The authors concluded that only 30% of the patients seen in clinical practice would be eligible for participation in randomised controlled clinical trials [11]. Wisniewski et al. evaluated in a comparable study whether phase II clinical trials recruited representative depressed outpatients. To that aim, patients meeting entry criteria for trials were compared to patients not meeting these criteria. This study showed many differences in sociodemographic and clinical characteristics between the two groups. Patients meeting the inclusion criteria for these trials had better outcomes, e.g. they had higher rates of response (51.6% versus 39.1%) and remission (34.4% versus 24.7%). These differences persisted even after adjustments for baseline differences. The authors concluded that these differences reduce the generalisibility of clinical trial results [12].

Also in other fields of medicine, similar findings were reported. For example, Wieringa reported large differences regarding sociodemographic variables and co-morbidities for users of cardiovascular drugs. The authors concluded that in addition to the discrepancies that were found in the prevalences of co-morbidities between pre- and post-marketing populations, another important finding was that the data regarding concomitant morbidities were not reported uniformly [13, 14].

In Chapters 2.4, 2.5 and 2.6, we analysed patient characteristics of patients using anti-obesity drugs. In Chapter 2.4 we used data from the General Practice Research Database (GPRD) to

compare patients with diabetes mellitus who started to use anti-obesity drugs with patients with diabetes not starting to use these drugs, and concluded that patients using anti-obesity drugs had approximately twice more often a history of cardiovascular and psychiatric disease. This finding was confirmed in Chapter 2.5, where we present a study performed in the Integrated Primary Care Information (IPCI) database. In this study, we analysed the patient characteristics of the general Dutch population between 1995 and 2007. The study revealed that cardiovascular disease was twice as prevalent among patients starting anti-obesity drugs as compared to patients not starting to use these drugs (odds ratio (OR) 2.3 (95% confidence interval (CI) 2.0-2.5)). For psychiatric disease, the odds ratio was even 2.5 (95% CI 2.2-2.9) [15]. This high baseline risk might have played a role in the increased reporting of psychiatric adverse drug reactions for rimonabant that was seen in the post-marketing setting [7]. To investigate general health care utilisation and especially the dynamics of health care utilisation that precede the start of anti-obesity drugs, we conducted a second study in the IPCI database (Chapter 2.6). This information was used to identify patterns of health care utilisation that may point at an early stage at the chance that an anti-obesity drug is started, thereby increasing the knowledge on the context in which this type of medicines is being used, which is of importance for assessment of benefit-risk profiles. The study showed that there is an increased health care utilisation in patients starting anti-obesity drugs compared to patients not starting these drugs, and differences increase gradually over the three-year period preceding the start of these drugs.

In Chapter 2.1, we analysed whether patients with a psychiatric history were included in randomised clinical trials (pre- and post-registration) of bupropion, rimonabant, and varenicline. We found that in the vast majority (89%) of the randomised clinical trials investigating these medicines, patients with psychiatric disease were excluded. In addition, the occurrence of psychiatric adverse drug reactions was significantly higher in absolute terms for trials including patients with psychiatric disease as compared to those excluding patients with psychiatric disease (resulting in an increased number needed to harm (NNH)), but when looking at the relative risks, the risk for psychiatric adverse drug reactions was comparable for trials in- and excluding patients with psychiatric disease. It is acknowledged that the pivotal randomised clinical trials are designed to show the efficacy of a drug, rather than providing information on the effectiveness of the drug, and therefore the choice of a "clean" population with as less as possible co-morbidities is understandable. However, as the close relation between tobacco dependence and obesity on the one hand and mental illness on the other hand is already known for years [16, 17], extrapolation of the results of these trials to the setting outside clinical trials is hampered and this makes it difficult to anticipate on the safety of a certain drug in daily clinical practice.

In summary, the large differences between the population using medicines in clinical trial populations and in daily practice affect the benefit-risk profile. By including healthier and younger patients in the clinical trial program, it is likely that the beneficial effects of these medicines will be smaller in daily practice (as described before for antidepressants

and cardiovascular drugs). In addition, the inclusion of a healthier population will lead to an increased risk of developing adverse drug reactions in daily practice compared to the clinical trial setting (as described before for the anti-obesity drugs). Both factors negatively affect the benefit-risk profile either by decreasing beneficial effects or by increasing adverse effects.

Influence of duration of use and usage patterns

For most drugs, it takes some time for beneficial effects to develop. In the mean time, patients may experience adverse drugs reactions before recovery from symptoms or development of these positive effects [18]. This is also the case for anti-obesity drugs. These medicines are indicated for weight loss, which in the long term may lead to a reduction of the risk of co-morbidities such as cardiovascular disease [19, 20] and certain types of cancer [21, 22]. Therefore, it is important to reduce weight structurally, and not only for a short period of time. There is no evidence that the short-term use of anti-obesity drugs will be helpful in reaching weight loss for a prolonged period. On the other hand, anti-obesity drugs are indicated for only a relatively short period of use, while effects on long term outcomes have never been proved. The clinical trials that have been conducted for orlistat, sibutramine and rimonabant as part of the registration dossier had a maximum duration of 2 years [23]. In Chapter 2.6, we found that the duration of use of anti-obesity drugs in clinical practice was even shorter; approximately three quarters of the patients stopped treatment with anti-obesity drugs within 90 days. This short duration of use will decrease the beneficial effects of anti-obesity drugs thereby influencing the benefit-risk profile in a negative way. To achieve a long-lasting decrease in weight leading to a reduction of the morbidity and mortality associated with excess weight in general, persistent use of anti-obesity drugs is necessary to obtain full benefits. Several studies have been conducted analysing different interventions aimed at improving treatment persistence, and although the results were not uniform, a combination of different strategies consisting of providing more detailed information, behavioural therapies, manual follow-up, and supportive care will be necessary for all anti-obesity drugs to cause maintained weight loss [24-27].

In Chapter 2.7, we specifically assessed the discontinuation of rimonabant, using the methodology of Modified Prescription-Event-Monitoring. This study showed that more than 70% of the patients stopped treatment with rimonabant (median observation time 323 days, interquartile range: 279-371 days). In addition, younger age, female gender, previous use of anti-obesity drugs, and a history of psychiatric disease were identified as important patient characteristics that were related to discontinuation, regardless of the reason for stopping. Hence, patients discontinued treatment because before the beneficial effects could develop, thereby negatively affecting the benefit-risk profile of rimonabant. This type of information can be used for the identification and characterisation of the early discontinuers and improvement of adherence to therapy, thus ultimately ensuring an optimal benefit-risk balance in daily practice.

The association between duration of use of (dex)fenfluramine and the development of valvular heart disease illustrates the effect of usage patterns on the benefit-risk profile. The observational study by Jick et al. showed that these problems were more pronounced when patients used dexfenfluramine and fenfluramine for four months or more [3]. For sibutramine, no data were available on the effects beyond one year of treatment and sibutramine was therefore indicated for short-term use. At the time of licensing, the Sibutramine Cardiovascular Outcomes Trial (SCOUT) was initiated to evaluate the long-term effects of sibutramine treatment on cardiovascular events among patients with pre-existing cardiovascular conditions. This study showed an increased risk of non-fatal myocardial infarction and non-fatal stroke after mean treatment duration of 3.4 years [5]. After long-term treatment with sibutramine, the benefit-risk balance turned out to be negative, while it was initially evaluated as positive for short-term therapy. These examples of (dex)fenfluramine and sibutramine also show the importance of the duration of use on the benefit-risk profile of these drugs.

Influence of the regulated availability of medicines' use

The regulated availability of medicines can also influence the benefit risk balance. In general, drugs can be assigned a prescription or non-prescription status. In the European Union (EU), orlistat was the first centrally authorised drug that was assigned a non-prescription status. Since 1998, orlistat 120 mg was registered in the EU as a prescription-only medicine (Xenical®) [28], but since 2007 also a lower dose of orlistat is available, 60 mg (Alli®) [29, 30]. In Chapter 2.8, we assessed the characteristics and treatment outcomes of users of Alli® and Xenical®. We found that patients using either orlistat formulation were comparable for self-reported co-morbidities, and did not differ regarding effectiveness in terms of change in body mass index (BMI), which was based on self-reported weight and length, and number of reported adverse drug reactions. The patients using orlistat were also compared to the general Dutch population to assess whether there were differences between the general population and users of orlistat. However, all medicines were more frequently used by users of both orlistat formulations compared to the usage in the general Dutch population, except anti-thrombotic agents and antibacterials for systemic use. This implies that patients using the prescription-only formulation of orlistat were sicker than users of the pharmacy-only formulation, whereas their BMI was comparable at initiation of the medication. This information is important for an adequate assessment of the benefit-risk profile from a regulatory point of view and illustrates that information from observational studies is valuable for benefit-risk evaluations.

