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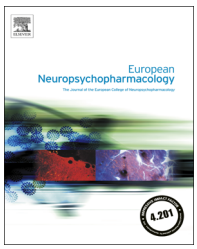

Psychiatric diseases moving towards adolescents and children: How much room is there for extrapolation?

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Abstract
Since medicines for psychiatric diseases are often studied in adults first, it would be useful if data from efficacy trials in adults could be extrapolated to children and adolescents. However, it is not sufficient to adapt the adult dosages to achieve systemic exposure levels similar to those effective in adults. This can be done with increasing predictive accuracy but before accepting that the same plasma levels should result in the same efficacy as in adults both the mechanism of action of the drug and the pathophysiology of the disease must be considered. For psychiatric disorders there is often insufficient evidence to support the assumptions for extrapolating efficacy as it is not even always sure that the same diagnostic categories correspond to the same disease in adults and children. Even when the basic biological alteration behind the disorder could be considered the same, the psychodynamic consequences and the role of non-pharmacological approaches to treatment may substantially differ across age groups. These facts, together with the absence of detailed historical data on the actual correlations between paediatric and adult responses for many types of psycho-therapeutic medicines, make it difficult to accept extrapolation as the main proof of efficacy in children and adolescents. A corollary is that since efficacy studies will normally be required, they should not be unduly postponed. For products addressing a medical need with good scientific plausibility, they should be initiated as soon as the anticipated safety concerns can be reasonably managed within the context of a paediatric clinical trial.

1. Introduction. Development of medicines for children and adolescents should be timelier

It is well known that medicines have often to be used off-label in children and adolescents since, as they are basically developed in adults, specific paediatric data are not available. This is

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the case for medicines to treat psychiatric disorders. With the exception of those primarily aimed at some basically paediatric conditions, such as ADHD or autism spectrum disorders, they are typically developed in/for adults first and only later, with the product already on the market, paediatric data are generated up to a variable extent. Until then, clinicians must rely on empirical clinical wisdom if they consider appropriate using the new product in children or adolescents (Emslie, 2012).

In the past years, new (Regulation (EC) No. 1901/2006) or updated (US Congress, 2012) legislation addresses this issue. In the EU, it is now compulsory to discuss with the Paediatric Committee (PDCO) of the European Medicines Agency (EMA) a Paediatric Investigation Plan (PIP) as early during the development of the product as the end of phase I, that is nearly always conducted basically in adults. Logically, although the plan is discussed early, the actual paediatric trials are normally scheduled to be conducted later, when sufficient adult data to justify exposing children to the drug become available. A PIP can (and in some cases must) be agreed with the PDCO also for products already on the market. Table 1 shows the numbers of PIP applications (and request for waivers when the product is considered unsuitable for children) dealt with by the EMA within the category psychiatry since 2007. The US approach to paediatric medicines is not dissimilar to that of the EU/EMA. A *Pediatric* Study Plan (PSP) is often established by the Food and Drug Administration (FDA).

2. Development in children would potentially be shorter if some data from adults could be extrapolated to them

In spite of the relevant biological differences between paediatric and adult populations and amongst the different paediatric age groups in relation to medicines, the no less obvious similarities should not be disregarded. It would not make sense to switch from a situation where children were hardly considered during the development of many new drugs to the opposite extreme where every adult clinical trial with every new product had to be repeated in every paediatric age group in which the disease is felt to be present. Even if this were feasible, it would be inefficient, leading to a number of largely unnecessary trials and, consequently, particularly since children are involved, questionable from an ethical point of view (Nelson et al., 2010). The possibility of adapting and/ or extrapolating data from adults to paediatric populations is already mentioned in the first 'global' attempt to reach a harmonized regulatory approach to the specific development of medicines for children, the "tripartite" (EU, Japan and USA) ICH E11 guideline adopted in July 2000 and then incorporated into the guidance of the three participating 'regions', e.g. in the EU as the EMA's "Note for guidance on clinical investigation on medicinal products in the paediatric population" (EMA, 2001).

Table 1 Applications to the EMA for PIP[a]/Waivers[b] within the category psychiatry 2007–July 2014. Source EMA data.

With published opinion	New products: 15 Authorized products: 6 PUMAs[c]: 1
Withdrawn/ongoing	New products: 22 Authorized products: 4
Total	48

[a]PIP: Paediatric Investigation Plan.
[b]Waiver: when a PIP is not required for different reasons (e.g. the disease does not exist in children, the product is unnecessary or felt to be too toxic to children etc.)
[c]PUMA: Paediatric Use Marketing Authorisation. It can be granted to old products, already off patent, being further developed for children.

Traditionally, adult dosages have been adapted to children, with varying success, by scaling down the adult dose according to rules based on allometric body characteristics such as weight or surface. More complex systems using techniques of 'modelling and simulation' are being developed (e.g. Manolis and Pons, 2009). They can incorporate variables such as the age-dependent level of maturity of the drug eliminating systems (biotransformation or excretion) or of the target structures as well as integrating pharmacodynamic markers when they exist. Such approaches will be useful to predict the dose needed in the different paediatric age groups to achieve similar systemic exposure levels as in adults with increased precision so that less "exploratory" trials are needed before performing the required pharmacokinetic "bridging" studies in children. But this is only part of the problem since it cannot always be taken for granted that the same plasma levels will result in the same efficacy in the paediatric age groups as in adults. Only when this can be considered to be the case (i.e. when it is felt that extrapolating efficacy is justified) can pharmacokinetic bridging studies aimed at reproducing the adult target exposure be the only efficacy requirement. Accepting extrapolation of efficacy depends not only on the maturity of the target structures, but also on the mechanism of action of the drug and on the pathophysiology of the disease. When these are known to be similar across the relevant age groups it is easier to conclude on the appropriateness of extrapolating efficacy.

The discussion on safety is not strictly parallel to that on efficacy and specific paediatric data need normally to be collected including because many paediatric safety concerns (e.g. on cognition and learning, psychological maturation, sexual development, body growth, etc.) cannot, obviously, be extrapolated from adults.

3. The FDA algorithm for determining the need for paediatric studies

The best known (and in my view still the most useful) decision tree to establish the need for paediatric studies with products well characterized in adults that explicitly considers the possibility of extrapolating efficacy is sometimes referred to as the FDA algorithm (Fig. 1). It was formulated at around the time of the adoption of the ICH-E11 tripartite guideline (see Section 2). Fig. 1 is adapted from Nelson et al. (2010) who discuss the algorithm in the context of prevention of a serious infectious disease. It can be seen that the case where less paediatric studies are required is that of (a) a disease in which it is reasonable to assume that progression is similar in children and adults, (b) it is reasonable to assume that children and adults have similar response to the modification (mechanism) produced by the medicine and (c) it is reasonable to assume that the exposure–response relationship is also similar in children and adults. Only in such a favourable situation (i.e.