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Elles Marleen Kemper, Maruschka Merkus, Peter Wierenga, Petra van Rijn-Bikker, Désiree B.M. van Der Werff, Loraine Lie a Huen, Martin Offringa

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TOWARDS EVIDENCE BASED PHARMACOTHERAPY IN CHILDREN

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SUMMARY

In daily practice is it difficult to find a registered drug for children, because about 70% of the drugs prescribed in children are not studied, off-label or unlicensed in this age group. Clinical trials have usually been performed in adults and then in daily practice dosages are adjusted for children without proper studies in that age group. In some countries national formularies are being established to overcome the existing variance in prescribing between physicians. Complicating factors in finding the correct dosage for children include the heterogeneity between different age groups in the developmental stages of the organs influencing the absorption, distribution, metabolism and excretion as well as differences in body composition during growth. Growth may also influence the effects and adverse effects of a drug used in a child. For oral administration of drugs in children, the bioavailability, the taste, composition and the absence of toxic ingredients for that age group are additional important factors. The EU has recently introduced legislation to stimulate the pharmaceutical industry to investigate the pharmacological effect and safety of new medicines in children. In response to this legislation research networks are being established to provide the optimal infrastructure for paediatric drug investigation. The goal of this paper is to review the current problems in daily practice and to address the needs for evidence based pharmacotherapy in children.

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INTRODUCTION

Before any medicine is approved for use in adults, the product must have undergone extensive testing including pre-clinical tests and clinical trials to ensure that it is safe and effective (1).

The same is frequently not true for medicines used to treat children. It is a major concern

that about 70% of the medicines used in the care of children are not studied, off-label or

unlicensed in one or more of their age groups. This often leaves no alternative to the

prescriber than to use an unlicensed drug (for example a syrup made by the local pharmacy

with a different formulation than originally licensed) or to use a drug off-label (a licensed

drug used outside the license in terms of age, indication, route of administration, dose or

contraindications) (2-5). In newborns this percentage of thus unlicensed and off-label use of

medicines is even higher, up to 80-90% (2;3).

In the past children have suffered from serious toxic effects due to exposure to inadequately

investigated medication. An example of such harm in children is the 'grey baby syndrome'

after the administration of chloramphenicol in newborns, because a deficiency in glucuronide

conjugation (the main pathway of chloramphenicol metabolism) in the first few days of life

caused elevated and prolonged plasma concentrations of chloramphenicol (6). Another

example is the use of verapamil to treat infants with supraventricular tachycardia resulting in

bradycardia, apnoea and cardiac death (7). In addition for some drugs higher drug doses are

required in children in order to achieve the same target plasma concentration as in adults. E.g.

children need a higher infusion rate of propofol compared to adult patients due to a higher

clearance expressed as mg/kg/min in children compared with adults (8;9).

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2 Another issue is the absence of suitable, approved medicinal products to treat young children
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4 and infants, i.e., age appropriate formulations. Pharmaceutical companies have often been
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6 reluctant to invest in the reformulation of existing medicines for infants and young children.
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8 This is mainly because the market is small and therefore of lower commercial interest and
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10 studies can be difficult, long and expensive. Furthermore, a reason why pharmaceutical
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12 companies are reluctant to conduct research in children, and particular in neonates, may be the
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14 fear of litigation if there is an adverse outcome.
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18 Thus there is still a gap between the performed research and the available evidence based
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20 medicines in paediatrics compared to those in adults (10). To address this lack of paediatric
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22 research, the United States and Europe have enacted legislation to encourage the investment
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24 of pharmaceutical companies in clinical trials involving children. In the field of paediatric
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26 anaesthesia there is an increasing number of publications, however, there are still issues
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28 which should be investigated. An example is the lacking information on the safety and
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30 pharmacokinetics of prolonged use of opioids in the mechanically ventilated newborn (11), or
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32 the use of benzodiazepines. Another example is the use of anaesthetic agents and neuronal
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34 apoptosis, i.e. neonatal rats exposed to ketamine suffered widespread neuronal apoptosis and
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36 long-term memory deficits (12;13). The applicability of extrapolating rodent data to the care
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38 of human neonates continues to be debated (14;15), but should be taken into account in their
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40 usage. However, studies to evaluate those compounds would be difficult to perform due to the
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42 many confounding factors in these situations and the additional ethical and emotional aspects
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44 associated with studies in children.
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47 The above often leaves no alternative to the prescriber than to use products in children
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49 without evidence-based information for a proper risk-benefit assessment. However, the
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American Academy of Pediatrics in conjunction with the Food and Drug Administration have specifically commented on the fact that a practitioner should use a drug in a child if the indication is the same as for an adult as a child. In particular they suggested that it would be immoral to deprive a child of the benefits of the medication (16).