In addition to the legal prescription status, the licensed indication for medications can affect the use and the place of drugs in the therapeutic spectrum, e.g. the setting in which medicines are used. Confounding by indication and channelling of drug treatment are factors affecting the outcomes of medicine use. For example, most drugs for the treatment of type 2 diabetes mellitus are initially indicated as add-on therapy in case monotherapy with metformin or a sulfonylurea derivative is not sufficient to adequately control diabetes [31]. Thus, those drugs

are channelled towards patients with more difficult-to-treat diabetes, who are in general more severely ill and suffer from more co-morbidities. The baseline risk for cardiovascular disease for example is higher in these patients compared to the patients who are treated with metformin monotherapy [32, 33]. This potential effect of channelling is an important factor to consider when assessing the adverse drug reactions for antidiabetic drugs. In Chapter 2.3, we used a before-after study design to diminish the effect of channelling of these drugs towards the more severely diseased patients on the relationship between DPP-4 inhibitors and infections. Although debated by some [34, 35], patients with more severe diabetes may have an increased baseline risk for infections [36-38]. In this study, we analysed the risk of infections by comparing treatment courses for antibiotic, antimycotic and antifungal drugs for systemic use as a measure of infection risk between patients initiating DPP-4 inhibitors and patients starting with other classes of antidiabetic drugs. A significant increase in the number of treatment episodes for bacterial infections in patients starting DPP-4 inhibitors (relative risk 1.58 (95% CI 1.07-2.34), but not in starters of any other antidiabetic drug was found.

Similar findings were reported in the field of epilepsy. Schiller et al. reported on the response to anti-epileptic drugs [39]. For these drugs, resistance is a well-known but difficult-to-handle problem. This study showed that the number of previously used anti-epileptic drugs that did lead to unsatisfactory treatment results, is a prognostic factor for reduced seizure-free rates and decreased rates of patients with a significant reduction in seizure frequency [39], thus channelling of new anti-epileptic drugs towards these non-responders. Consequently, the benefit-risk profile of these medicines will be less positive than when these medicines are widely being used by less difficult-to-treat patients. In his thesis, Knoester described the case of lamotrigine, for which the use was also restricted to severely ill patients who did not adequately respond to other therapies. He showed that the use of lamotrigine in daily practice shifted from this selected patient population towards use as a first-line therapy. The effectiveness of lamotrigine thereby increased, and consequently the benefit risk balance of lamotrigine changed positively [40].

Furthermore, the use of medicines is also affected by the reimbursement status. In Europe, decisions on the financing of health care systems and the reimbursement of medicines falls within the competence of each national authority. Stolk et al. examined the impact of limiting reimbursement for oral contraceptives on utilisation patterns. The study showed that the discontinuation rate increased in the year following the restricting, and that this differed between age groups [41]. Although not evaluated in this study, it is likely that patients with a lower income are more likely to discontinue treatment, and lower socioeconomic status has been linked to a higher burden of disease [42, 43]. Therefore, the reimbursement status is expected to influence the patient population in which medicines are being used, and as described before this will affect the benefit-risk profile.

ADDED VALUE OF DIFFERENT STUDY SOURCES IN THE LIFE CYCLE OF MEDICINES

Randomised clinical trials are still considered as the gold standard in drug research [44]. However, this study design also has several limitations. Randomised clinical trials are a good way to study drug effects in a (highly) selected patient population and under (highly) controlled circumstances [45]. The patients in trial are in general younger and healthier than those who will eventually use the medicine in daily practice as described above. Frequently occurring adverse drug reactions may be detected in these trials, although more adverse events that are rare or occur late are difficult to detect, due to the relatively small number of participants and the limited follow-up of patients [46]. Treatment adherence in clinical trials is generally high, and may not reflect the situation in daily practice [47, 48].

To understand the full spectrum of the effectiveness and safety of drugs, especially in daily practice, information from other sources and different study designs is necessary. Case reports and case series are often the first step in the identification of emerging new safety signals. A well-known example is the thalidomide-disaster, which was first described as a case report in the New England Journal of Medicine [49].

Spontaneous reporting systems have proven their value in the evaluation of safety signals [50]. In Chapter 2.2, this is illustrated with a study using the WHO Vigibase to investigate the risk of infections in relation to the use of DPP-4 inhibitors. Based on the mechanism of action of the DPP-4 inhibitors, immunological effects could be expected. Consequently, the pivotal clinical trials provided a first signal regarding an increased risk of infections. The results of this disproportionality analysis indicated an increased reporting of infections (reporting odds ratio (ROR) 2.3 (95% CI 1.9-2.7)). In particular upper respiratory tract infections (ROR 12.3 (95% CI 8.6-17.5)) for users of DPP-4 inhibitors compared to users of other antidiabetic drugs.

Additionally, a before-after study was conducted to evaluate the baseline risk of infections for patients initiating DPP-4 inhibitors and to assess the impact of these medicines on the number of infection-episodes (Chapter 2.3). This study indeed confirmed the potential relation between DPP-4 inhibitors and infections. Because clinical trials are in general aimed at studying the intended drug effects, and are not the most appropriate study design to evaluate the safety of drugs [51], the type of infections and especially the implications thereof in daily practice remains unknown. In Chapter 2.2 and 2.3, we were able to further evaluate and characterise this safety signal and thereby showed the benefit of spontaneous reporting systems and observational studies in addition to randomised clinical trials. Thus to study the context of medicine use, only observational studies can be used. Depending on the research question, available time and resources, different study designs can be used (e.g. case-control studies, cohort studies).

An issue that is often neglected, regardless of the type of studies, is the uniform reporting of outcomes. Pitrou et al. showed that large heterogeneity and variability in the reporting of safety related outcomes in clinical trials exist [52]. The same was found for the reporting of

outcomes in observational studies, which is often inconsistent [53, 54]. In Chapter 2.1 of this thesis, we assessed whether patients with a psychiatric history were included in randomised clinical trials (pre- and post-registration) of bupropion, rimonabant, and varenicline, and how this inclusion influenced the reported absolute and relative incidence estimates of psychiatric adverse drug reactions. Because the publications of the clinical trials that were included in this study did not contain all information that was needed for this study, and because of the large differences in presentation of safety information in the publications, use of the full clinical study reports was necessary. Assessment of psychiatric disease and psychiatric adverse events in randomised clinical trials may be even more complicated because of the use of different methods that are being used to measure and report psychiatric disease. Further harmonisation of both standardised measurement scales and the methods for the collection of adverse drug reactions in general will be helpful. The development of guidelines for the conduct and presentation of studies such as CONSORT (for randomised clinical trials) [55], PRISMA (meta-analysis and systemic reviews) [56] and STROBE (observational studies) [57] is supportive in this, although a more stringent approach would be helpful, also focussing more on the conduct of the studies.

LESSONS LEARNED FOR REGULATORY AUTHORITIES, PHARMACEUTICAL INDUSTRY AND RESEARCH INSTITUTIONS

Adequate information on the context is necessary for further improvements of benefit-risk assessments, especially given the trend towards a life cycle approach with continuous benefit-risk evaluations instead of conducting a single benefit-risk assessment at a certain (fixed) point in time, for example at the moment of registration. With the increasing call for earlier market access to medicines, new strategies are needed [58-61]. The collection of knowledge of new medicines should be performed in a more structured and step-wise way, for which the use of conditional approval is often suggested. This will mean that medicines are licensed with a higher level of uncertainty for both the efficacy and the safety of the product. After licensing, additional data are requested to reduce the uncertainty and to get a (more) complete picture of both the beneficial and adverse effects of the drugs.

A second strategy is to put more emphasis on the risk management plans. Risk Management Plans (RMPs) are an obligatory part of the registration dossier in the EU since 2005. They aim at identification of safety issues based on molecular structures, class effects, and on the results of the drug development program, in order to monitor, review and further characterise safety issues in the post-marketing setting [62]. RMPs are currently aimed at the identification and minimisation of risks related to medicine use. However, to get a complete picture of the effectiveness and safety of a medicine, thus to collect all information that is needed for a continuous benefit-risk evaluation, we suggest to broaden the purpose of RMPs by including information

on the beneficial effects of medicines. By doing that, a "benefit-risk management plan" will become a dynamic document, that can be used for continuous benefit-risk evaluation.

