

## MYTH AND REALITY OF PRAGMATIC TRIALS

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For some time now, there has been an ongoing debate on the benefits of so called ‘atypical’ antipsychotics (a.k.a. second-generation antipsychotics) over older, typical drugs in treatment of schizophrenia (Lewis & Lieberman 2008, Jakovljević 2009). Initially Geddes et al. (2000), followed by others, questioned the presumed superior efficacy of the atypicals and claimed that they did not perform better than classical antipsychotics prescribed in low doses. Although their conclusions were subsequently rebutted by several meta-analyses (e.g., Davis et al. 2003, Leucht et al. 2008a), their interpretations received wide attention and publicity.

We, as a group of regional experts, are concerned that results of several recent large pragmatic schizophrenia trials (CATIE, EUFEST, CUtLASS, Finnish cohort study) continue to be misinterpreted in a similar way. We feel that the data and results have to be read and interpreted carefully and correctly. In addition to the cited meta-analyses and reviews of the evidence (WPA statement: Tandon et al. 2008), there are several important points that should be noted and taken in to consideration.

First, the fact that there are substantial differences in efficacy and safety between first-, second- and third-generation antipsychotics have been now convincingly confirmed by the latest meta-analysis by Leucht et al. (2008a). Moreover, detailed scrutiny revealed significant and consistent drug-drug differences within the group of so called atypical antipsychotics (Leucht et al. 2008b) and validated thus results of earlier post hoc analyses with alternative statistical approaches (e.g., NNT and NNH) (Citrome 2008). The group comparisons may obscure the fact that there are individual differences: some “atypical” antipsychotics are more effective than other “atypicals” and even some “typical” antipsychotics are more effective than some “atypical” drugs. Clearly, there is an overlap in efficacy between the groups which are more heterogeneous than originally thought, and thus our current group comparisons are meaningless and conclusions

based on them are false and misleading. The individual drug differences are also apparent in the results of the discussed pragmatic trials. For example, reading carefully the design of EUFEST, one should be aware that on the primary efficacy measure (loss of retention), there was a discernible difference between the studied drugs. Unfortunately, authors of the major publication were forced to generalize otherwise, based on the results of secondary analysis (Volavka 2008).

Second, it is misleading to refer to the studied population as being representative of the whole patient population. In some of the above mentioned studies (CATIE, CUtLASS), the subjects were drawn from a pool of chronic patients who are the group which is difficult-to-treat per se. If the titles of the papers refer to ‘schizophrenia patients’, without any specifications, they do not tell us the whole truth.

Third, the choice of a comparator further complicates any quick conclusions. Somewhat surprisingly, we still do not know much about pharmacodynamics of some of the oldest drugs. For example, recent data indicate that perphenazine (performing well in CATIE) has a receptor profile identical to that observed in “atypical” antipsychotics (Sweet et al. 2000). Similarly sulpirid, unusually frequent in the CUtLASS study, belongs in the opinion of many authors to the group of “atypicals” (analogously as the newer compound amisulpride).

Fourth, the results of the cohort study from Finland (Tiihonen et al. 2006) remind us of the importance of compliance and adherence. There is no other way how to explain the fact that the best performing drug studied in the relapse prevention was perphenazine depot (long-acting injection), while oral form was about average, no better than most of the “atypical” antipsychotics.

Last but not least, one should be aware of the methodological limitations and shortcomings that are inherited in the naturalistic, pragmatic study design (Möller 2008). Although they provide valuable data and information that are complementary to those obtained in the randomized controlled

trials, their findings cannot be automatically accepted and translated into different clinical settings.

The negative perception of the “atypical” antipsychotics as a group, based on misinterpretation of the available data, could lead to distrust of mental health professionals, patients and their families, and care payers. False conclusions may then ultimately jeopardize access to the best care possible for the needed, schizophrenia patients.

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