In this review we discuss the current challenges facing the pharmacotherapy in children and briefly review the regulatory and legal aspects.

1. LACK OF EVIDENCE BASED PHARMACOTHERAPY

A. Dosing

In daily practice, health care providers experience various challenges with regard to the prescription and the administration of medicines to children and the major area of difficulty is neonates and infants. In drug prescribing the physician often relies on different paediatric textbooks, the internet, personal hand-held devices, online formularies, and other sources, and differences exist between countries, hospitals and even between physicians in the same institution. Due to the lack of age and formulation specific research in children, the prescribing physician often relies upon the evidence from studies in adults, while effectiveness and adverse effects may be significantly different for children compared to adults (17).

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Children may differ from adults in physiology and disease pathophysiology which in turn may result in a difference in the pharmacodynamic and pharmacokinetic profile of a drug. These differences in profile may be a result of the various developmental stages of a child that influence the absorption, distribution, metabolism and clearance of medicines (1;18). The glomerular filtration capability of the kidney reaches its peak between 6 and 12 months after

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2 birth and this should be taken into account when prescribing medicines depending on renal
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4 clearance (19;20). An example of the effect of the immature kidney is the prolonged clearance
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6 of d-tubocurarine in neonates compared to infants and adults (21).

7
8 Due to maturation of phase I (e.g. cytochrome P450 families) and phase II (e.g. glucuronide
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10 conjugation) enzymes in the liver the metabolism of many drugs is reduced in newborns. This
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12 may result in reduced excretion and increased potential for toxicity and adverse effects

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14 (22;23). For example, a smaller dosage of fentanyl and morphine is needed in newborns,

15 because of a prolonged clearance due to undeveloped metabolism of respectively, CYP3A4

16 and glucuronide conjugation (24;25). However, with morphine and fentanyl, other issues also

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17
18 play a role. Bolus dosing is determined by the volume of distribution and this is reduced for

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20 morphine in term postoperative neonates, so the bolus dose should be reduced in that situation

21
22 (26), but it is increased in premature ventilated neonates (25) and the dose should then be

23
24 increased. Maintenance dosing and infusion are determined by the clearance. A higher per

25
26 kilogram bolus fentanyl dose is usually better tolerated in neonates than adults because the

27
28 distribution volume is increased and redistribution rapid.

29
30 Another factor is the blood brain barrier function, which improves gradually with age,

31
32 possibly only reaching maturity by full-term age and with small molecules thought to access

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34 foetal and neonatal brains more readily than adult brains. Kernicterus, for example, is more

35
36 common in preterm neonates than in full-term neonates.

37
38 When prescribing drugs, especially to newborns and infants, also the pharmacodynamic

39
40 response can be different from the response in adults. Even in older children the

41
42 pharmacodynamic response may differ from adults and an example is the paradoxical reaction

43
44 of midazolam (restlessness, excitement and agitation) when administered to children (27). The

45
46 minimal alveolar concentration (MAC) for almost all vapours is also higher in infants than

47
48 neonates or adolescents (28-30).

Deleted: However, the underdeveloped blood brain barrier in neonates should also be taken into account with these compounds, because lipid insoluble compounds such as morphine as compared to fentanyl more easily pass the underdeveloped blood brain barrier and should therefore be reduced in dosage.

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4 The lack of evidence to guide prescribing and the unawareness of the role of developmental
5 pharmacology in children may also lead to ineffective treatment. An example is the
6 inadvertent but systematic underdosing of HIV infected children in the United Kingdom and
7 Ireland with antiretrovirals. In their paper the authors identify three serious issues in
8 prescribing antiretrovirals, which are relevant to paediatric prescribing in general: inadequate
9 dosing before the incorrect recommendation at licensing was revised, incorrect guidance
10 regarding dosage by weight or surface area, and lack of dose adjustment with growth (31).
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20 To overcome the existing prescribing practice variance, and to provide adequate existing
21 information, physicians and pharmacists have worked together in different countries to
22 establish national formularies (32;33). These formularies are based on the available evidence
23 in the literature combined with best-practice guidelines and opinions and experience of
24 paediatric experts. In the process of preparing these national formularies, the gaps in
25 knowledge have become apparent, and the positive result is that a problem driven research
26 agenda has been developed.
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35 **B. Choosing route of administration**