In Risk Management Plans, the information obtained from the (mainly pre-approval) randomised clinical trials is complemented by information from other data sources and there is an increase of post-marketing research activities. Increasing interaction with research institutions is therefore necessary, because of the availability of both experienced researchers and availability of data. The "old" model of regulatory authorities working together with pharmaceutical companies is shifting towards a triangle approach with researchers from academia working together with both regulatory authorities and the pharmaceutical industry.

Starting already in the pre-marketing phase of drug development, and continuing post-marketing, the monitoring of patient populations and patterns of medicine use in daily practice should become more important. Differences between clinical practice and the clinical trials should be identified by comparing populations and usage patterns in these two different settings. Consequently, the impact of these differences on the benefit-risk profile should be evaluated and if necessary additional measures should be taken to either increase the benefits or minimise the risks related to the medicine use.

New European legislation for pharmacovigilance will be put into force in 2012, and this will be in line with the issues addressed before. That legislation is aiming at increasing the transparency of the regulatory process and pharmacovigilance, which was also the main criticism of Frau et al. who evaluated the Risk Management Plans as they are currently used [63]. In addition, the new legislation aims at further establishment of the life cycle approach of drug evaluation. It is expected that the number of post-marketing studies will increase, including both post-marketing randomised clinical trials and observational research. Indeed, Risk Management Plans will become more important as in providing an adequate and continuously updated overview of all knowledge and knowledge gaps regarding a single product.

DIRECTIONS FOR FUTURE RESEARCH

With the increasing importance of knowledge on the context in which medicines are being used, studies investigating the patient populations, usage patterns and influence of the system in which medicines are being used, should become more important. A close collaboration between the regulatory authorities, pharmaceutical industry and academia or research associations is therefore necessary, because this type of data is often collected in large databases that are owned by academia and independent research associations.

A second important field of research is to improve benefit-risk evaluations. Currently, only few studies have attempted to measure the benefit-risk ratio of medicines in a more objective way [64, 65]. This is a new field of science where development of methodology is an impor-

tant need. The outcomes of this research are important for both regulatory authorities and pharmaceutical industry.

A third important point concerns the increasing interest for risk minimisation activities. These are part of the Risk Management Plans and are aimed at decreasing the risk of medicine use. Risk minimisation activities encompass both "routine" risk minimisation, e.g. strict indications, warnings and contraindications in the Summary of Product Characteristics, but also the so-called "additional" risk minimisation activities, involving the use of educational material for healthcare professionals and/or patients, and specific training programmes for health care professionals. Under the new EU legislation, the effects of the risk minimisation activities will be monitored more closely. The outcomes of risk minimisation activities will then be measured and assessed. This opens up a new field of research, combining traditional epidemiology with the assessment of communication strategies that are being used here.

A fourth point is already been addressed in many publications, and concerns the issue of adequate clinical trial design. The fact that this is still an important issue was shown in Chapter 2.1. It is acknowledged that the pivotal RCTs are designed to show the efficacy of a drug, rather than providing information on the effectiveness of the drug, and therefore the choice of a "clean" population with as less as possible co-morbidities is understandable. However, for the extrapolation of the results of such trials and to anticipate the safety of a certain drug in the real world, these trials are of limited use. Regulatory authorities, pharmaceutical industry and researchers from academia should be aware of the implications of using relatively clean and healthy patient populations. We advocate that in addition to the first "proof of concept" trials, additional studies in controlled clinical settings should be performed [1]. These studies with less stringent in- and exclusion criteria should include a more realistic study population that more adequately reflects the real users of a drug.

FINAL CONCLUSIONS

For an adequate benefit-risk evaluation of a medicinal product, information on the complete context in which medicines are being used. This complies of extensive information on the patient population in which medicines are being used, usage patterns including the duration of use, and the effect of the regulated availability of medicines. In addition, the need for objective and transparent methods for the evaluation of these benefits and risks is evident. Thus, to get a (more) complete picture of both the beneficial and adverse effects of the drugs, information from randomised clinical trials need to be complemented with information from spontaneous reporting systems and observational studies. Risk Management Plans are a good approach to continuously evaluating the risks related to medicines use, but the use of this regulatory tool may be broadened thereby including the evaluation of effectiveness of medicines. With the trend towards a life cycle approach including continuous benefit-risk evaluations instead of conducting a single benefit-risk assessment at a certain (fixed) point in time, information from different study designs is needed.

REFERENCES

1. Eichler HG, Bloechl-Daum B, Abadie E, Barnett D, Konig F, Pearson S. Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers. Nat Rev Drug Discov 2010; 9 (4): 277-291.
2. Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 1997; 337 (9): 581-588.
3. Jick H, Vasilakis C, Weinrauch LA, Meier CR, Jick SS, Derby LE. A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. N Engl J Med 1998; 339 (11): 719-724.
4. Moore TJ, Psaty BM, Furberg CD. Time to act on drug safety. JAMA 1998; 279 (19): 1571-1573.
5. James WPT, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med 2010; 363 (10): 905-917.
6. Committee for Medicinal Products for Human Use (CHMP). European Medicines Agency recommends suspension of marketing authorisations for sibutramine. Available at: http://www.ema.europa.eu/pdfs/human/referralsibutramine/3940810en.pdf (last accessed: 09 February 2010).
7. Rumsfeld JS, Nallamothu BK. The hope and fear of rimonabant. JAMA 2008; 299 (13): 1601-1602.
8. Tlusta E, Handoko KB, Majoie M, Egberts TC, Vlcek J, Heerdink ER. Clinical relevance of patients with epilepsy included in clinical trials. Epilepsia 2008; 49 (8): 1479-1480.
9. Zimmerman M, Chelminski I, Posternak MA. Generalizability of antidepressant efficacy trials: differences between depressed psychiatric outpatients who would or would not qualify for an efficacy trial. Am J Psychiatry 2005; 162 (7): 1370-1372.
10. Knoester PD, Belitser SV, Deckers CL, Keyser A, Renier WO, Egberts AC, et al. Patterns of lamotrigine use in daily clinical practice during the first 5 years after introduction in the Netherlands. J Clin Pharm Ther 2004; 29 (2): 131-138.
11. Goedhard LE, Stolker JJ, Nijman HL, Egberts TC, Heerdink ER. Trials assessing pharmacotherapeutic management of aggression in psychiatric patients: comparability with clinical practice. Pharmacopsychiatry 2010; 43 (6): 205-209.
12. Wisniewski SR, Rush AJ, Nierenberg AA, Gaynes BN, Warden D, Luther JF, et al. Can phase III trial results of antidepressant medications be generalifzed to clinical practice? A STAR*D report. Am J Psychiatry 2009; 166 (5): 599-607.
13. Wieringa NF, Vos R, van der Werf GT, van der Veen WJ, de Graeff PA. Co-morbidity of 'clinical trial' versus 'real-world' patients using cardiovascular drugs. Pharmacoepidemiol Drug Saf 2000; 9 (7): 569-579.
14. Wieringa NF, de Graeff PA, van der Werf GT, Vos R. Cardiovascular drugs: discrepancies in demographics between pre- and post-registration use. Eur J Clin Pharmacol 1999; 55 (7): 537-544.
15. Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Leufkens HG, Egberts AC, Sturkenboom MC. Cardiovascular and psychiatric risk profile and patterns of use in patients starting anti-obesity drugs. Pharmacoepidemiol Drug Saf 2009; 18 (7): 631-638.
16. John U, Meyer C, Rumpf HJ, Hapke U. Smoking, nicotine dependence and psychiatric comorbidity - a population-based study including smoking cessation after three years. Drug Alcohol Depend 2004; 76 (3): 287-295.
17. Sarwer DB, Wadden TA, Fabricatore AN. Psychosocial and behavioral aspects of bariatric surgery. Obes Res 2005; 13 (4): 639-648.

18. Hansen HV, Kessing LV. Adherence to antidepressant treatment. Expert Rev Neurother 2007; 7 (1): 57-62.

19. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE, Hong CP, et al. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. Arch Intern Med 2000; 160 (14): 2117-2128.

20. Rexrode KM, Buring JE, Manson JE. Abdominal and total adiposity and risk of coronary heart disease in men. Int J Obes Relat Metab Disord 2001; 25 (7): 1047-1056.

21. McMillan DC, Sattar N, Lean M, McArdle CS. Obesity and cancer. BMJ 2006; 333 (7578): 1109-1111.

22. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. JAMA 2007; 298 (17): 2028-2037.

23. Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for obesity and overweight. Cochrane Database Syst Rev 2004; (3): CD004094.

24. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Effectiveness of interventions by community pharmacists to improve patient adherence to chronic medication: a systematic review. Ann Pharmacother 2005; 39 (2): 319-328.

25. Nietert PJ, Tilley BC, Zhao W, Edwards PF, Wessell AM, Mauldin PD, et al. Two pharmacy interventions to improve refill persistence for chronic disease medications: a randomized, controlled trial. Med Care 2009; 47 (1): 32-40.

26. Machado M, Bajcar J, Guzzo GC, Einarson TR. Sensitivity of patient outcomes to pharmacist interventions. Part I: systematic review and meta-analysis in diabetes management. Ann Pharmacother 2007; 41 (10): 1569-1582.

27. Machado M, Bajcar J, Guzzo GC, Einarson TR. Sensitivity of patient outcomes to pharmacist interventions. Part II: Systematic review and meta-analysis in hypertension management. Ann Pharmacother 2007; 41 (11): 1770-1781.

28. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Xenical® - Initial marketing authorisation details. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000154/WC500058424.pdf (last accessed: 11 November 2010).

29. Committee for Medicinal Products for Human Use (CHMP). European Public Assessment Report (EPAR) for Alli® - Initial marketing authorisation documents. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000854/WC500024117.pdf (last accessed: 11 November 2010).

30. Committee for Medicinal Products for Human Use (CHMP). European Medicines Agency recommends first switch from prescription-only to non-prescription for a centrally authorised medicine. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500014828.pdf (last accessed: 12 December 2010).

31. Nederlands Huisartsen Genootschap (NHG). Diabetes mellitus type 2 (M01). 2006. Available at: http://nhg.artsennet.nl/kenniscentrum/k_richtlijnen/k_nhgstandaarden/Samenvattingskaartje-NHGStandaard/M01_svk.htm (last accessed: 30 June 2010).

32. Zoungas S, Patel A. Cardiovascular outcomes in type 2 diabetes: the impact of preventative therapies. Ann N Y Acad Sci 2010; 1212 (1): 29-40.

33. Patel A, Joshi R, de Galan B. Trials of cardiovascular risk factor management in type 2 diabetes. Curr Opin Cardiol 2009; 24 (4): 288-294.

34. Rayfield EJ, Ault MJ, Keusch GT, Brothers MJ, Nechemias C, Smith H. Infection and diabetes: the case for glucose control. Am J Med 1982; 72 (3): 439-450.

35. Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. N Engl J Med 1999; 341 (25): 1906-1912.

36. Duncan BB, Schmidt MI. The epidemiology of low-grade chronic systemic inflammation and type 2 diabetes. Diabetes Technol Ther 2006; 8 (1): 7-17.

37. Alexandraki K, Piperi C, Kalofoutis C, Singh J, Alaveras A, Kalofoutis A. Inflammatory process in type 2 diabetes: The role of cytokines. Ann N Y Acad Sci 2006; 1084: 89-117.

38. Muller LM, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AI, et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis 2005; 41 (3): 281-288.

39. Schiller Y, Najjar Y. Quantifying the response to antiepileptic drugs: effect of past treatment history. Neurology 2008; 70 (1): 54-65.

40. Knoester PD. Assessment of the value of lamotrigine in daily practice [dissertation]. Nijmegen: Nijmegen Medical Centre; 2005.

41. Stolk P, Schneeweiss S, Leufkens HGM, Heerdink ER. Impact analysis of the discontinuation of reimbursement: the case of oral contraceptives. Contraception 2008; 78 (5): 399-404.

42. Fiscella K, Tancredi D. Socioeconomic status and coronary heart disease risk prediction. JAMA 2008; 300 (22): 2666-2668.

43. Mackenbach JP, Stirbu I, Roskam AJ, Schaap MM, Menvielle G, Leinsalu M, et al. Socioeconomic inequalities in health in 22 European countries. N Engl J Med 2008; 358 (23): 2468-2481.

44. Kaul S, Diamond GA. Trial and error. How to avoid commonly encountered limitations of published clinical trials. J Am Coll Cardiol 2010; 55 (5): 415-427.

45. Martin K, Begaud B, Latry P, Miremont-Salame G, Fourrier A, Moore N. Differences between clinical trials and postmarketing use. Br J Clin Pharmacol 2004; 57 (1): 86-92.

46. Vandenbroucke JP, Psaty BM. Benefits and risks of drug treatments: how to combine the best evidence on benefits with the best data about adverse effects. JAMA 2008; 300 (20): 2417-2419.

47. Andrade SE, Walker AM, Gottlieb LK, Hollenberg NK, Testa MA, Saperia GM, et al. Discontinuation of antihyperlipidemic drugs--do rates reported in clinical trials reflect rates in primary care settings? N Engl J Med 1995; 332 (17): 1125-1131.

48. Cardinal H, Monfared AA, Dorais M, LeLorier J. A comparison between persistence to therapy in ALLHAT and in everyday clinical practice: a generalizability issue. Can J Cardiol 2004; 20 (4): 417-421.

49. McBride WG. Thalidomide and congenital abnormalities. Lancet 1961; 278 (7216): 1358.

50. Stahl M, Edwards IR, Bowring G, Kiuru A, Lindquist M. Assessing the impact of drug safety signals from the WHO database presented in ‚SIGNAL': results from a questionnaire of National pharmacovigilance Centres. Drug Saf 2003; 26 (10): 721-727.

51. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. PLoS Med 2008; 5 (3): e67.

52. Pitrou I, Boutron I, Ahmad N, Ravaud P. Reporting of safety results in published reports of randomized controlled trials. Arch Intern Med 2009; 169 (19): 1756-1761.

53. Pocock SJ, Collier TJ, Dandreo KJ, de Stavola BL, Goldman MB, Kalish LA, et al. Issues in the reporting of epidemiological studies: a survey of recent practice. BMJ 2004; 329 (7471): 883.

54. Groenwold RH, Van Deursen AM, Hoes AW, Hak E. Poor quality of reporting confounding bias in observational intervention studies: a systematic review. Ann Epidemiol 2008; 18 (10): 746-751.

55. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010; 152 (11): 726-732.

56. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339: b2700.

57. Von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007; 370 (9596): 1453-1457.

58. Boon WP, Moors EH, Meijer A, Schellekens H. Conditional approval and approval under exceptional circumstances as regulatory instruments for stimulating responsible drug innovation in Europe. Clin Pharmacol Ther 2010; 88 (6): 848-853.

59. Bjerrum OJ. New safe medicines faster: A proposal for a key action within the European union's 6th framework programme. Pharmacol Toxicol 2000; 86 (Suppl 1): 23-26.

60. Rawson NS, West R, Appel WC. Could conditional release of new drugs provide the information required to study drug effectiveness? - A discussion paper. Can J Clin Pharmacol 2000; 7 (4): 185-190.

61. Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. Nat Rev Drug Discov 2008; 7 (10): 818-826.

62. European Commission. Volume 9A of the rules governing medicinal products in the European Union: guideline on pharmacovigilance for medicinal products for human use. Available at: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9a_09-2008.pdf (last accessed: 23 August 2010).

63. Frau S, Font Pous M, Luppino MR, Conforti A. Risk Management Plans: are they a tool for improving drug safety? Eur J Clin Pharmacol 2010; 66 (8): 785-790.

64. Van Staa TP, Smeeth L, Persson I, Parkinson J, Leufkens HG. What is the harm-benefit ratio of Cox-2 inhibitors? Int J Epidemiol 2008; 37 (2): 405-413.

65. Galfrascoli E, Piva S, Cinquini M, Rossi A, La Verde N, Bramati A, et al. Risk/benefit profile of bevacizumab in metastatic colon cancer: A systematic review and meta-analysis. Dig Liver Dis 2010; E-published ahead of print.

Chapter 4

Summary

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SUMMARY

The World Health Organization defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems. In the introduction of this thesis (Chapter 1) we describe the shift in the way pharmacovigilance is approached. Starting in the 1960s, the area was "molecule driven", implying that the detection and interpretation of adverse outcomes was mainly based on the molecular characteristics of a drug. More recently, the role of the context in which a medicine is being used has been recognised as an important factor for pharmacovigilance. This "landscaping" of drug use is also affecting regulatory decision-making.

Disease severity and co-morbidities may modulate the vulnerability for the development of adverse drug reactions, especially when disease, outcome, and adverse drug reaction are closely related. This is especially true for patients with obesity and/or diabetes mellitus, because both conditions are risk factors for cardiovascular disease and associated with multiple co-morbidities (e.g. cancer, arthritis, and depression). In this thesis, we therefore use these diseases to illustrate the influence of the context of medicine use on the benefit-risk balance and the process of regulatory decision-making.

