Bridging from drug registration trials to meaningful clinical evidence: The case of schizophrenia

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Chapter 1

General introduction
General introduction

Placebo controlled randomised clinical trials are the gold standard for testing the efficacy of new pharmaceutical compounds. After these studies are completed and the product is assessed by the responsible authorities, at least some of the trials are published and the data may be included in meta-analyses and can contribute to evidence based medicine, which is still the way forward in drawing up treatment guidelines, despite the several critical issues which may hamper the reliability of conclusions based on published studies, such as external validity of results. However, the data of many trials remains unpublished and unused, ranging from complete studies that are not published to publication of only a limited set of the variables from these trials. The reasons for selective reporting and publishing vary and can be caused by the behaviour of the study sponsors and/or the policy or evaluation of the results by journals. Demanding companies to publicly share data which is their intellectual property may be difficult to accomplish by legislation. Therefore, sharing these data should rather be a voluntary act arising from sense of responsibility and governance. After all, significant numbers of patients have participated in the trials to generate data that could have an impact on health policies and public health.

In awaiting advances in transparency a subsequent availability of all clinical trial data, raw study data from drug registration trials may provide an option to not only analyse efficacy but also to test additional hypotheses, for example questions related to the natural course of the disease or the influence of prognostic factors (1). Testing additional hypotheses using raw study data from drug registration trials can improve our understanding of the studied disorder, explore new aspects that might affect the use of a drug and even help to optimize clinical trial design. This is particularly interesting in the field of psychiatry, including schizophrenia, where drug development has been declining in recent years (2,3). The heterogeneous nature of schizophrenia creates challenges in designing, performing and interpreting the results of clinical trials (4). Re-analysis of existing trial data may help to clarify the problem and find solutions for future trials with better assay sensitivity.

The benefits of using drug registration trial data in examining research questions relevant for clinical and regulatory practise were widely demonstrated in recent work by Welten and colleagues, in the context of acute mania. Welten and colleagues were able to investigate methodological aspects in acute mania trials which affect extrapolation between different study populations (5) and trial success (6,7), as well as factors which might predict treatment response (8). This set of studies is an excellent example of the vast possibilities of individual patient data analysis.

The Medicines Evaluation Board (MEB) is the national authority in the Netherlands
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responsible for assessment and monitoring of efficacy, safety and quality of medicinal products, and independently decides about the authorisation and monitoring of these products. Within this role, the MEB receives clinical trial reports of studies performed for the purpose of obtaining a marketing authorisation for a new medicinal product. The MEB considers communication and transparency over medicinal products as their responsibility. Together with the Department of Psychiatry of the Academic Medical Centre (AMC) at the University of Amsterdam and NEFARMA, the industry association for the Dutch branches of innovative pharmaceutical companies, the MEB initiated a project aimed at making more extensive use of the data available in registration trials. NEFARMA enabled the contact with pharmaceutical companies which were requested to deliver their raw study data from registration trials that were submitted for marketing authorisation application of the specific disorders obsessive compulsive disorder, schizophrenia and bipolar disorder. Clinical trials performed with medicinal products intended for the treatment of psychiatric disorders were selected as target because the complexity of these disorders create difficulties in designing and performing the studies as well as interpreting the results. One of the reasons for this is the generally limited effect sizes related to the heterogeneity of psychiatric populations with serious variability in the clinical characteristics of the patients and other patient and context variables of patients included in the trials. The response from the pharmaceutical companies resulted in 62 submitted clinical trials: 20 in obsessive compulsive disorder (five different compounds), 20 in bipolar disorder (seven different compounds) and 22 in schizophrenia (five different compounds). The analyses on these data and reporting of results were independent from company influence.

This thesis aims to highlight some of the current challenges in schizophrenia research and to demonstrate how analyses on raw study data from drug registration trials can answer a variety of research questions related to these challenges and subsequently aid decision making in regulatory and clinical practise.
Outline of this thesis

Chapter 1 is the general introduction and presents the aims and the outline of the thesis. Chapter 2 presents our findings on the extent of publication bias and its impact on evidence based medicine. Chapters 3 - 5 present our findings on examining three current challenges in schizophrenia research, including hypotheses on the generalization of study results across geographic regions, and some disease specific questions. In chapter 6 the main findings of this thesis are summarized, discussed and both regulatory and clinical implications are addressed.