36 Besides prescribing the correct drug and dose, the formulation and route of administration are
37 also important. Since oral solutions and suspensions are often preferred in newborns and
38 young children, nurses have to measure small volumes accurately and mathematic errors can
39 easily occur.
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45 Especially with the administration of a concentrated solution, a small mistake in volume will
46 result in a large dosage variation. This also is important when administering drugs
47 intravenously to children and Allegaert et al showed that adult vials of the antibiotic amikacin
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2 for paediatric use may result in dose inaccuracy, and that a paediatric formulation improves
3 dosing accuracy of amikacin (34). However, it is important to emphasize that confusion and
4 administration errors may occur when two formulations of a drug are available in a hospital as
5 stressed for IV paracetamol formulations (35). To prevent dosing errors in small children it is
6 very important to have protocols for the preparation of drugs administered to small children
7 and the need to at least double check the dosage with the patient.
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16 Another concern is the need for a child friendly oral formulation appropriate for the child's
17 age or the ability of the child to ingest solid dosage formulations. Moreover, children often
18 refuse anything that does not taste or smell good to them. For adults the original taste and
19 smell of the drug can be masked by film coating the tablet or by placing the 'offending'
20 ingredients in a capsule. However, due to the lack of commercially available liquid
21 formulations for children, hospital and community pharmacies often reformulate medicines
22 designed for adults to a suitable liquid formulation or develop a new formulation from raw
23 material(36).
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31 When designing a (re)formulation it is important that all ingredients are compatible with each
32 other and suitable for children. Besides the active ingredient, excipients (i.e. substances added
33 to confer a suitable consistency or form to a drug such as bulk fillers, sweeteners,
34 preservatives, coloring agents, surfactants, anti-oxidants, etc.) could lead to adverse drug
35 events, altered absorption and/or bioavailability, or other symptoms (37).
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41 This (re)formulation creates its own safety issues since absorption may be negatively affected
42 by the excipients. A further concern is that the preservative is free of toxic adverse effects.
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45 For example, benzyl alcohol as a preservative in intravascular flush solutions has been
46 associated with a number of deaths and intraventricular hemorrhage in low-birth-weight
47 infants (38). Hemolysis, central nervous system depression, hyperosmolality and lactic
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2 acidosis have been reported after intravenous administration of propylene glycol, commonly
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4 used in parenteral medication (39).

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8 Unfortunately, despite the necessity of proper formulations for children in different age
9
10 groups, the scientific literature has paid little attention to the formulation of drugs; only 37%
11
12 of studies performed in children younger than 12 years old provided sufficient information
13
14 about the formulation (40). This is likely to be considered company-sensitive information, but
15
16 information about the global contents of the excipients may still be useful.

Deleted: if the preparation procedures and the exact amounts of each constituent are not provided companies can still inform properly about the global contents of the excipients.

20 21 **C. Risks of off label use of medicines**

22
23 In paediatric healthcare about 70% of the drugs used are either unlicensed or off-label and this
24
25 percentage is even higher in newborns; up to 80-90% (2;3). These percentages are much
26
27 higher than the off-label use of medication in adults, reportedly on average approximately
28
29 21% and with extremes for anticonvulsants (74%), antipsychotics (60%) and antibiotics
30
31 (46%) (41;42). This is of course also a matter of concern as companies are evidently not
32
33 performing trials in adults on new indications of their registered drug. Based upon the age-
34
35 dependent changes in pharmacokinetics and pharmacodynamics and, therefore, different
36
37 mechanisms of drug metabolism, children, like the elderly, are considered a vulnerable group
38
39 of patients in terms of patient safety. The use of unlicensed and off label drugs in these high
40
41 risk groups of patients may result in unwanted adverse drug reactions (ADRs) (43-47).
42
43 Although, the relation between ADRs and the prescription of unlicensed or off-label drugs is
44
45 not yet well established, studies have suggested a 2 to 5 fold increase in risk for ADRs when
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47 those drugs are administered to children.
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2 Safety is also an issue in drug trials in children. A recent literature review showed that only 13
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4 (2%) of 739 paediatric trials had a safety monitoring committee (48). Five hundred twenty-
5
6 three (71%) trials reported adverse drug reactions (ADRs) and 151 (20%) of these trials
7
8 reported a serious ADR. In about 11% of the trials a moderate or severe ADR occurred. The
9
10 authors recommend that all future paediatric clinical trials should have a safety monitoring
11
12 committee.