The objective of this thesis is to unravel how the context in which a medicine is used adds to the assessment of the benefit-risk profile, and to gain more insight in the value of this information for both drug development and regulatory decision-making. This medicines' use context (patient characteristics, patterns of drug use and the regulated availability of medicines) is studied for the two disease areas that are intertwined and both involve patients with multiple co-morbidities, namely diabetes mellitus and obesity.

Chapter 2 contains eight studies that address the above-mentioned issues, which are important for the evaluation of benefits and risks of medicines.

In *Chapter 2.1*, we analysed data from randomised clinical trials. In this study, three drugs that have been associated with psychiatric adverse events, bupropion, varenicline and rimonabant, were used to evaluate whether patients with a known psychiatric history were included in their respective randomised clinical trials (pre- and post-registration), and how this inclusion influenced the reported absolute and relative incidence estimates of psychiatric adverse drug reactions. This study showed that in the vast majority (89%) of randomised clinical trials for these three drugs, patients with psychiatric disease were excluded. The similar relative risk ratio's but diverging numbers-needed-to-harm (NHH) in studies in- and excluding patients with psychiatric disease again emphasised the importance of selecting the appropriate patient population for randomised clinical trials, especially if both the pharmacological working mechanism and the expected patient population outside the clinical trial setting indicate that safety issues will focus within a certain area.

In *Chapter 2.2,* we assessed the association between use of dipeptidyl peptidase-4 (DPP-4) inhibitors and the reporting of infections. This new class of antidiabetic drugs has been associated with increased infection rates during the pivotal clinical trials and are known to have effects on the immune system. For this study we used a spontaneous reporting system for adverse drug reactions, the WHO-ADR database VigiBase. This study showed that infections were approximately two times more frequently reported for DPP-4 inhibitors compared to biguanides in the WHO Vigibase (Reporting Odds Ratio (ROR) 2.3 (95% confidence interval (CI) 1.9-2.7)). In particular, upper respiratory tract infections (including amongst others nasopharyngitis and sinusitis) were reported more frequently for DPP-4 inhibitors although the reporting of upper respiratory tract infections was also increased for users of thiazolidinediones, insulin monotherapy and concomitant use of three or more antidiabetic drugs, but all to a much lesser extent than for the DPP-4 inhibitors. Although infections may be related to diabetes, a direct effect of the medication on the occurrence of infections should be considered; physicians and patients should remain vigilant on the occurrence of infections and continue the reporting of infections as possible adverse events.

We further evaluated this risk of infections for patients initiating DPP-4 inhibitors in *Chapter 2.3* by assessing the impact of these medicines on the number of infection-episodes of antibiotic, antimycotic and antifungal drugs for systemic use as a measure of infection risk before and after start of a new diabetes medicine. Therefore we used data from the PHARMO Record Linkage System (RLS), containing demographic details and complete medication history of more than two million community-dwelling residents of more than twenty-five population-defined areas in the Netherlands from 1985 onwards. The results of this study were in line with what we found in Chapter 2.2: patients initiating DPP-4 inhibitors had a statistically significant increased risk of antibiotic courses as a measure for bacterial infections within 3-months after initiation compared to the three-month period before (Relative Risk (RR) 1.59 (93% CI 1.07-2.34)). In contrast, for starters of biguanides, SU-derivatives, thiazolidinediones, and insulins, the risk of infection decreased in the three months after start of the drug. An additional finding was that for the treatment with antimycotic drugs, the use of antimycotics decreased by approximately 50% for all antidiabetic drugs.

The results of these two studies, in combination with the biologic plausibility may suggest a potential relation between DPP-4 inhibitors and infections. Further research is deemed necessary to evaluate the clinical and regulatory consequences of this finding.

To further characterise the patient population in which anti-obesity drugs are being used, we studied patients using these drugs in Chapters 2.4, 2.5 and 2.6. First, in *Chapter 2.4* we assessed whether the baseline risk of psychiatric and cardiovascular disease in patients with diabetes mellitus differed between those starting to use anti-obesity drugs and those not starting to use these drugs. Therefore we used the General Practice Research Database, a computerized database containing medical records from general practitioners in the United Kingdom. This study showed that patients with diabetes mellitus, who started to use anti-obesity drugs,

suffered more frequently from psychiatric disease (Odds Ratio (OR) 1.7 (95% CI 1.2-2.4)) and to a lesser extent cardiovascular disease than patients not starting these drugs (OR 1.2 (95% CI 1.0-1.5)). We concluded that these patients starting to use anti-obesity drugs seemed to be more vulnerable especially to psychiatric morbidity. This might be independent of the anti-obesity drugs itself which may induce additional side effects. These findings urge us to be very careful in interpreting the benefits and risks of such anti-obesity drugs, both in terms of preventing possible exposure of drugs associated with psychiatric events in susceptible patients and in the evaluation of causality when a possible drug induced problem occurs.

In different fields of medicine, changes in medication or health care utilisation were found to be predictive for hospital admissions or specific diagnoses. Therefore, we investigated general health care utilisation and especially the dynamics of health care utilisation that preceded the start of anti-obesity drugs in *Chapter 2.5*, using data from the Integrated Primary Care Information (IPCI) database. The main finding of the study in this chapter was that the difference in physician contacts (either GP or medical specialist) and the total number of issued prescriptions for both males and females increased gradually over the whole 3-year period but we were not able to identify a specific point in time before anti-obesity drug initiation where differences between patients starting anti-obesity drugs and patients not starting to use drugs began to appear. This suggests that anti-obesity drugs were selectively prescribed to patients with a higher burden of obesity-related co-morbidities, such as cardiovascular disease, diabetes mellitus and arthritis, but that initiation of anti-obesity drugs was not preceded by a sudden, sharp increase in health care utilisation.

In addition to the patient characteristics, which are of importance in benefit-risk evaluations, also treatment duration plays a role. In the case of anti-obesity drugs, the cardiovascular benefits are expected only after long-term use, whereas the adverse effects may occur already after short-term use. The aim of the study presented in *Chapter 2.6* was to assess whether the cardiovascular and psychiatric risk profile differed between patients who started and those who did not start to use anti-obesity drugs, or differed between the different anti-obesity drugs, we compared baseline characteristics between users of different anti-obesity drugs and non-users. In addition, we described the pattern of use of the anti-obesity drugs and evaluated a possible relation between the risk profile at baseline and the duration of use of anti-obesity drugs. The study, which was also conducted using IPCI data, revealed that patients starting to use anti-obesity drugs had more often a prior history of psychiatric and cardiovascular morbidities. This constitutes a baseline risk, which in itself may translate in higher occurrence of psychiatric and cardiovascular diseases during use of anti-obesity drugs, independent of the drugs. The duration of anti-obesity drug use was limited (77.7% stopped within 90 days), which might reduce the possible cardiovascular benefits of weight reduction induced by these drugs. Knowledge of both baseline characteristics and duration of use are important for the interpretation of benefit- risk balance of anti-obesity drugs.

In *Chapter 2.7* we used the method of Modified-Prescription-Event-Monitoring (M-PEM) to explore relations between patient characteristics and reasons for and time to discontinuation of rimonabant therapy in a general practice population. Thereby, the focus was on psychiatric events, because these were the main safety concern for rimonabant. This study confirmed the findings from the study described in Chapter 2.6, namely that patients using rimonabant stopped treatment after a relatively short period of use (72% of the patients stoppen; median observation time 323 days (interquartile range: 279-371 days). Another important finding was that patients with a history of psychiatric illness were at increased risk of early discontinuation of rimonabant therapy for all reasons, but more pronounced due to psychiatric events (RR 1.79 (95% CI 1.54-2.09)). In contrast, patients with cardiovascular disease, type 2 diabetes mellitus, dyslipidaemia or hypertension tended to be at a lower risk of discontinuation than those without. This implies that patients discontinue treatment because of psychiatric events before the beneficial effects could develop, thereby negatively affecting the benefit-risk profile of rimonabant. Although in June 2008 the marketing authorisation for rimonabant was suspended, this type of information can be used for the identification and characterisation of early discontinuers and ultimately may add to further improvement of adherence to therapy and thus to optimalisation of treatment benefits and drug safety.