Potential bias in the published evidence on effects of medicinal products can influence treatment choices and subsequently may have a detrimental impact on public health and on health care costs. The increasing use of meta-analyses and systematic reviews of published articles in formulating treatment guidelines has increased the interest in the possible consequences of biased clinical information. The impact of publication bias is of particular relevance in psychiatric conditions, where the public interest in efficacy of medications and their side effects is. Therefore missing results on clinical trials in the public domain can have a large impact on the overall picture of efficacy of the compounds. Chapter 2 addresses publication bias and its implication for clinical practise in the context of insomnia medications. Selective publication and selective reporting were examined by comparing publications in peer reviewed journals with information provided in the European Public Assessment Reports, which present all the performed trials in a given marketing authorization application (published by the European Medicines Agency). In addition, an aggregate meta-analysis on data retrieved from the EPARs was performed to examine whether the effect size of insomnia medications reported in the literature reflects the true effect size observed in drug registration trials.

In recent years there is a globalisation in conducting clinical trials with shift in locations from traditional sites in North America and Western Europe to emerging regions, such as Eastern Europe and Asia. Regional differences in factors such as health care availability, medicinal practice, disease definition and patient characteristics (e.g. race and treatment compliance) may lead to different results with respect to efficacy and/or safety in the different geographic regions, and therefore generalizability of the results across geographic regions has been questioned. Extrapolation of results across regions is currently addressed by regulatory authorities such as the European Medicines Agency (EMA) and the USA Food and Drug Administration (FDA) on a case-by-case assessment. In Chapter 3 I examine the geographic variation in short-term efficacy studies of different atypical antipsychotics in the acute treatment of schizophrenia using individual patient data meta-analysis, taking into account the potential confounding effect of the different compounds that were used in different geographic regions.
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Another factor that may affect generalization of study results from drug registration trials is the diagnostic criteria that were used and are updated at regular intervals, e.g. versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM): DSM-III (1980) (9), DSM-III-R (1987) (10), DSM-IV (1994) (11), DSM-IV-TR (2000) (12), DSM-5 (2013) (13). If considerable amendments take place, one might doubt whether results obtained in a patient population diagnosed according to the criteria at one time are applicable to the patients diagnosed at another time. Many of the drugs used in psychiatric disorders have been developed and tested in trials decades ago. In some other nervous system disorders, such as multiple sclerosis, changes in diagnostic criteria have affected the diagnosed patient population (14,15). In contrast, in a recent study in adult attention deficit disorder (ADHD), it was shown that the change in diagnostic criteria from DSM-IV to DSM-5 did not result in a significant increase or decrease in patients falling under the diagnostic criteria (16).

In Chapter 4 I examine the effect of changes in diagnostic criteria for schizophrenia from the fourth to the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV and DSM-5) on clinical practise and the applicability of past clinical trials to present day patients.

Poor insight is highly prevalent in patients with schizophrenia and opinions on whether insight is only an artefact of symptoms or an independent dimension of schizophrenia vary among clinicians (17). Study publications usually do not report results on individual symptoms or items in the assessment scales, therefore systematic reviews and most meta-analyses cannot answer whether antipsychotics have an effect on insight. Furthermore, a serious limitation of the few studies that have addressed this issue is the lack of placebo control, which is considered crucial in a population with a high overall placebo response to antipsychotics (18). Therefore I performed a study, described in Chapter 5, to examine whether the previously reported effects of antipsychotics on insight in patients with schizophrenia (19,20,21) can be confirmed using an IPD meta-analysis on a new large dataset (N=4,243) of randomized, double-blind, placebo-controlled trials.

In Chapter 6, I summarize the findings of the previous chapters, discuss the general strengths and limitations and provide an integrated view on the regulatory meaning and the clinical usefulness of our studies.
References

Chapter 1