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14
15 Full reporting of ADR's is of paramount to give insight in the actual adverse effects of
16
17 medication, in adults and children. The national formularies make recommendations on how
18
19 to monitor ADR's in children when prescribing unlicensed and off-label drugs. Paediatric
20
21 professionals and also pharmacists need to stay alert for possible harm by an ADR and they
22
23 need to be encouraged to report all ADRs to national pharmacovigilance centers. Through the
24
25 collection and analyses of such data the extent of these ADRs can become apparent, and
26
27 means to prevent them in the future can be developed. There is a growing societal awareness
28
29 of medication safety for groups at risk, including children. Hospital management is
30
31 responsible for the availability of a proper medication safety system where physicians, nurses
32
33 and hospital pharmacists are encouraged to work together in a multidisciplinary team to
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35 prevent harm in their patients.

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36 37 38 39 **2. REGULATION**

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41 The lack of information on paediatric drugs has been caused, at least in part, that clinical trials
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43 in children are difficult, take long, are costly, and even are unethical. To improve and speed
44
45 up the development of safe and effective medication for children, the legislators in the US and
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47 in the EU have enacted paediatric regulations (49;50).
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2 On the 26th of January in 2007, the European Commission enacted 'the EU Paediatric
3 Regulation 1901/2006 on Medicinal Products for Paediatric Use'. The purpose of this new
4
5 legislation is to improve the healthcare of children in Europe by providing data on the efficacy
6
7 and safety of new agents and to support the development and availability of medicines. It will
8
9 ensure that these products are of high quality and approved.
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13 The implications are manifest. For each new drug that is developed in the European Union,
14
15 the manufacturer is obliged to develop a Paediatric Investigation Plan (PIP); in return they
16
17 will be rewarded with a six-month patent extension (51). The goal is to achieve this without
18
19 children undergoing unnecessary studies, or delay in the registration of medicines in adults.
20

21
22 However, the FDA then requires the pharmaceutical industry to carry out that plan to the
23
24 satisfaction of the FDA in order to obtain the six-month patent extension. This patent
25
26 extension only applies to studies of drugs that have the same indication in children as in
27
28 adults. It does not apply to paediatric-specific trials of drugs that are aimed at particular and
29
30 unique paediatric populations. Most recently, the European ERA-NET PRIOMEDCHILD
31
32 (work Package 5) project identified 216 research topics as key research priorities for
33
34 medicines for children (52). The next step is to allocate public money as well as industry
35
36 resources to this agenda.
37

38
39 In the USA there is already about ten years of experience with paediatric legislation. The
40
41 introduction of the Food and Drug Administration Modernization Act (1997), the Best
42
43 Pharmaceuticals for Children Act (2002), the Pediatric Research Equity Act (2003) and the
44
45 Pediatric Medical Device Safety and Improvement Act (2007) resulted in a dramatic increase
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47 in the number of paediatric studies performed from a few dozen before 1997 up to more than
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2 600 after 1997 (4). However, so far a substantial number of these studies have not yet been
3
4 published (53), but it is now required to publish the results on the FDA website.

5
6 An overall examination of the paediatric studies performed under this new legislation showed
7
8 that the types of drugs studied tended to mirror those most commonly used by the adult
9
10 market rather than drugs commonly used in children (54). This reflects the lack of a genuine
11
12 problem driven paediatric research agenda.

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15 The National Institute of Child Health and Human Development (NICHD) and the National
16
17 Institutes of Health (NIH) encourage studies in children. The Pediatric Research Equity Act
18
19 and the Best Pharmaceuticals Act both earmarked money to the NIH to encourage study of
20
21 drugs that were no longer patent protected, i.e., generic drugs. The European Medicines
22
23 Agency, however, as stated on its website "installed paediatric-use marketing authorisation
24
25 (PUMA) as a new type of marketing authorisation. It may be requested for a medicine which
26
27 is already authorised, but no longer covered by intellectual property rights (patent,
28
29 supplementary protection certificate), and which will be exclusively developed for use in
30
31 children. This type of marketing authorisation will cover the indication and appropriate
32
33 formulation for the paediatric population. A paediatric-use marketing authorisation will
34
35 benefit from 10 years of market protection as a reward for the development in children."(51)

36
37 Although the EU has followed the US to enact paediatric legislation there are still existing
38
39 differences between the regulation of the EU and US. For pharmaceutical companies it is
40
41 difficult to comply to both the requirements of the EU as the US and therefore harmonisation
42
43 between the regulations would be an enormous step forward.
44

