

## Editorial

# European perspectives in psychiatry: antidepressants as an example

While public mental health issues have traditionally been followed also by supra-national or international organizations like WHO and EC, specific professional aspects of mental health care and disease management were so far regarded as locally specific matters, almost exclusively in the competence of local governments. Health care has been often politically directed from lower than national level of government, i.e. by cantons, counties and municipalities. This is also why it is so difficult to introduce real medicine to European agenda and why international professional associations, like EPA, have had almost zero influence on the quality of mental health care including treatment (there are no European standards or guidelines as yet) and ethics (coercion measures, involuntary treatment). Nevertheless, as many times before, the reality outran policy. Recently, article of Irving Kirsch et al. (1) triggered worldwide emotional discussion by provocative conclusion that antidepressants are generally no more effective than placebo. This was immediately grasped by journalists and anti-psychiatrists, largely publicized in media, misused by mental health care payers and misunderstood by patients and their relatives, who felt in the long term terribly cheated. So beyond our intention a pan-European medical cause was suddenly here. This was recently reflected in several editorials of psychiatric journals (2, 3) and in a hot debate at 16th European Congress of Psychiatry, held in April in Nice, France. The debate between one of the authors (B. J. Deacon) and an opponent (H.-J. Möller) was recorded and the webcast is available on the internet (4).

Let us briefly summarize how it happened. Kirsch et al. (1) report a meta-analysis of clinical trials, in which all data were available, submitted to the U.S. Food and Drug Administration (FDA) for approval of four new-generation antidepressants. Authors assessed linear and quadratic effects of initial illness severity expressed as a total score of Hamilton Rating Scale for Depression (HAMD) on clinical improvement both in subjects on active compound and on placebo, and also the difference between the active compound and placebo. This

difference increases as a function of initial severity. They found that antidepressants have a limited impact relative to placebo except in samples with highest levels of depression. Authors conclude that the difference between active compound and placebo in the trials involving fluoxetine, venlafaxine, nefazodone and paroxetine increases with the initial severity of the illness being clinically significant only in the most severe cases. In general, the difference does not reach the NICE criterion for clinically significant effect size. In addition, authors suggest that the initial severity-dependent increase of response to antidepressants is attributable rather to decreasing efficacy to placebo than to the effect of antidepressants.

The discussion, which followed, impugns methodology of the meta-analysis and drastically limits its interpretation. The 'law of initial value' says that the worse is the patient at the beginning of the study, the higher is the improvement (i.e. difference between initial and final measure). At the same time, however, we often see that the worse is the patient at the beginning the worse is also at the end of the study. In other words, the correlation between the initial value (of a scale) and the improvement is positive, but the correlation between the initial and final value is positive as well. This could be avoided by expressing this relationship as a ratio of final and initial value, which is unfortunately only exceptionally used. In the discussion in PLoS I wondered how the results of the meta-analysis would change if authors took into account not the difference, but only a final value of HAMD. Could it significantly change the conclusion? It would be clinically more relevant because we do not care as much how the patient improved in a study but rather how he/she is finally doing! P.J. Leonard responded to this challenge, recalculated the results of the meta-analysis and published it on his blog (5). And then, behold some of Kirsch evaluated antidepressants do reach NICE recommended effect size, which is clinically relevant (the difference in response to a drug and to placebo higher than 3 points of HAMD total score). After all, some other opponents (2) doubt the concept of clinically relevant

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effect size as problematic because it transforms effect size, a continuous measure, into a yes or no measure, thereby suggesting that drug efficacy is either totally present or absent, even when comparing values as close together as 0.51 and 0.49.

Moreover, our experience shows that effect of placebo decreases with time. It means that the biggest differences between placebo and an active drug do not occur during the 5–8 week period of clinical trials, but later on. Could it be possible from available data to calculate such a trend and hypothesize that the difference between placebo and an active drug could be observed later on during the treatment? The interpretation that with the severity of depression the effect of placebo decreases and the (negligible and non-significant) effect of active drug remains unchanged seems logically unacceptable: patients in double-blind randomized controlled trial namely do not know if they take placebo or active drug, so the decrease observed for placebo applies for active drug as well. If it does not occur, it means efficacy (not inefficiency) of the drug.

Furthermore, as Turner and Rosenthal (2) pertinently point out, if antidepressants are not worth taking, then what should doctors and patients do? Kirsch and colleagues recommend that if antidepressants are to be used at all they should be used only when alternative treatments have failed to provide a benefit. They may have had psychotherapy in mind. But before we accept any treatment as first line, we should ask whether its efficacy is based on evidence. For psychotherapy trials, there is nothing like FDA records we can examine, so how can we recommend such a treatment more than drugs?

Another limitation of the study is a selection bias. Only first studies needed for FDA registration were included. The main features of any compound, including long-term efficacy, adverse effects, etc, however, could be discovered only upon introduction of a drug on a market. Only then it is possible to evaluate its real effectiveness.

And this period is absolutely uncovered by the meta-analysis of Kirsch et al. (1).

So it seems that gutter press was this time overhasty again. It is up to us to set it right with equanimity, sooner than suicide rate and years in disability for depression will rapidly increase as happened everywhere after drop of prescriptions of antidepressants, e.g. in US children and adolescents (6). Moreover, wherever the ratio of prescribed antidepressants to benzos or just amount of prescribed antidepressants increased, suicide rate significantly decreased, as happened in Sweden (7), Hungary (8) and in other countries. This also should be seriously taken into account if thinking about the practical importance of antidepressants in mental health care system. Here the European perspective helps a lot.

*Acta Psychiatrica Scandinavica*  
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Invited Guest Editor

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