In the Netherlands, two strengths of orlistat are available since 2007, 120 mg (Xenical®, only available on prescription) and 60 mg (Alli®, available without prescription, pharmacy-only in the Netherlands). Because the benefit-risk profile, is at least partly, dependent on the patient population in which medicines are being used, the aim of the study presented in *Chapter 2.8* was to investigate whether patients using the pharmacy-only formulation and the prescription-only formulation were different regarding general and disease-related patient characteristics. In this study, we found that patients using the prescription-only formulation of orlistat were less healthy than users of the pharmacy-only formulation (42.3% versus 21.1% of the patients reporting three or more comorbidities), whereas their Body Mass Index (BMI) was comparable at initiation of the medication. When analysing effectiveness, measured by changes in BMI, the change in BMI for the prescription-only formulation was borderline significnanly larger than for patients using the pharmacy-only formulation (-1.28 (standard deviation (sd) 1.92 kg/m2, versus -0.90 (sd 1.49)). This information is important for an adequate assessment of the benefit-risk profile from a regulatory point of view and illustrates that user information from observational studies is also valuable for benefit-risk evaluations of one active component that is being used in two different settings.

In **Chapter 3**, we discuss the findings of this thesis and provide several recommendations to further improve the benefit-risk evaluation of medicines. We concluded that for an adequate benefit-risk evaluation of a medicinal product, information on the complete context in which medicines are being used is necessary. This consists of extensive information on the patient

population in which medicines are being used, usage patterns including the duration of use, and the effect of the regulated availability of medicines.

In addition, we discuss the need for information from various sources and different study designs, e.g. observational studies. Although randomised clinical trials provide very useful information to study drug effects in a (highly) selected patient population and under (highly) controlled circumstances, extrapolation of the results to the general population is often not possible. Thus, to obtain a (more) complete picture of both the beneficial and adverse effects of the drugs during the whole life cycle of the drug, information from randomised clinical trials needs to be complemented with information from spontaneous reporting systems and observational studies. Therefore, a close collaboration between the regulatory authorities, pharmaceutical industry and academia or research associations is necessary, because this type of data is often collected in large databases that are owned by academia and independent research associations.

Important directions for future research consist first of developing methodologies to measure the benefit-risk ratio of medicines in a more objective way during their whole life cycle. Second, given the increasing interest for risk minimisation activities, which are part of the Risk Management Plans, the outcomes and effectiveness of risk minimisation activities need to be measured and assessed. This opens up a new field of research, combining traditional epidemiology with the assessment of communication strategies that are being used here. A third important point has already been addressed in many publications, and concerns the issue of adequate clinical trial design. Regulatory authorities, pharmaceutical industry and researchers from academia should be more aware of the implications of using relatively clean and healthy patient populations in randomised clinical trials. We advocate that in addition to the first "proof of concept" trials, additional studies in controlled clinical settings should be performed. These studies with less stringent in- and exclusion criteria should include a more realistic study population that more adequately reflects the real users of a drug.

To summarise, information on the complete context in which medicines are being used is necessary for an adequate benefit- risk evaluation of a medicinal product. Therefore information from randomised clinical trials needs to be complemented with information from spontaneous reporting systems and observational studies, especially with the trend towards a life cycle approach including continuous benefit-risk evaluations instead of conducting a single benefit-risk assessment at a certain (fixed) point in time.

SAMENVATTING

De Wereld Gezondheids Organisatie (WHO) definieert geneesmiddelenbewaking als de wetenschap en activiteiten die gerelateerd zijn aan het ontdekken, beoordelen, begrijpen en voorkomen van bijwerkingen of andere problemen die verband houden met het gebruik van geneesmiddelen. In de introductie van dit proefschrift (**Hoofdstuk 1**) beschrijven we hoe de manier waarop geneesmiddelenbewaking beoefend wordt, veranderd is. In de jaren '60 van de vorige eeuw was geneesmiddelenbewaking vooral gebaseerd op het molecuul, wat betekende dat de ontdekking en interpretatie van bijwerkingen voornamelijk gebaseerd werd op de eigenschappen van dat molecuul. In de loop der tijd is de hele context waarin een geneesmiddel gebruikt wordt steeds belangrijker geworden binnen geneesmiddelenbewaking, waarbij het in kaart brengen van de omgeving waarin een middel gebruikt wordt informatie oplevert die van toenemend belang is bij de besluitvorming rondom de registratie van geneesmiddelen.

De ernst van ziektes en het hebben van verschillende aandoeningen kunnen de gevoeligheid van patiënten voor het ontwikkelen van bijwerkingen beïnvloeden, vooral wanneer ziekte, effect en bijwerking nauw met elkaar verweven zijn. Dit is bijvoorbeeld het geval bij patiënten met obesitas of diabetes mellitus, twee aandoeningen die belangrijke risicofactoren zijn voor het ontwikkelen van cardiovasculaire aandoeningen en die allebei vaak samen met andere ziektes (zoals kanker, artritis, en depressie) voorkomen.

Het doel van dit proefschrift is om inzicht te krijgen hoe kennis over het bredere verband, de context, waarin een geneesmiddel gebruikt wordt, bijdraagt aan de beoordeling van de balans werkzaamheid-schadelijkheid en daarmee wat de waarde van deze kennis is voor het besluitvormingsproces. Om deze context van geneesmiddelgebruik (patiënteigenschappen, patronen van geneesmiddelgebruik en de gereguleerde beschikbaarheid van geneesmiddelen) te bestuderen, hebben we twee aandoeningen gekozen die met elkaar samenhangen en die beide patiënten met relatief veel co-morbiditeiten betreffen. Dat zijn obesitas en diabetes mellitus.

Hoofdstuk 2 bestaat uit een achttal studies waarin bovenstaande onderwerpen onderzocht worden. In *Hoofdstuk 2.1* hebben we gegevens van gerandomiseerde klinische onderzoeken geanalyseerd. Daarvoor hebben we drie geneesmiddelen bestudeerd die geassocieerd worden met psychiatrische bijwerkingen: bupropion, varenicline en rimonabant. Voor deze middelen hebben we onderzocht of patiënten waarvan bekend is dat zij een psychiatrische voorgeschiedenis hebben, deelgenomen hebben aan de klinische onderzoeken (zowel vóór als ná registratie van de middelen) en hoe dit het optreden van psychiatrische bijwerkingen in absolute en relatieve zin beïnvloedde. De resultaten laten zien dat in het overgrote deel van de onderzoeken (89%) patiënten met psychiatrische aandoeningen in de voorgeschiedenis uitgesloten werden. We vonden een vergelijkbaar relatief risico (1.56 (95% betrouwbaarheidsinterval (BI) 1.33-1.84) en 1.33 (95% BI 1.25-1.41)) maar een aanzienlijk groter verschil in absoluut risico

("Number Needed to Harm" 8.3 vs. 11.9) in meldingen van psychiatrische bijwerkingen voor de onderzoeken waarin patiënten met een psychiatrische voorgeschiedenis wel respectievelijk niet aan deelnamen. Dit benadrukt hoe belangrijk het is om de juiste patiënten te selecteren voor klinische onderzoeken, zeker als zowel het farmacologische werkingsmechanisme als de eigenschappen van de dagelijkse gebruikers erop wijzen dat veiligheidsproblemen van een geneesmiddel in één bepaald gebied te verwachten zijn.

In *Hoofdstuk 2.2* hebben we gekeken naar een mogelijke relatie tussen het gebruik van dipeptidyl peptidase-4 (DPP-4) remmers en het rapporteren van infecties als mogelijke bijwerking van deze middelen. In de eerste klinische onderzoeken werd voor deze nieuwe klasse van middelen voor de behandeling van type 2 diabetes een verhoogd risico op het ontstaan van infecties gemeld. Daarnaast is uit preklinisch onderzoek gebleken dat deze middelen een effect kunnen hebben op het immuunsysteem. Voor deze studie hebben we gebruik gemaakt van een systeem van spontane meldingen van bijwerkingen, de WHO-ADR Vigibase. Deze studie laat zien dat infecties ongeveer twee keer zo vaak gemeld werden voor DPP-4 remmers in vergelijking tot de biguanides (o.a. metformine) (Reporting Odds Ratio (ROR) 2.3 (95% betrouwbaarheidsinterval (CI) 1.9-2.7)). Vooral infecties van de bovenste luchtwegen (onder andere nasopharyngitis en sinusitis) werden vaker voor DPP-4 remmers gerapporteerd, hoewel het aantal meldingen van dit soort infecties ook verhoogd was voor gebruikers van thiazolidinedionen, insuline monotherapie en gelijktijdig gebruik van drie of meer soorten antidiabetica, maar veel minder dan voor de DPP-4 remmers. Ondanks dat infecties in het algemeen mogelijk vaker voorkomen bij patiënten met diabetes, kan een direct effect van de DPP-4 remmers niet uitgesloten worden, en dienen zowel artsen als patiënten alert te blijven op het optreden van deze bijwerking en dienen deze te blijven rapporteren. Omdat dit effect wellicht gedeeltelijk te verklaren is doordat DPP-4 remmers gebruikt worden in een later stadium van de ziekte en omdat in dit stadium infecties mogelijk vaker optreden, zou het gevonden effect vertekend kunnen zijn.