45 46 47 **3.RESEARCH INFRASTRUCTURE/NETWORKS** 48 49 50

1
2 Conducting clinical trials in children is more complex than in adults (Table 1). The target
3
4 population of children suffering from a specific disease is generally smaller than in adults,
5
6 different age categories need to be considered, specific drug formulations for different age
7
8 categories are needed, accepted endpoints and validated outcome assessment tools are lacking
9
10 and children should be studied in environments appropriate for children. Furthermore, the
11
12 consent process is more complex and it is often difficult to convince parents of the importance
13
14 of conducting research even in newborns and assuring them that the utmost will be done to
15
16 protect the safety of their child (55;56). The consent process will be even more complex when
17
18 emergency situations have to be studied, as for example the treatment of supraventricular
19
20 tachycardia. It is therefore questionable if a prospective study would have prevented the
21
22 bradycardia, apnoea and cardiac death after treatment of verapamil, the example already
23
24 mentioned in the introduction and reported in case reports (7).
25
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27

28 To address these problems, properly resourced research infrastructures are needed. Recently,
29
30 national research networks have been established or are evolving in several European
31
32 countries, including the United Kingdom (Medicines for Children Research Network
33
34 (MCRN)), The Netherlands (MCRN), Germany (the German Paediatric Research Network,
35
36 PAED-net), Finland (Finnish Investigators Network for Pediatric Medicine, Finpedmed),
37
38 France (Réseau d'Investigations Pédiatriques des Produits de Santé, RIPPS, translated into
39
40 English The Investigation Network for Paediatric Health Products) and Belgium (Belgian
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42 Pediatric Drug Network, BPDN). These networks provide advice and support on all aspects of
43
44 trial-design, patient recruitment, data collection and management involving trials of medicines
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46 for children.
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2 The EU Paediatric Regulation requires the European Medicines Agency (EMA) to coordinate
3
4 the establishment of a European Paediatric Clinical Trials Network of existing national and
5
6 European networks, investigators and centres with specific expertise in the performance of
7
8 studies in the paediatric population. This aims to coordinate studies, to build up the necessary
9
10 competencies at the European level, to increase cooperation and to avoid duplication of
11
12 studies.

13 14 15 16 **4. CONCLUSION**

17
18 There is an increasing awareness of the importance of evidence based medicine in paediatric
19
20 anesthesia. However, good research into the safety and efficacy of medicines for children is
21
22 still highly needed and is a shared responsibility of health care providers, pharmaceutical
23
24 industry and parents. Standardization in the design of paediatric trials will contribute to the
25
26 development of a methodologically valid and relevant evidence base for paediatric care. All
27
28 future paediatric clinical trials should have a safety monitoring committee. Adequate
29
30 reporting of the studies' findings and updating of existing national formularies will enable
31
32 health care providers to translate the highly needed information into rational prescribing in
33
34 their daily practice.

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1
2 **Table 1: Current barriers & challenges in paediatric research**
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- 4 • Financing problems
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6 • Political problems
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8 • Legal problems
9
10 • Ethical concerns
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12 • Need to investigate different age groups
13
14 • Specific formulation requirement
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16 • Late-onset adverse effects
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18 • Small numbers of patients
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20 • Lack of accepted endpoints & validated assessment tools
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22 • No research infrastructure
23
24 • Convincing parents of the importance of paediatric research
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Reference List

