

Towards a Better Drug Treatment for Patients in Child and Adolescent Psychiatry (CAP) – The European Approach

Authors: Aribert Rothenberger, Tobias Banaschewski

1. General view on psychoactive drugs in children

In February 2002 the European Commission (EC) launched a consultation document on “Better Medicines for Children” (<http://pharmacos.eudra.org/F2/home.html>). This touches a highly sensitive part of child and adolescent medicine, since the absence of suitable authorized medicinal products to treat diseases in children is an issue that has been of concern for some time. It led to the use of “off-label” and unauthorized products and to risks of inefficacy and/or adverse effects. Fortunately, it led also to a resolution of the EC Health Council in 2000, the European Guidelines in 2000 and the Directive 2001/20/EC on Good Clinical Practice (GCP) in 2001. Nevertheless, there are many steps to go, but it seems worthwhile to discuss, what the above mentioned document may tell us about the political frame concerning drug treatment in CAP.

In the European Union, children, the 0 – 16 years old population, represent about 75 million people, i.e. 20% of the total population. Although this population may appear relatively large, the majority of medicines are still only developed and assessed for use in adults. This is further confounded by the fact that this 0 – 16 years group may be divided into specific sub-populations ranging from neonates to teenagers, with different developmental and behavioral characteristics which need to be addressed.

It is estimated that somewhere between 50 and 90 % of medicinal products, depending on therapeutic areas, used in children have never been specifically evaluated for use in children. However, even if there is a clear therapeutic need for drugs in children, there are currently no legal provisions for obliging these studies to be performed if the pharmaceutical company does not present the product for use in the pediatric population.

Prerequisites for any European regulatory action to solve the problems identified include the need to ensure that the measures taken would benefit European children throughout the community, thus emphasizing the importance of a truly European approach and the need to ensure that any studies performed in children fully comply with the highest ethical principles

as laid down in the recently adopted Directive 2001/20/EC on good clinical practice. Additional and specific provisions to protect children in this directive include the need to ensure that appropriate informed consent procedures are developed and used, the wishes of the child are respected, measures to minimize pain and distress are taken and that the responsible ethics committee has involved specific expertise in the field of pediatric populations.

Six sets of objectives can be described:

- Increasing the availability of drugs in CAP by appropriate studies of new and existing drugs for children of different age groups
- Ensuring that pharmacovigilance mechanisms are adapted
- Facilitating the avoidance of unnecessary studies
- Establishment of a list of priority for research on drug treatment in children
- Developing European excellence in the field of research, development and assessment of clinical trials
- Ensuring that the highest ethical criteria are met

As avenues to achieve these objectives are proposed:

- Incentives for pharmaceutical companies research with protection of intellectual property and periods of market exclusivity
(for new and already marketed drugs)
- Creation of a fund for drug research in children
A safety and efficacy study may cost between \$ 1 and \$ 7.5 million. The new recently adopted US act allocated 200 million \$ annually. In Europe, based on an average estimate of 5 million \$ per trial 20 studies could be performed annually at a cost of about 100 million \$.
- Funding of drug research in children by the Sixth European Framework Program with a possible topic on pharmacogenetics and/or at the national level by governmental authorities and pharmaceutical industry
- Routinely requiring studies in CAP as part of the marketing authorization of drugs for adult psychiatric patients
- Creation and on-line availability of a central database
(i.e. drug monitoring including “off-label” and unauthorized use)

- Establishing an EU expert group or working party within the European Medicines Evaluation Agency (EMA) with specific responsibility for all aspects relating to the development, availability and follow up of medicines in childhood.
(Such a group was recently founded at the corresponding German agency)
- Encouraging submission of trials in Europe that have been accepted internationally.
(This holds already true for drug studies in CAP with risperidone, fluvoxamine, sertraline, methylphenidate preparations)
If a clinical study has been performed according to internationally accepted GCP standards and in accordance with the internationally accepted guidelines on medicinal products in children (ICH E 11) than it would be expected that this clinical study would be accepted in all European countries with minimal additional request for information. If acceptable and robust studies have been performed, than it can not be ethically justified either to repeat these studies or to require significant additional data. Ideally any studies that have already been performed outside of the EU should be used to introduce useful information, in particular to support or to contra-indicate CAP indications in medicinal products that are on the EU market
- Creation of a PAN-European network of clinical excellence for performance of studies in child populations
(So far, there has been little attempt at cross border collaboration; but there seem to be some European activities upcoming).

In conclusion, similar measures to those already taken in the USA are urgently needed for European children. These must take account of the specificities and structure of the EU market and the European pharmaceutical regulatory system. Achieving the right combination of incentives and regulatory obligations which will ensure that both existing and new medicinal products are suitably adapted for the needs of pediatric populations in the community in a resource efficient manner is a challenge that must be met in order to ensure the best and safest treatment for our children. The aim of the referenced document is to outline potential options of addressing this challenge by new pharmaceutical legislation.

