

Child Psychopharmacology – Gaps in Knowledge

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Child psychopharmacology is a relatively new field. The 1937 publication by Charles Bradley reporting the effects of administering racemic amphetamine sulphate to 30 children 5 to 14 years of age with various behavioural disturbances is usually considered to mark the beginning of the modern era of child psychopharmacology.

The rapid growth of child psychopharmacology has been nothing short of being phenomenal. Not only have the types of medications available increased dramatically, but so have their annual rates of production and prescription. But There is, however, inadequate research on the physiological and behavioural effects of psychoactive medications; their long term effects, the mechanisms of their action, their side effects and their interactions with other treatments, both pharmacological and psychoeducational.

Because of several difficulties in conducting psychopharmacological research on the safety and efficacy of psychoactive drugs in children and younger adolescents, the investigation and introduction into clinical practice of psychoactive drugs in children has always lagged somewhat behind that for adults.

Extreme caution is required in employing psychoactive medications. The long terms effects of psychoactive medications on the maturation and development of children and adolescents are at best only partially known, and many of their known untoward effects are potentially harmful.

Children are not simply miniature adults. You can't just make milligram-per-kilogram assumptions with psychotropic drugs. From the perspective of pharmacotherapy, the process of development and growth in childhood represents an unstable and dynamic condition. The immaturity of the paediatric patient and the continuous state of development of body and organ functions influence both drug effects and drug disposition. Age-related differences in drug handling (pharmacokinetics) and drug sensitivity (pharmacodynamics) occur throughout childhood and account for many of the differences between drug doses at various stages of childhood (Routledge, 1994).

Therefore, children should not be considered as scaled down adults as the differences in doses are not purely dependent upon body mass. Processes controlling the

absorption, distribution, metabolism, excretion and pharmacologic effects of drugs are likely to be immature or altered in infants (Ebert, 2003).

A full 75% of the psychotropic drugs prescribed for children have not been tested for their use in well controlled trials, according to AAP. Instead, weight based dosing is used to estimate the necessary dosages for younger, smaller patients (Kaufmann, 2005).

Wide variations in drug dose recommendations for children of the same or different ages reflect the inadequacy of data on pharmacokinetics and pharmacodynamics in children. Selected aspects of available literature on pharmacokinetics of drugs used in children have been reviewed with special attention to calculation of an age-appropriate dose. In childhood, a greater rate of elimination from plasma than in adults has been observed for many drugs, notably phenobarbitone, phenytoin, carbamazepine, ethosuximide. Consistent with this, it has been shown that drugs exhibit a lower plasma level /dose ratio in childhood as compared with in adulthood. This is true for phenobarbitone, phenytoin and ethosuximide. Some age groups of children remain uninvestigated with regard to pharmacokinetics, even for the drugs reviewed. Therefore, paediatric therapy remains empirically based for many drugs (Rane & Wilson, 1976).

A number of physiologic and metabolic processes differ qualitatively as well as quantitatively when compared to adults. For example, different metabolic pathways predominate in the biotransformation of drugs. The impact of development on hepatic phase I (i.e. oxidation, reduction, hydroxylation) and phase II (i.e. glucuronidation, glutathione conjugation, sulfonation, methylation) enzymes can result in different metabolic profiles for a particular drug in children and some pathways may also be proportionally more active in children than in adults (Schwab, 2004).

Children and adolescents may require larger doses of psychoactive medication per unit of body weight than adults to attain similar blood levels and therapeutic efficacy. It is usually assumed that two factors explain this situation: 1) more rapid metabolism by the liver and an increased glomerular filtration rate in children compared with that in adults (Campbell et al, 1984).

The catecholamine (norepinephrine, epinephrine and dopamine) systems are not fully anatomically developed and operationally functional until adulthood. The relatively high prevalence of ADHD in younger children and its spontaneous improvement in many children over time may reflect maturational changes in catecholamine function. Interestingly, both the fact that children respond to stimulant medication differently from older adolescents and adults with respect to affect or mood (do not report elation, excitation or euphoria); and the fact that mania and euphoria are relatively rare in childhood may also be explained by the immaturity of the catecholamine systems (Puig-Antich, 1987).

Children and adolescents do not always respond to treatment with psychotropic drugs in a similar way compared to adults. For example, despite the fact that tricyclic antidepressants are traditionally the gold standards of pharmacotherapy for depressed adults, it does not seem that children with depression benefit from treatment with these agents. Similarly, it appears that early age at onset is associated with a reduced

propensity to respond to neuroleptics for patients with schizophrenia. In addition young patients have been noted to be at higher risk for developing neuroleptic induced extrapyramidal side effects when compared to adults. Simply put, what is known about the safety and effectiveness of psychotropic compounds in adults cannot necessarily be presumed to be applicable to teenagers or children (Findling, 2001).

Many psychoactive drugs have significant side effects. Because of the increased risk of acute liver failure, which has resulted in deaths or the need for liver transplants in some cases, magnesium pemoline is no longer recommended as a first line drug for Attention Deficit Hyperactivity Disorder (ADHD) (Green, 2001).

Disturbances in growth (decrements in both height and weight percentiles) have been reported for both methylphenidate and dextroamphetamine, and the long-term untoward consequences of these effects have been of particular concern (Safer et al, 1972).

Thioridazine has been labelled as causing prolonged QT intervals in a dose related manner and it was noted that drugs with this potential have been associated with torsade de pointes-type arrhythmias and sudden deaths in children (Green, 2001).

The causes for sudden death reported for children and adolescents taking desipramine are still not fully understood (Green, 2001).

One study revealed that after 19 weeks of treatment, paediatric patients taking Prozac (fluoxetine) gained an average of 1.1 cm less in height and about 1 kg less in weight than those taking placebo (Kulpa & Hurley, 2003).

Child psychopharmacology is now recognised as a distinct subspeciality of both the fields of child psychiatry and psychopharmacology. Much debate continues as to the ethics and morality of medicating children, particularly because they are often not the ones initiating their own treatment. Much remains to be learned about the use of psychotropic medications in children. Improvement of research programs in developmental pharmacokinetics including pharmacogenomic strategies seems to be necessary to allow a more rational approach to the pharmacological treatment of children of different age-groups.

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