- 1
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- 3
- 4 (1) Caldwell PH, Murphy SB, Butow PN *et al.* Clinical trials in children. *Lancet* 2004
- 5 Aug 28;**364**(9436): 803-811.
- 6 (2) Conroy S, Choonara I, Impicciatore P *et al.* Survey of unlicensed and off label drug
- 7 use in paediatric wards in European countries. European Network for Drug
- 8 Investigation in Children. *BMJ* 2000 Jan 8;**320**(7227): 79-82.
- 9 (3) 't Jong GW, Vulto AG, de HM *et al.* Unapproved and off-label use of drugs in a
- 10 children's hospital. *N Engl J Med* 2000 Oct 12;**343**(15): 1125.
- 11 (4) Roberts R, Rodriguez W, Murphy D *et al.* Pediatric drug labeling: improving the
- 12 safety and efficacy of pediatric therapies. *JAMA* 2003 Aug 20;**290**(7): 905-911.
- 13 (5) Cote CJ, Alexander J. Drug development for children: the past, the present, hope for
- 14 the future. *Paediatr Anaesth* 2003 May;**13**(4): 279-283.
- 15 (6) Weiss CF, Glazko AJ, Weston JK. Chloramphenicol in the newborn infant. A
- 16 physiologic explanation of its toxicity when given in excessive doses. *N Engl J Med*
- 17 1960 Apr 21;**262**: 787-794.
- 18 (7) Garson A, Jr. Medicolegal problems in the management of cardiac arrhythmias in
- 19 children. *Pediatrics* 1987 Jan;**79**(1): 84-88.
- 20 (8) McFarlan CS, Anderson BJ, Short TG. The use of propofol infusions in paediatric
- 21 anaesthesia: a practical guide. *Paediatr Anaesth* 1999;**9**(3): 209-216.
- 22 (9) Engelhardt T, McCheyne AJ, Morton N *et al.* Clinical adaptation of a pharmacokinetic
- 23 model of Propofol plasma concentrations in children. *Paediatr Anaesth* 2008
- 24 Mar;**18**(3): 235-239.
- 25 (10) Cohen E, Uleryk E, Jasuja M *et al.* An absence of pediatric randomized controlled
- 26 trials in general medical journals, 1985-2004. *J Clin Epidemiol* 2007 Feb;**60**(2): 118-
- 27 123.
- 28 (11) Bellu R, de Waal KA, Zanini R. Opioids for neonates receiving mechanical
- 29 ventilation. *Cochrane Database Syst Rev* 2008;(1): CD004212.
- 30 (12) Fredriksson A, Archer T, Alm H *et al.* Neurofunctional deficits and potentiated
- 31 apoptosis by neonatal NMDA antagonist administration. *Behav Brain Res* 2004 Aug
- 32 31;**153**(2): 367-376.
- 33 (13) Wang C, Sadovova N, Fu X *et al.* The role of the N-methyl-D-aspartate receptor in
- 34 ketamine-induced apoptosis in rat forebrain culture. *Neuroscience* 2005;**132**(4): 967-
- 35 977.
- 36 (14) Soriano SG, Anand KJ, Rovnaghi CR *et al.* Of mice and men: should we extrapolate
- 37 rodent experimental data to the care of human neonates? *Anesthesiology* 2005
- 38 Apr;**102**(4): 866-868.
- 39 (15) Anand KJ, Soriano SG. Anesthetic agents and the immature brain: are these toxic or
- 40 therapeutic? *Anesthesiology* 2004 Aug;**101**(2): 527-530.
- 41 (16) Uses of drugs not described in the package insert (off-label uses). *Pediatrics* 2002
- 42 Jul;**110**(1 Pt 1): 181-183.
- 43 (17) Cramer K, Wiebe N, Moyer V *et al.* Children in reviews: methodological issues in
- 44 child-relevant evidence syntheses. *BMC Pediatr* 2005;**5**: 38.
- 45 (18) Kearns GL, bdel-Rahman SM, Alander SW *et al.* Developmental pharmacology--drug
- 46 disposition, action, and therapy in infants and children. *N Engl J Med* 2003 Sep
- 47 18;**349**(12): 1157-1167.
- 48 (19) DeWoskin RS, Thompson CM. Renal clearance parameters for PBPK model analysis
- 49 of early lifestage differences in the disposition of environmental toxicants. *Regul*
- 50 *Toxicol Pharmacol* 2008 Jun;**51**(1): 66-86.
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- (20) Rhodin MM, Anderson BJ, Peters AM *et al.* Human renal function maturation: a quantitative description using weight and postmenstrual age. *Pediatr Nephrol* 2009 Jan;**24**(1): 67-76.
- (21) Fisher DM, O'Keeffe C, Stanski DR *et al.* Pharmacokinetics and pharmacodynamics of d-tubocurarine in infants, children, and adults. *Anesthesiology* 1982 Sep;**57**(3): 203-208.
- (22) WEISS CF, Glazco AJ, WESTON JK. Chloramphenicol in the newborn infant. A physiologic explanation of its toxicity when given in excessive doses. *N Engl J Med* 1960 Apr 21;**262**: 787-794.
- (23) Johnson TN. The development of drug metabolising enzymes and their influence on the susceptibility to adverse drug reactions in children. *Toxicology* 2003 Oct 1;**192**(1): 37-48.
- (24) Santeiro ML, Christie J, Stromquist C *et al.* Pharmacokinetics of continuous infusion fentanyl in newborns. *J Perinatol* 1997 Mar;**17**(2): 135-139.
- (25) Anand KJ, Anderson BJ, Holford NH *et al.* Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: secondary results from the NEOPAIN trial. *Br J Anaesth* 2008 Nov;**101**(5): 680-689.
- (26) Bouwmeester NJ, Anderson BJ, Tibboel D *et al.* Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. *Br J Anaesth* 2004 Feb;**92**(2): 208-217.
- (27) Massanari M, Novitsky J, Reinstein LJ. Paradoxical reactions in children associated with midazolam use during endoscopy. *Clin Pediatr (Phila)* 1997 Dec;**36**(12): 681-684.
- (28) Lerman J, Robinson S, Willis MM *et al.* Anesthetic requirements for halothane in young children 0-1 month and 1-6 months of age. *Anesthesiology* 1983 Nov;**59**(5): 421-424.
- (29) LeDez KM, Lerman J. The minimum alveolar concentration (MAC) of isoflurane in preterm neonates. *Anesthesiology* 1987 Sep;**67**(3): 301-307.
- (30) Taylor RH, Lerman J. Minimum alveolar concentration of desflurane and hemodynamic responses in neonates, infants, and children. *Anesthesiology* 1991 Dec;**75**(6): 975-979.
- (31) Menson EN, Walker AS, Sharland M *et al.* Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study. *BMJ* 2006 May 20;**332**(7551): 1183-1187.
- (32) www.bnfc.org (British National Formulary for Children), (at October 20th 2010).
- (33) www.kinderformularium.nl (Dutch children's formulary), (at October 20th 2010).
- (34) Allegaert K, Anderson BJ, Vrancken M *et al.* Impact of a paediatric vial on the magnitude of systematic medication errors in neonates. *Paediatric & Perinatal Drug Therapy* 2006;**7**(2): 59-63.
- (35) Allegaert K, Murat I, Anderson BJ. Not all intravenous paracetamol formulations are created equal.. *Paediatr Anaesth* 2007 Aug;**17**(8): 811-812.
- (36) Schirm E, Tobi H, de Vries TW *et al.* Lack of appropriate formulations of medicines for children in the community. *Acta Paediatr* 2003 Dec;**92**(12): 1486-1489.
- (37) Pawar S, Kumar A. Issues in the formulation of drugs for oral use in children: role of excipients. *Paediatr Drugs* 2002;**4**(6): 371-379.
- (38) Hiller JL, Benda GI, Rahatzad M *et al.* Benzyl alcohol toxicity: impact on mortality and intraventricular hemorrhage among very low birth weight infants. *Pediatrics* 1986 Apr;**77**(4): 500-506.
- (39) Arulanantham K, Genel M. Central nervous system toxicity associated with ingestion of propylene glycol. *J Pediatr* 1978 Sep;**93**(3): 515-516.

