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Drug safety and the impact of drug warnings: An interrupted time series analysis of diabetes drug prescriptions in Germany and Denmark

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ABSTRACT

Objective: To analyse the impact of drug safety warnings from the European Medicines Agency (EMA) on drug utilisation and their interaction with information released through national reimbursement bodies.
Methods: Insurance claims data on anti-diabetic drug prescriptions in primary care in Germany and Denmark were analysed using interrupted time series analysis, with EMA drug warnings for thiazolidinediones (TZDs) in 2007 and 2011 as the intervention. Monthly drug utilisation data per substance in defined daily dosages (DDD) consumed per 1000 insurees were retrieved from the Danish national drug prescriptions register and one large statutory sickness fund in Germany.
Results: TZDs were generally reimbursed in Germany but restricted to individual reimbursement in Denmark. Consequently, utilisation of TZDs was much higher in Germany in 2007 compared with Denmark. For rosiglitazone, the drug warning had a significant impact on utilisation, reducing the number of DDD per 1000 insurees per day by −0.0105 in Denmark and −0.0312 in Germany (p-values < 0.05). For pioglitazone, neither of the drug warnings had a significant effect on utilisation.
Conclusion: The impact of EMA drug warnings differed across countries and might be mediated by information released through national reimbursement bodies and physician associations. Increasing complexity of new drugs and modified approval procedures require a strengthening of information exchange between drug regulation bodies and physicians to ensure patient safety.

1. Introduction

During the last decade, a number of newly released drugs have become subject to post-marketing drug safety warnings. Facing rising complexity in making prescription decisions, physicians need to keep up to date on new products and safety information. For example, when prescribing diabetes medication, prescribers can choose between large numbers of oral anti-diabetics, many of which have become available in recent years [1].

Drug authorisation is typically based on evaluations of the drug's safety and efficacy profile. To inform their decisions, authorisation bodies demand randomised controlled

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clinical trials (RCTs) with high scientific validity and reliability to inform their decisions. These trials usually have high internal validity, whereas external validity may be low. The patient population recruited for clinical trials is typically characterized by few or no comorbidities and, thus, it does not fully represent the patient population in clinical practice. Moreover, RCTs are often not large enough in sample size or with a time frame that is too short to detect rare adverse events and side-effects.

This is a particular problem for diabetes drugs, as patients are often subject to multiple comorbidities. Moreover, during the last decade, a number of drugs have been introduced that affect the basic functioning and control mechanisms at the cellular level. The pharmacological effects of these drugs on other organ systems are often not well documented or even unknown upon approval [2,3]. Therefore, there is an increased risk of detecting side-effects or dangerous interactions with other drugs after the granting of initial market authorisation, which may trigger drug warnings. Thus, patients may need to switch to other therapies once a severe drug safety warning is released or a product is fully withdrawn from the market. Accordingly, physicians not only need to learn about newly introduced drugs, but also have to keep up to date on changing drug effectiveness and safety profiles.

This problem is not confined to diabetes medication, and new regulation may intensify the issue. The new *adaptive pathways approach* introduced by the European Medicines Agency (EMA) provides possibilities for early provisional approval for drugs based on lower levels of evidence, in exchange for increased post-marketing pharmacovigilance monitoring. This approach is available for drugs intended to treat patients in whom unmet clinical need is high. For these patients, it is difficult to recruit a sufficient study population to conduct phase III RCTs to prove that the drug is safe and efficacious under ideal conditions [4]. Thus, the evidence level at the time of market approval for these drugs is lower, and the risk of detecting adverse events after the drugs are approved is larger compared with drugs in the standard approval pathway.

Existing evidence on the effect of drug warnings on drug utilisation focuses on either studies with a short time horizon or case studies of single products or countries. For the United States, mixed effects of drug warnings from the Food and Drug Administration (FDA) by drug class were found for pain medication [5]. In the domain of diabetes, where side-effects are frequent, several US-based studies assessed the prescription pattern of glucose-lowering drugs for a short period around the publication of the FDA safety alert for the substance rosiglitazone in May 2007 [6–9]. For Europe, studies from the Netherlands and the UK, which analysed changes in prescribing behaviour after the drug warnings were made and switching of drug regimens by prescribers, found a decline in prescriptions for rosiglitazone [10–12]. However, the evidence of a spillover effect to other glucose-lowering drugs such as pioglitazone is mixed [6–8,11–13]. Thus, existing evidence has not studied interactions with national reimbursement regulation, which ensures the affordability of new substances, as this requires data from more than one country. In this study, we use data from two countries that are similar with respect to their patient population, but differ in their regulation of drug reimbursement. We analyse whether drug utilisation and the reaction to EMA drug warnings differed between Denmark and Germany. This is done to evaluate whether the reactions to drug safety warnings among health professionals also depend on other factors such as reimbursement regulation. Thiazolidinediones (TZDs) are used as a case study.

2. The case of thiazolidinediones (TZDs)

TZDs exemplify the complexity of the latest diabetes drugs very well. TZDs are one class of a number of oral antidiabetics used to treat type 2 diabetes that have emerged during the last decade. TZDs affect the basic cell functioning by reducing insulin resistance, helping the body's own insulin to work more effectively and offering patients improved glycaemic control. The hope was that this would slow the deterioration in health in the long run. However, evidence from patient case reports available to the FDA based on post-marketing observational studies suggested that the new mechanism of action – which stimulates genes that act on more than blood glucose – is responsible for its adverse effects, which ultimately led to the drug safety warnings [14].

Type 2 diabetes accounts for over 85% of diabetes cases and is managed by a 'step-up regimen', starting with diet and exercise, followed by the addition of oral blood glucose-lowering drugs. If good metabolic control is not maintained otherwise, patients are finally transferred to insulin [15]. Most type 2 diabetes patients are over the age of 50 and comorbidities are very common. In particular, the prevalence of cardiovascular comorbidities is high [16]. Thus, there is an increased probability that side-effects or drug interactions do not become apparent until used in clinical practice.

The substances we study are rosiglitazone and pioglitazone. At the peak of their sales in 2006, both drugs had reached blockbuster status with annual worldwide sales exceeding US$ 1 billion. Upon the drugs' marketing approval, only a few non-insulin glucose-lowering drugs (sulphonylureas and metformin) were available [17]. The delay in transferring patients to insulin was considered a major benefit of TZDs as part of the 'step-up regimen' employed in the care of diabetes patients [18]. Both drugs received European marketing authorisation in 2000 [19,20]. The EMA granted both TZDs marketing authorisation for defined patient populations: (1) in obese patients in combination with metformin; and (2) in patients who show intolerance to metformin in combination with a sulphonylurea.

Side-effects have been an issue for TZDs from the start. The first TZD – troglitazone – showed side-effects of liver toxicity. It was quickly withdrawn from the US market and was never marketed in Europe [21]. This led to a lot of scepticism towards TZDs. However, the manufacturers of rosiglitazone and pioglitazone managed to provide convincing evidence to clear concerns on liver toxicity. Yet, the public's attention and clinical study design focused on liver problems, potentially neglecting the cardiovascular and cancer risks to some extent. By the time the two