De mogelijke relatie tussen het gebruik van DPP-4 remmers en een verhoogd risico op infecties hebben we daarom verder onderzocht in *Hoofdstuk 2.3*, waar we gekeken hebben naar het effect van deze middelen op het aantal periodes van infecties in de drie maanden voor en na de start van een nieuw geneesmiddel voor de behandeling van diabetes. Hiervoor hebben we het gebruik van antibiotica, antischimmel- en antivirale middelen voor systemisch gebruik als maat gebruikt voor het risico op infecties. De data voor deze studie komen uit het PHARMO Record Linkage System (RLS), dat vanaf 1985 demografische gegevens en complete apotheekhistories van receptgeneesmiddelen bevat van meer dan twee miljoen mensen in meer dan 25 regio's in Nederland. De resultaten van deze studie komen overeen met de bevindingen in Hoofdstuk 2.2: patiënten die beginnen met het gebruik van DPP-4 remmers hadden een statistisch significant verhoogd risico op het gebruik van antibiotica in de drie maanden na het starten van de DPP-4 remmer in vergelijking tot de drie maanden ervoor (Relatief Risico (RR) 1.59 (93% CI 1.07-2.34)). Voor mensen die startten met een ander middel voor de behandeling van diabetes (biguanide,

SU-derivaat, thiazolidinedion, of insuline) zagen we dat het risico op een infectie in de drie maanden na start juist afnam vergeleken met de drie maanden voor start. Een andere bevinding in deze studie was dat voor alle antidiabetica het gebruik van antischimmelmiddel in de drie maanden na start met ongeveer 50% afnam in vergelijking met de drie maanden ervoor. De resultaten van deze twee studies, in combinatie met de bevindingen uit het preklinische onderzoek duiden op een mogelijke relatie tussen het gebruik van DPP-4 remmers en infecties. Meer onderzoek is nodig om de klinische en regulatoire gevolgen van deze bevindingen verder in kaart te brengen.

Om de patiëntenpopulaties waarin geneesmiddelen voor de behandeling van obesitas gebruikt worden verder te karakteriseren, hebben we deze patiënten onderzocht in de hoofdstukken 2.4, 2.5 en 2.6. In *Hoofdstuk 2.4* hebben we gekeken of het uitgangsrisico op psychiatrische en cardiovasculaire aandoeningen bij patiënten met diabetes mellitus verschilde voor patiënten die wel of geen middel voor de behandeling van obesitas gebruikten. Daarvoor hebben we de gegevens uit de General Practice Research Database gebruikt, een database die elektronische patiëntendossiers van huisartsenpraktijken in het Verenigd Koninklijk bevat. De studie toont aan dat patiënten met diabetes die begonnen met het gebruik van geneesmiddelen voor de behandeling van obesitas bijna twee keer vaker een psychiatrische aandoening hadden (Odds Ratio (OR) 1.7 (95% BI 1.2-2.4)) en in iets mindere mate ook vaker cardiovasculaire aandoeningen hadden dan mensen die niet met dit type middelen begonnen (OR 1.2 (95% CI 1.0-1.5)). We concludeerden dat deze patiënten kwetsbaarder leken voor het ontwikkelingen van vooral psychiatrische aandoeningen. Dit effect is waarschijnlijk onafhankelijk van het geneesmiddel, dat zelf ook bijwerkingen kan geven. De bevindingen in dit hoofdstuk maken duidelijk dat het belangrijk is om voorzichtig te zijn met de interpretatie van de voor- en nadelen van middelen voor gewichtsverlies, zowel met betrekking tot het initiëren van gebruik in patiënten die gevoelig zijn voor de ontwikkeling van psychiatrische bijwerkingen als wel in de evaluatie van de causaliteit wanneer zich een geneesmiddelgerelateerd probleem zich voordoet.

In verschillende gebieden binnen de geneeskunde zijn veranderingen in geneesmiddelgebruik of zorggebruik in het algemeen voorspellend voor ziekenhuisopname of een specifieke diagnose. Daarom hebben we het zorggebruik en in het bijzonder de dynamiek die vooraf gaat aan de start van het gebruik van een geneesmiddel voor de behandeling van obesitas in *Hoofdstuk 2.5* onderzocht. Hiervoor hebben we gebruik gemaakt van de Nederlandse Integrated Primary Care Information (IPCI) database. De belangrijkste bevinding in dit hoofdstuk was dat het verschil in contacten met een arts (zowel huisarts als medisch specialist) en het totaal aantal recepten voor zowel mannen als vrouwen gestaag toenam over de hele driejaars periode voorafgaand aan het gebruik van een middel voor gewichtsverlies zonder dat we een specifiek moment in de tijd konden identificeren waar de verschillen begonnen te ontstaan tussen patiënten die wel en niet met zo'n middel begonnen. Dit suggereert dat middelen voor de behandeling van overgewicht specifiek worden ingezet bij patiënten met een hogere

ziektelast, zoals cardiovasculaire aandoeningen, diabetes en artritis, maar dat het starten van deze middelen niet voorafgegaan werd door een plotselinge, scherpe toename van het gebruik van zorg.

Naast patiëntkarakteristieken die belangrijk zijn in de evaluatie van de balans werkzaamheid-schadelijkheid van geneesmiddelen, speelt ook de duur van het geneesmiddelgebruik een rol. In het geval van de middelen voor de behandeling van obesitas kunnen de cardiovasculaire voordelen alleen na een lange periode van gebruik verwacht worden, terwijl de bijwerkingen al op kunnen treden bij kortdurend gebruik. Het doel van de studie in *Hoofdstuk 2.6* was om te onderzoeken of de cardiovasculaire en psychiatrische basisrisico's verschillend waren voor patiënten die wel of niet begonnen met het gebruik van een middel voor de behandeling van obesitas. Daarvoor hebben we de patiëntkarakteristieken van gebruikers van verschillende geneesmiddelen voor de behandeling van obesitas en van patiënten die dit soort middelen niet gebruikten met elkaar vergeleken. Daarnaast hebben we in deze studie het patroon van gebruik van dit type middelen beschreven en een mogelijke relatie tussen het basisrisico en de gebruiksduur in kaart gebracht. Deze studie, waarin ook gebruik is gemaakt van de IPCI-database, laat opnieuw zien dat patiënten die begonnen met een middel voor de behandeling van obesitas, vaker een psychiatrische en cardiovasculaire voorgeschiedenis hadden. Dit betekent dat deze patiënten mogelijk een verhoogde kans hebben op de ontwikkeling van psychiatrische en cardiovasculaire bijwerkingen tijdens het gebruik van deze middelen. De gebruiksduur van de middelen voor de behandeling van overgewicht was beperkt (77.7% stopte binnen 90 dagen), wat de mogelijke cardiovasculaire voordelen van deze middelen op de lange termijn kan verminderen. Daarmee verandert de balans werkzaamheid-schadelijkheid van deze geneesmiddelen in de dagelijkse praktijk. Deze studie toont dus aan dat zowel kennis van patiëntkarakteristieken als van gebruikspatronen van belang is voor de interpretatie van de deze balans.

In *Hoofdstuk 2.7* hebben we de rimonabant onderzocht met methode van "Modified-Prescription-Event-Monitoring" (M-PEM). Hierbij hebben we relaties tussen patiëntkarakteristieken en redenen voor stoppen en de tijd daartoe geanalyseerd in een algemene populatie. De focus lag daarbij op de psychiatrie, omdat dat het belangrijkste veiligheidsprobleem voor rimonabant was. Deze studie bevestigde de resultaten uit Hoofdstuk 2.6, namelijk dat patienten rimonabant relatief kort gebruikten (72% van de patiënten stopte, waarbij de mediane observatietijd 323 dagen bedroeg (interquartile range: 279-371 dagen). Een andere belangrijke bevinding was dat patiënten met een psychiatrische aandoening in hun voorgeschiedenis een verhoogde kans hadden om te stoppen met het gebruik van rimonabant, en dat dit het meest uitgesproken was voor stoppen vanwege psychiatrische gebeurtenissen (RR 1.79 (95% CI 1.54-2.09)). Daarentegen hadden patiënten met cardiovasculaire aandoeningen, type 2 diabetes mellitus, dyslipidemie of hypertensie juist een lager risico om te stoppen. Dit wijst erop dat patiënten met rimonabant stopten vanwege (psychiatrische) bijwerkingen voordat de gunstige effecten van het middel kunnen optreden, waardoor de balans werkzaamheid-schadelijkheid

negatief beïnvloed werd. Ondanks dat de registratie van rimonabant in juni 2008 geschorst werd, kan deze informatie bijdragen aan de identificatie van mensen die te vroeg met een behandeling stoppen en kan daarmee bijdragen aan het verbeteren van de therapietrouw en het optimaliseren van de balans tussen de voordelen van behandelingen en de veiligheid van geneesmiddelen.