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56
57
58
59
60
- (40) Standing JF, Khaki ZF, Wong IC. Poor formulation information in published pediatric drug trials. *Pediatrics* 2005 Oct;**116**(4): e559-e562.
- (41) Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med* 2006 May 8;**166**(9): 1021-1026.
- (42) Stafford RS. Regulating off-label drug use--rethinking the role of the FDA. *N Engl J Med* 2008 Apr 3;**358**(14): 1427-1429.
- (43) Gill AM, Leach HJ, Hughes J *et al*. Adverse drug reactions in a paediatric intensive care unit. *Acta Paediatr* 1995 Apr;**84**(4): 438-441.
- (44) Turner S, Nunn AJ, Fielding K *et al*. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatr* 1999 Sep;**88**(9): 965-968.
- (45) Horen B, Montastruc JL, Lapeyre-Mestre M. Adverse drug reactions and off-label drug use in paediatric outpatients. *Br J Clin Pharmacol* 2002 Dec;**54**(6): 665-670.
- (46) Neubert A, Dormann H, Weiss J *et al*. The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients. *Drug Saf* 2004;**27**(13): 1059-1067.
- (47) Schirm E, Tobi H, van Puijenbroek EP *et al*. Reported adverse drug reactions and their determinants in Dutch children outside the hospital. *Pharmacoepidemiol Drug Saf* 2004 Mar;**13**(3): 159-165.
- (48) Sammons HM, Gray C, Hudson H *et al*. Safety in paediatric clinical trials--a 7-year review. *Acta Paediatr* 2008 Apr;**97**(4): 474-477.
- (49) Steinbrook R. Testing medications in children. *N Engl J Med* 2002 Oct 31;**347**(18): 1462-1470.
- (50) Bosch X. Pediatric medicine. Europe follows U.S. in testing drugs for children. *Science* 2005 Sep 16;**309**(5742): 1799.
- (51) www.ema.europa.eu (at October 20th 2010).
- (52) www.priomedchild.eu (at October 20th 2010).
- (53) Benjamin DK, Jr., Smith PB, Murphy MD *et al*. Peer-reviewed publication of clinical trials completed for pediatric exclusivity. *JAMA* 2006 Sep 13;**296**(10): 1266-1273.
- (54) Boots I, Sukhai RN, Klein RH *et al*. Stimulation programs for pediatric drug research--do children really benefit? *Eur J Pediatr* 2007 Aug;**166**(8): 849-855.
- (55) Davidson AJ, O'Brien M. Ethics and medical research in children. *Paediatr Anaesth* 2009 Oct;**19**(10): 994-1004.
- (56) Waisel DB. Moral responsibility to attain thorough pediatric drug labeling. *Paediatr Anaesth* 2009 Oct;**19**(10): 989-993.

