Research Briefing

Identification of drivers of effectiveness in Schizophrenia (D2.2)

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Key points

- The accumulation of exclusion criteria can lead to biased estimates of drugs effect, sometimes even underestimating the true effect.
- A practical implication of these findings is that before designing a trial, the impact of exclusion criteria – especially the ones not mandated by safety – should be assessed.

Background

RCTs often have limited external validity for several reasons, one being that they are performed in highly-selected patient populations [1, 2] recruited in hospital centres and screened using many inclusion and exclusion criteria. As a consequence of the trial setting and the selection of physicians and patients, the population in which the drug is tested before it is granted market authorization is a subset of the population which will actually receive the drug in the medical services. The choice in trial design parameters may have an impact on a drug effect estimate whenever they imply that one (or several) key characteristic(s) which interacts with/modify the drug effect, is not captured or not distributed as in routine clinical practice. These key characteristic or attributes that drive the difference between efficacy and effectiveness may be called "drivers of effectiveness".

In schizophrenia, most pre-authorization RCTs performed on antipsychotic drugs (APD) include highly-selected patients [3, 4] and thus, the effectiveness of APD which is of great importance for clinicians and healthcare policy makers, remains unknown when the drug is launched [1].

Objectives

The present study aimed:

1. to identify effect-modifiers of APD among the characteristics that are frequently used as exclusion criteria in RCTs
2. to quantify the impact of applying these exclusion criteria on the estimation of APD effect.

Methods

The study was performed in three main steps: (1) identification of potential drivers of effectiveness through the literature and (2) structured expert interviews, followed by (3) data analyses of these potential drivers of effectiveness and their impact on drug effect estimation, when used as exclusion criteria.

<u>Preliminary selection of key patient and drug use characteristics</u>

A first literature review aimed at identifying patient-related and disease-related characteristics which may act as effect-modifiers of APD in schizophrenia. The search strategy used the PICOS framework. Overall, 18 patient-related or disease-related characteristics were identified as potential effect-modifiers of APD effect and reviewed by clinical experts who considered the following characteristics as being clinically relevant: severity of illness at onset, disease stage/chronicity, current severity of negative symptoms, use/abuse of nicotine, cannabis or psychostimulants and adherence to medication.

A second focused literature review aimed at listing exclusion criteria used in pre-authorization phase-3 RCTs, with a focus on second-generation APD authorized for adult schizophrenia patients in the US and in Europe. The PICOS framework was used. Then, using cross checks with ClinicalTrial.gov and the websites of the European Medicines Agency and the Food and Drug Administration, we selected only "pivotal" RCTs.

In the end of this process, the possible effect modifiers of APD that were also frequently used as exclusion criteria in pivotal RCTs were: (1) disease chronicity, (2) substance use disorder (SUD) (excluding nicotine) and (3) poor adherence to medication.

<u>Analyses of potential drivers of effectiveness</u>

Data were drawn from the European Schizophrenia Outpatient Health Outcome (SOHO) cohort, an observational prospective cohort study [5-7]. Between 2001 and 2002, up to 1100 psychiatrists from ten countries included 10,218 outpatients with schizophrenia. All patients initiated or switched to an APD at baseline.

We selected the 8250 (80.7%) patients who initiated one of the 3 most frequently-prescribed drugs in the database: drug A (n=5439), drug B (n=2027) or drug C (n=784), all drugs being oral short-acting. The outcome of interest was the improvement of schizophrenia symptoms severity (using the Clinical Global Impression-Severity – CGI-S – scale) 3 months after baseline in patients initiating drug A, B or C.

"Exclusion Criteria of Interest" (ECoI) were defined as follows: a "short duration of illness" (yes/no) was defined as a delay since first APD treatment ≤3 years (vs. >3 years); "SUD" (yes/no) was defined as use/dependence of alcohol or another substance (excluding nicotine) and "adherence issues" corresponded to the physician rating of the past patient behaviour as "severe non-adherence".

An ECoI was likely to act as an effect-modifier of APD when the two patients strata (corresponding to meeting or not the criterion) had a statistically-significant difference in terms of mean level of symptoms improvement at 3 months. The impact of applying ECoI on the absolute effect of APDs, was quantified by measuring the outcome before and after the sequential (i.e., one by one) and combined (all applied) application of the ECoI.

Results

2436 (31.9%) patients had a short duration of illness, 395 (4.8%) patients had a comorbid SUD and 320 (3.9%) had severe non-adherence problems. The 2902 (35.2%) patients with any of the three characteristics would have been excluded from a "typical" RCT, leaving 5348 (64.8%) patients in the "RCT-like" subset of patients.

Patients with a shorter duration of illness had a higher mean level of symptoms improvement at 3 months than patients with a duration of illness >3 years (ΔCGI-S=-0.89 *vs.* ΔCGI-S=-0.73 respectively; p-value<0.001) and patients with severe non-adherence to the APD used before switch had a higher mean level of symptoms improvement at 3 months than patients without severe non-adherence issues (ΔCGI-S=-0.89 *vs.* ΔCGI-S=-0.78 respectively; p-value=0.044). Duration of illness and non-adherence were thus possible effect modifiers of APD (drugs A, B and C combined).

The "estimated effectiveness" of initiating an APD (drug A, B or C) computed in the SOHO cohort was ΔCGI-S=-0.78 (SD=1.0; n=8250) while the "estimated efficacy" computed in the "RCT-like" subset of SOHO patients with none of the 3 ECoI was ΔCGI-S=-0.73 (SD=0.96; n=5348). This suggests that excluding patients with at least one ECoI led to an underestimation of APD effect overall.

Excluding patients with a "short duration of illness" had the greatest impact on APD effect, whereas excluding patients with SUD or with severe non-adherence only did not modify the estimation of APD in the remaining patients.

Discussion

The exclusion criteria used in pivotal RCTs for APD are numerous and they often focus on characteristics of patients which are frequent in real life (psychiatric comorbidity, poor adherence, substance abuse, etc.). When the exclusion criteria act as effect-modifiers of the drug, this may impact the drugs effect estimate.

We suggest that duration of illness is an effect-modifier of APD effect, patients with a shorter duration of illness showing a more important drug response than patients with a longer duration of illness.

Patients with a shorter duration of illness should not be systematically excluded from RCTs.

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