In Nederland zijn sinds 2007 twee sterktes van orlistat beschikbaar, 120 mg (Xenical®, alleen op doktersrecept verkrijgbaar) en 60 mg (Alli®, verkrijgbaar zonder doktersrecept, maar in Nederland alleen via apotheken). Omdat de balans van werkzaamheid en schadelijkheid van geneesmiddelen (in ieder geval gedeeltelijk) afhankelijk is van de patiëntenpopulaties die de middelen gebruiken, was het doel van de studie in *Hoofdstuk 2.8* om te onderzoeken in hoeverre de receptplichtige en niet receptplichtige variant van orlistat door hetzelfde type patiënten gebruikt worden, waarbij we gekeken hebben naar algemene patiëntkarakteristieken, aandoeningen die samenhangen met overgewicht en gelijktijdig gebruik van andere geneesmiddelen. In deze studie vonden we dat de patiënten die de receptplichtige variant van orlistat gebruikten minder gezond waren in vergelijking met de patiënten die de niet-receptplichtige variant gebruikten (42.3% versus 21.1% van de patiënten meldde drie of meer co-morbiditeiten), terwijl hun Body Mass Index (BMI) vergelijkbaar was aan het begin van het orlistatgebruik. Antitrombotica, geneesmiddelen voor de behandeling van cardiovasculaire en middelen voor de behandeling van psychiatrische aandoeningen werden significant vaker gebruikt door patiënten die Xenical® gebruikten dan door patiënten die Alli® gebruikten. Beide groepen gebruikten echter meer geneesmiddelen dan de Nederlandse bevolking in het algemeen. De effectiviteit, gemeten als verandering van BMI, was groter voor patiënten die de receptplichtige variant gebruikten in vergelijking met de patiënten die de niet receptplichtige variant gebruikten (-1.28 (standaard deviatie (sd) 1.92 kg/m^2, versus -0.90 (sd 1.49) kg/m^2). Deze informatie is belangrijk voor een goede evaluatie van de balans werkzaamheid-schadelijkheid en laat tevens zien dat de resultaten van observationeel onderzoek waardevol zijn in het geval van een actieve stof die via verschillende kanalen verkregen kan worden.

In **Hoofdstuk 3** bediscussiëren we de bevindingen van dit proefschrift en doen we een aantal aanbevelingen die bij kunnen dragen aan een verdere verbetering van de evaluatie van de balans werkzaamheid-schadelijkheid van geneesmiddelen. We concluderen dat voor een goede beoordeling van deze balans informatie over de hele context waarin een geneesmiddel gebruikt wordt van belang is. Dit bestaat uit goede informatie over de patiëntengroepen die geneesmiddelen gebruiken, informatie over gebruikspatronen en gebruiksduur en informatie over het effect van de gereguleerde beschikbaarheid van geneesmiddelen.

Daarnaast bespreken we de noodzaak om informatie van verschillende bronnen en verschillende studieopzetten, zoals klinische en observationele studies, met elkaar te combineren. Ondanks dat gerandomiseerde klinische onderzoeken zeer bruikbare en adequate informatie over de beoogde effecten van geneesmiddelen geven in een geselecteerde populatie onder

gecontroleerde omstandigheden, is extrapolatie van deze resultaten naar de algemene patientenpopulatie vaak niet mogelijk. Om een completer beeld van zowel de voor- als nadelige effecten van een geneesmiddel te krijgen dient de informatie uit de klinische onderzoeken aangevuld te worden met informatie uit de dagelijkse praktijk, zoals spontane meldingssystemen en observationele studies. Daarvoor is een nauwe samenwerking nodig tussen de regulatoire autoriteiten, de farmaceutische industrie, en universiteiten en andere onderzoeksinstellingen, omdat dit soort informatie vaak in grote databases wordt verzameld die door universiteiten en onafhankelijke onderzoeksinstituten worden beheerd.

Ten slotte identificeren we een aantal belangrijke gebieden voor toekomstig onderzoek. Allereerst zal er aandacht besteed moeten worden aan het verder ontwikkelen van methodes om de balans werkzaamheid-schadelijkheid van geneesmiddelen op een objectieve manier te meten. Ten tweede worden er steeds vaker maatregelen genomen om de risico's van het gebruik van geneesmiddelen te minimaliseren en het effect van deze methoden moet verder onderzocht worden. Hierbij zou een combinatie van traditionele epidemiologie en communicatiestrategieën een nieuw onderzoeksgebied kunnen worden. Een derde, vaakgenoemd punt betreft het ontwerp van de klinische onderzoeken. De regulatoire autoriteiten, farmaceutische industrie en onderzoekers moeten zich bewust zijn van de gevolgen van het includeren van relatief jonge en gezonde patiënten in klinische onderzoeken. We stellen voor dat in aanvulling op de fase 3 onderzoeken, extra studies onder gecontroleerde omstandigheden uitgevoerd worden. Deze studies, met minder strenge inclusiecriteria, zouden een realistischere weergave van de effecten bij de daadwerkelijke gebruikers van geneesmiddelen moeten zijn, en daardoor meer inzicht moeten geven in de effecten van geneesmiddelen in de dagelijkse praktijk.

Samenvattend is informatie over de gehele context waarin geneesmiddelen gebruikt worden van belang voor een goede beoordeling van de balans werkzaamheid-schadelijkheid. Daarvoor dient informatie uit klinische onderzoeken gecombineerd te worden met informatie uit spontane rapportages en observationeel onderzoek, zeker gezien de verschuiving van een eenmalige naar een continue beoordeling van de balans werkzaamheid-schadelijkheid.

Chapter 5

Dankwoord

List of co-authors

List of publications

About the author

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LIST OF PUBLICATIONS

Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Meyboom RH, Egberts AC, Leufkens HG. Use of DPP-4 inhibitors and the reporting of infections: a disproportionality analysis in WHO Vigibase. *Diabetes Care 2011; 34: 369-374*.

Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Leufkens HG, Egberts AC, Sturkenboom MC. Cardiovascular and psychiatric risk profile and patterns of use in patients starting anti-obesity drugs. *Pharmacoepidemiol Drug Saf 2009; 18 (7): 631-638*.

Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Leufkens HG, Egberts AC. Psychiatric and cardiovascular co-morbidities in patients with diabetes mellitus starting anti-obesity drugs. *Obesity (Silver Spring) 2008; 16 (10): 2331-2335*.

Willemen MJC, Mantel-Teeuwisse AK, Straus SMJM, Leufkens HGM, Egberts ACG. Reporting of psychiatric adverse events in randomised clinical trials. *Submitted for publication*.

Willemen MJC, Mantel-Teeuwisse AK, Souverein PC, Straus SMJM, Leufkens HGM, Egberts ACG. Initiation of DPP-4 inhibitors and infection risk. *Submitted for publication*.

Willemen MJC, Mantel-Teeuwisse AK, Straus SMJM, van Soest EM, Leufkens HGM, Egberts ACG, Sturkenboom MCJM. Dynamics in health care utilisation in patients prior to initiation of anti-obesity drugs. *Submitted for publication*.

Willemen MJC, Mantel-Teeuwisse AK, Buggy Y, Layton D, Straus SMJM, Leufkens HGM, Egberts ACG. Reasons for and time to discontinuation of rimonabant therapy. *Submitted for publication*.

Willemen MJC, Mantel-Teeuwisse AK, Winters NA, Straus SMJM, Leufkens HGM, Egberts ACG. Effect of the prescription status on the orlistat user population: prescription-only versus pharmacy-only. *Submitted for publication*.

Stolk P, Willemen MJ, Leufkens HG. Rare essentials: drugs for rare diseases as essential medicines. Bull World Health Organ 2006; 84 (9): 745-751 (not related to this thesis).

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