2. The special case of stimulants

It is an empirically well based fact that ADHD reflects a distinct nosological entity and methylphenidate plays a major role within the treatment program of this disorder (Barkley et

al. 2002). It is also clear that in Europe only a small portion of children with ADHD receives the necessary and helpful drug treatment with stimulants (e.g. Schubert et al. 2001, Caspers-Merk 2002). Hence, it is not acceptable that some people still present perseveratively a non-evidenced based opposing view, using the latter to gain national influence via European political pathways. Without being supported by scientific facts such groups/persons develop non-qualified critics on CAP positions to undermine the state of the art in the field.

One of their main concern is the fact that the prescription of stimulants increased in many European countries within the last years. This was also the reason why the Council of Europe (CoE) focussed on the diagnosis and treatment of hyperactive children at the end of 1998. Therefore, the so-called Pompidou-Group, initiated by World Health Organisation and CoE in 1971 to combat drug abuse and illicit trafficking in drugs, was asked to critically shed some light on ADHD and stimulants. The resulting publication in 2000 (Pompidou-Group 2000) showed clearly that there were no problems with increased drug abuse in ADHD on the basis of regular stimulant treatment. The latter is supported by recent publications (e.g.: Biederman et al. ##, Lojewski et al. 2002, Huss personal communication).

Despite this empirical evidence, several European politicians under the leadership of the Swedish parliamentarian Gustafsson formulated a Motion for an Order (April 2000; Doc. 8727) with the title “Ending the misdiagnosis of children”. The latter reflects mainly anti-psychiatric and anti-ritalin positions. The motion led to an expert hearing of the European Parliamentary Assembly on “The diagnosis and treatment of hyperactive children” (Paris, November 2001). This meeting was also biased in the sense of the motion (e.g.: the “expert” Dr. Baughman, neurologist from the USA, who is known as a militant anti-psychiatrist was given an broad audience by the politicians without critics about his strange positions). On the other hand, parent organizations were excluded from the hearing and the participating politicians tried to ignore the presented evidence based data and arguments of leading European child and adolescent psychiatrists like Prof. Eric Taylor from London. Fortunately, the protest of European child and adolescent psychiatrists led to a less biased but still unacceptable report of the hearing: “Controlling the diagnosis and treatment of hyperactive children in Europe” (Doc. 9456, 7 May 2002; <http://assembly.coe.int/Main.asp?link=http%3A%2F%2Fassembly.coe.int%2Fdocuments%2Fworkingdocs%2Fdoc02%2Fedoc9456.htm>).

This report includes some suggestions to the CoE, the WHO and 43 Member Countries of CoE¹. It was accepted by the Parliamentarian Assembly in the end of May 2002 and unfortunately with final decision, by the Committee of Ministers in June 2002.

Ongoing protest by European parent organizations for ADHD and European child and adolescent psychiatrists (specially in Germany) involving open-minded politicians and organizations may lead to a more balanced and evidence based view of the issue in the near future and thus reduce the practical impact of this scandal.

In Germany, the working group for a consensus on ADHD (first conference at the German Ministry of Health in June 2002), has the objective in mind to develop regional networks of competence for patient care and research and includes all bodies involved in diagnosis and multimodal treatment of ADHD along the lifespan (selfhelp organizations, child and adolescent psychiatry, pediatrics, adult psychiatry, schools, governmental agencies, political administrations etc.).

The preliminary consensus of this working group is evidence based and reflects the scientific state of the art in ADHD, including the empirical data behind the practice parameters for the use of stimulant medications of the American Academy of Child and Adolescent Psychiatry (2002). This gives hope that ideological activities which try to ignore evidence based medicine, will be overcome – to the wellbeing of the patients and their families.

References

- Barkley et al. (2002). Consensus Statement. *European Child and Adolescent Psychiatry* 11: 96-98
- Biederman JT, Wilens E, Mick T, Spencer SV, Faraone SV (1999). Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk for substance use disorder. *Pediatrics* 104(2): e20-25.
- Caspers-Merk M. (2002). Aufmerksamkeitsdefizit- und Hyperaktivitätssyndrom. Keine „Modeerkrankung“. *Deutsches Ärzteblatt* 24: A1644-A1645.
- Schubert I, Lehmkuhl G, Spengler A, Döpfner M, von Ferber L (2001). Methylphenidat bei hyperkinetischen Störungen. *Deutsches Ärzteblatt* 9: A541-A544 .
- Pompidou-Group (2000). Attention Deficit/Hyperkinetic Disorders. Their diagnosis and treatment with stimulants. Council of Europe.
- Lojewski I, Wismann B, Höger C, Rothenberger A (2002). Sind mit Methylphenidat therapierte Menschen einem erhöhten Mißbrauchs- und Abhängigkeitsrisiko ausgesetzt? In: Richter G, Rommelspacher H, Spies C (Hrsg.), *Alkohol, Nikotin, Kokain ... und kein Ende?* Pabst, Lengerich, pp. 457-463.

¹ e.g.: The European Committee for Health should coordinate and step up research of ADHD, control diagnosis and treatment of ADHD more closely, monitor especially longterm effects of stimulants, look more closely into possible social and cultural factors involved in ADHD, work out safeguards and guidelines, support research into alternative treatments.