Position paper
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Off-label use of antipsychotics

Main lecturer: Guy M. Goodwin, United Kingdom
Discussants: Ravi Anand, Switzerland
Camilla Haw, United Kingdom

Off-label use of antipsychotics is a common phenomenon that may deal with a variety of psychiatric and non-psychiatric clinical situations. The off-label use may be acute and chronic and may refer to special patient populations, e.g. children, elderly demented.

Most off-label use of antipsychotics is not supported by high quality data of the kind required for regulatory approval. Occasionally off-label use is supported by and is based on scientific evidence produced by investigators in academia and/or supported by sponsors indicating favourable risk-benefit ratio.

Off-label use of antipsychotics as add-on therapy within the licensed indications has a wider justification in scientific and clinical terms, as clinical studies are often available to demonstrate its clinical validity.

Off-label use of antipsychotics in special populations such as children requires a higher attention. In fact the Regulatory Bodies are in the process of requiring more data in this regard. This is because off-label use of antipsychotics in children may have a high clinical impact due to the possible neurological and metabolic side-effects of these drugs.

The regulatory management of off-label use of drugs and, in particular, of antipsychotics may vary in the different European countries. A harmonisation of an off-label protocol in Europe is necessary.

Antipsychotics in BPSD and PAD

Main lecturer: Peter De Deyn, Belgium
Discussants: Josef Marksteiner, Austria
Emilio Sacchetti, Italy

Behavioural and psychological symptoms of dementia (BPSD) and psychosis of Alzheimer's disease (PAD) are two pathological situations that may complicate the clinical evolution of Alzheimer's disease (AD).

PAD may be considered as a possible separate nosologic entity, but further neurobiological and neuropathological studies are needed.

The use of antipsychotics in BPSD and PAD is very common, although it is mostly based on an off-label criterion. Among second generation antipsychotics only risperidone presents a clinical indication in some but not all European countries in these disturbances.

The review of literature in this area suggests that the use of antipsychotics in BPSD and PAD is only justified in those cases that do not experience adverse effects. Because of the low efficacy, there is a low benefit-risk ratio of these drugs in demented patients.

Because of lack of positive data from several randomized placebo-controlled trials and the small effect sizes demonstrated in systematic metanalysis (except post-hoc analysis studies), there is no consensus on antipsychotics' management of BPSD and PAD with antipsychotics. There is however significant data demonstrating efficacy on agitation and aggression in dementia, specifically for risperidone. Furthermore, there are no beneficial effects of these drugs on the cognitive function of demented patients.

The increased incidence of cerebro-vascular adverse events (CVAE) in demented patients treated with antipsychotics appears to be a class effect, where no substantial difference exists between first and second generation antipsychotics.

The biological base of this phenomenon is not known, however it is clear that elderly patients have an increased incidence of CVAE. Some co-morbidity increases the risk for CVAE in elderly demented, however, it should be noted that risk factors were identified in post-hoc analyses. More pre-clinical data are requested in order to clarify the mechanism of antipsychotic-induced increased incidence of CVAE in demented patients.

Safety of antipsychotics: from clinical evidence to regulatory restrictions

Main lecturer: Michael Davidson, Israel
Discussants: Milou-Daniel Drici, France
Christine C. Gispen-de Wied, The Netherlands

The occurrence of sudden death, cerebrovascular accidents (CVAs), and metabolic adverse effects has increased in both controlled phase III trials as well as from post marketing trials and pharmacovigilance reports.

Work by the US and European regulators have concluded that not all antipsychotics increase the risk for cardio-toxicity and that the metabolic adverse effects also differ.

Furthermore, the notion that tardive dyskinesia has disappeared with the advent of second generation antipsychotics appears not to be supported by data