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The placebo arm in clinical studies for treatment of Psychiatric Disorders: A Regulatory Dilemma ☆

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Abstract
Background: The use of placebo in clinical trials, and, related to this, ethical and feasibility aspects, are often debated. However, regulatory authorities must ensure that only new drugs with a positive benefit/risk would be granted a marketing authorization. It is therefore not surprising that they often put forward the need for placebo control in clinical trials in an area where many trials fail, and assay sensitivity is not self-evident. To illustrate the complexity that regulatory authorities encounter when faced with the registration dossier of products in the main psychiatric therapeutic areas, Major Depressive Disorder (MDD) and schizophrenia, the trial outcome for products receiving an opinion in the EU during the past 15 years were reviewed.
Data source: European Public Assessment Reports and registration files.
Results: A total of 45 studies qualified for analysis. For the indication MDD 38% of the studies (10/26) were recorded as failed, and another 15% (4/26) as negative. For schizophrenia, these figures were 16% (3/19) and 11% (2/19). Further exploration of the trials in MDD revealed an inconsistent pattern in terms of magnitude of placebo- and drug-mediated response (i.e. similar studies with consistent placebo response provided different treatment outcomes).
Conclusion: From a regulatory perspective the dilemma of *a priori* exclusion of the placebo arm in clinical trials in the domains of depression or schizophrenia cannot be solved at this time as long as factors influencing trial variability are not better identified or understood. This counts in particular for MDD where the added drug effect is not consistent across trials with almost identical inclusion criteria. Unfortunately, this trend has not changed over the past 15 years.

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However, all efforts should be taken to optimize the clinical development of drugs in the psychiatric domain, and improve the intrinsic quality of the clinical trials in order to allow for a different viewpoint.

1. Introduction

A main role of regulatory authorities is to ensure that the benefit–risk balance of new medicines is positive. Ineffective and/or unsafe drugs should not be allowed into the market. However, there is an inherent degree of uncertainty in pre-marketing drug assessment, not only because infrequent (particularly rare and long-term) adverse effects are very unlikely to be detected with the number of subjects/patients that can feasibly be studied prior to marketing authorization, but also because demonstration of relevant efficacy may prove difficult (Raine et al., 2011; Eichler et al., 2011).

Assessment of efficacy could be easier when the beneficial effect of a product is obvious and clear-cut as it is in certain therapeutic areas. Examples are for instance significantly changing/restoring a critical endpoint linked to the disease to be treated (e.g. vitamin C supplementation in scurvy; removing a sensitive pathogen from an infection) or increasing survival in patients with short life-expectancy. However, even with outcomes such as time to event or death rate (which should be straightforward to measure), waiting for them to occur may be unfeasible and could mean delaying availability of potentially needed new drugs (Eichler et al., 2008). For that reason, alternative outcome variables are often considered such as surrogate end-points, biomarkers, etc.

The assessment becomes more challenging when efficacy relates to effects less easy to define as in the case of some psychotherapeutic drugs and in specific therapeutic psychiatric areas. This is particularly relevant in absence of objective diagnostic criteria and in the emergence of dimensional classification of mental disorders that may contribute to blurring the measurable endpoints. Concepts like apparent sadness, sense of guilt or suicidal ideation may be difficult to validate and harmonize across multisite clinical trials. It is even more complex to address issues such as emotional instability or neurodevelopmental maturation. In the best scenario the effects of a new compound are measured by means of scales which are at different stages of validation and are sometimes sensitive to the expected effect of drugs already existing in the market, rather than detecting what could constitute real benefit of the studied compound in the target disorder (Harmer et al., 2011). In addition in psychiatry most disorders under study represent a rather heterogeneous condition where no biomarkers are accepted so far.

With the above considerations in mind, it is not surprising that regulatory authorities are preparing and publishing ''guidelines'' in order to clarify what is expected from drug developers before submission for Marketing Authorization Application. Relevant to this article is the fact that the European Medicines Agency (EMA) is currently in the last stages of updating the guidelines on clinical investigation for medicinal products for treatment of depression and schizophrenia (http://www.ema.europa.eu). During the revision process (or at the drafting stage) guidelines are released in the so-called ''out for consultation'' period and every involved/interested stakeholder may provide comments on the draft document. Depending on the general opinion and provided that well argued comments are integrated, a final version is adopted. Even so, these guidelines cannot always coincide fully with regulatory guidance from other sources, and therefore are not legally binding. Companies are allowed, although not encouraged, to follow different approaches and, if a positive benefit/risk balance is demonstrated, still succeed in having their requested Marketing Authorization Application (MAA) granted (Regnstrom et al., 2010)

It must be recognized that a balance should be reached between the amount of evidence to be collected before any drug can be reasonably considered safe and effective and the time required for generating such evidence without unduly delaying availability of needed drugs. The exact realm of this ''compromise'' is, in a way, a matter of opinion, mainly based on existing MAA for similar drugs (Boon et al., 2010).

Indeed, the current European legislation and even more so the upcoming new pharmaco-vigilance act (entry date July 2012) allows for a ''conditional approval'', meaning that some drugs can be registered based upon preliminary evidence for a positive benefit/risk balance, but additional evidence still needs to be generated in order to keep the drug in the market. This is bound to a post-marketing commitment by the company to continue with agreed trials after the initial and conditional (i.e. not full) marketing authorization. In spite of their intrinsic therapeutic properties in preventing life threatening conditions such as suicidal ideation, impulsivity and aggressiveness, psychotherapeutic drugs are seldom, if ever, considered for a conditional approval.

Generating the required amount of clinical evidence, particularly at the confirmatory stages, involves comparative clinical trials. The choice of the right comparator(s) is often a matter of debate (reflection paper on the need for active control in therapeutic areas where use of placebo is deemed ethical and one or more established medicines are available, 2011; http://www.ema.europe.eu). As it is discussed elsewhere in this journal, two of the most common options, placebo (when feasible/ethical) or active comparator, have pros and cons and are suitable to address different types of scientific questions. However, the high accountable nature of regulatory decisions requires that all data must be transparent, understandable, and amenable to scrutiny.

Caught in the dilemma of asking for placebo controlled trials in an area where many studies fail and assay sensitivity is not self-evident, and the lack of a golden standard as comparator or expected effectsize, we summarized the