

Editorial

Drug Safety Warnings: A Message in a Bottle

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INTRODUCTION

Before being launched on the market, the randomized clinical trials (RCTs) that investigate drug efficacy also investigate the safety profile of therapeutic drugs. Since RCTs are often conducted in populations which are not strictly representative of the population which will actually use them and because the study population size and the follow-up in an RCT is usually limited, the spectrum and frequency of adverse drug reactions (ADRs) detected is however very limited. As a result, it is possible that the true nature and frequency of potential ADRs may only emerge after large numbers of people are exposed to drugs in the real world of clinical practice [1]. After being identified, any new findings on drug safety must be effectively communicated to prescribers and patients with the aim of minimising the risk associated with drug use. Often this is done through black-box warnings or "Dear Doctor" letters.

The impact of safety warnings on antipsychotic use in dementia

The complexity of risk communication in the context of drug safety is illustrated by the case of antipsychotic drug use in elderly persons with dementia. As early as October 2002, Janssen-Ortho advised Canadian prescribers that the use of risperidone was associated with an increased risk of stroke in dementia patients [2]. A few years later, in March 2004, the European Medicines Agency (EMA) warned prescribers about the risk of cerebrovascular events with olanzapine use in dementia [3] and in the same month, the UK Committee on Safety of Medicines (CSM) issued a similar warning related to risperidone and olanzapine use in elderly patients with dementia [4]. These warnings triggered a series of observational safety studies and other warnings around the world. Attention was later shifted from olanzapine and risperidone to all atypical antipsychotics, and finally, to any antipsychotic, including conventional antipsychotic use in dementia patients.

Evaluating the impact of safety warnings on drug prescribing pattern is of great importance because it is the most basic measure of whether a warning has been successful in reaching a target population and of modifying prescribers' behaviors. Such investigations have been carried out in the context of the antipsychotic warnings and these highlight the different ways in which safety warnings change prescribing practices or otherwise [5-12]. As one would expect, a common finding

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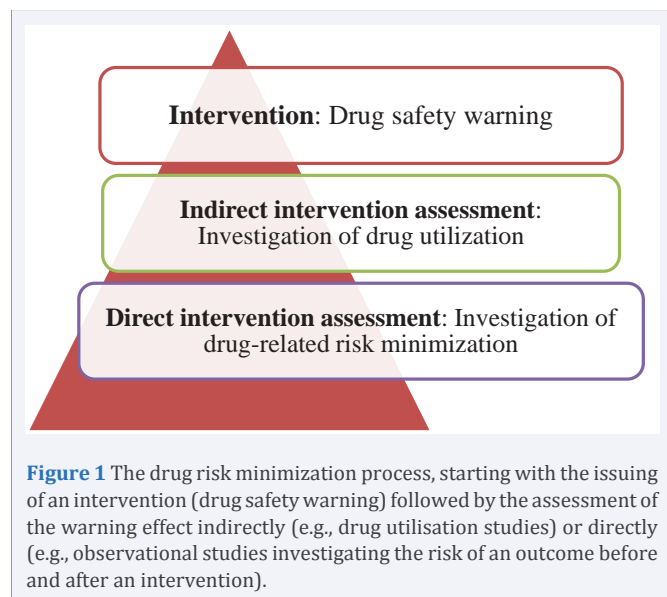
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among these studies is that warnings targeting the use of specific antipsychotics, such as those related to olanzapine and risperidone, reduced the prescription of specific target drugs but much less the overall prescribing of antipsychotics in dementia patients. However, the findings reported in these studies suggest that targeting the use of specific drugs in safety warnings comes with a caveat. The initial warnings concerning olanzapine and risperidone use in dementia specifically and successfully having an impact on these two antipsychotics resulted in a paradoxical and significant increase of a similar drug that had been recently marketed, quetiapine, to fill a void in the prescribing inventory. Similarly, several observational studies have reported a general increase in the prescription of conventional antipsychotic drugs in dementia patients that coincided with the warnings on the use of atypical antipsychotics in this population. This is significant because later safety warnings about the risk of stroke and all-cause mortality were extended to all atypical antipsychotic use, including quetiapine as well as the entire class of conventional antipsychotics. It can be argued that the reduction of olanzapine and risperidone use and the ensuing reduction in health risk were at least partly, and possibly significantly, offset by the increased use of conventional antipsychotics, which may be poorly tolerated especially in elderly patients compared to atypical antipsychotics, thus making the initial warnings counterproductive in this sense.

Do safety warnings lead to risk minimization?

Drug utilization studies aiming to evaluate the impact of drug warnings on antipsychotic prescribing have undoubtedly shed light on how such warnings impact antipsychotic use. However, it is important to note that the final objective of the safety warnings is not directly to reduce the use of a drug but to minimize the risk associated with drug use (**Figure 1**). On one hand, it can be argued that a reduction in the use of a drug may be correlated with a reduction in drug-associated risk. On the other hand, it is possible that the prevalence of drug use after a warning does not appear to change significantly in absolute numbers, but that the nature of the population to which the drugs are prescribed as well the daily dosage and treatment duration change in a way which translates into a reduced drug-related risk. For example in the case of antipsychotic prescribing in dementia, it would be possible for antipsychotics to be used more selectively



in a population with a lower risk of cardio-cerebrovascular adverse events, resulting in an effective risk minimizing effect of the warning. This impact of safety warnings is however not quantifiable using drug utilization studies alone. The challenge of the impact of health policy interventions has led the Food and Drug Administration (FDA) to launch an initiative, in the context of the Mini-Sentinel project, aiming to describe research approaches used to assess outcomes related to FDA regulatory actions and to recommend the most suitable research methods to evaluate such regulatory outcomes [13].

There is increasing acknowledgement that it is of paramount important to evaluate potential risk minimization after a safety warning is issued. Without such an evaluation of risk reduction, the real and intended impact of the warnings on the safe use of drugs in patients remains unknown. Until such an impact is identified and measured, it is not known whether drug safety warnings are just messages in a bottle.

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