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PAN-2009-0044.R1 TOWARDS EVIDENCE BASED PHARMACOTHERAPY IN CHILDREN

Amsterdam, November 14th 2010

Dear Dr Morton,

Thank you for reviewing our manuscript entitled “Towards Evidence based pharmacotherapy in children.” We are very grateful for the very quick review and the comments by this reviewer. It is obvious that this reviewer put an enormous effort in the details of our review to improve it.

The comments are incorporated throughout the text. In appendix 1 our responses to the comments of the reviewers are listed in detail. The changes in the manuscript are again done with track changes. The references are inserted with Reference Manager. We have chosen “Paediatric Anaesthesia” as output style and hopefully the references are correctly this way.

We would like to resubmit our paper for reconsideration for publication in Paediatric Anaesthesia.

However, not without sincerely thanking the reviewers for the major improvements they made in this manuscript!

With kindest regards, on behalf of all authors,

Marleen Kemper

Peer Review

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author

Bupivacaine clearance is through CYP3A4 (Mazoit JX Clin Pharmacokinet 2004; 43(1):17-32), not glucuronide conjugation.

We have to apologize for our statement that bupivacaine is metabolized by glucuronide conjugation. This information was generated from the Thompson Micromedex database. However, in the bupivacaine product information of Astra Zeneca, the metabolism of bupivacaine by CYP3A4 is mentioned as the main metabolic pathway of this drug as also stated by the reviewer. As this was not mentioned in the manuscript, we did not have to make changes.

I enjoyed reading this current revision. There remain a few minor considerations.

1. I think you have to be careful equating unlicensed or off-label with not studied.

We are in a bit of a predicament with this comment, because the other, previous reviewer insisted on changing unlicensed and off-label into not studied, with the argument that (completely) unlicensed medication is not the case. In principle, we agree on the change requested by the present reviewer and we changed "not studied" in "not studied, unlicensed or off-label" in the summary and in the first paragraph of the introduction.

2. Please use drug concentrations rather than levels with referring to amount in blood or serum or plasma.

The document was searched for "level" and on page 3 "plasma levels of chloramphenicol" was changed in "plasma concentrations of chloramphenicol".

3. p15 L12 ore=or

This was changed on page 3 (P15 for the reviewer).

4. p16 L40. I agree that investigations of neuronal apoptosis are difficult. However the quandry is being approached from 2 angles..a) a study looking at GA vs regional techniques in babies b) reviewing national data banks comparing neonates who had surgery with those who did not. I don't think you can say that ethical committees will be unwilling to endorse such studies. To not do so could be argued unethical! Perhaps you should simply say that such studies are difficult etc

We have deleted "with difficulties to point a certain effect to the study drug and most likely unwillingness of ethical committees to endorse such studies and this sentence is now: "However, studies to evaluate those compounds would be difficult to perform due to the many confounding factors in these situations and the additional ethical and emotional aspects associated with studies in children."

5. P17 L34 Efficacy is commonly confused with effectiveness. Efficacy in pharmacology is the max response on a dose or concentration response curve.

We agree on this and "efficacy was replaced by effectiveness" on p5 (for the reviewer page 17) line 34.

6. Side effects =adverse effects

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3 The document was searched for "side effects" and this was changed in "adverse effect" on
4 page 2, 5, 6, 8, 10 and in the table on page 15 (P14, P17, P18, P20, P22 and P27 for the
5 reviewer).
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8 7. P18 L6 Please define CYP the first time it is used. Perhaps this line could read *Due to*
9 *maturing phase I (e.g. cytochrome P450 families) and phase II (e.g. glucuronide*
10 *conjugation)*...

11 Line 6 on page 6 (P18 for the reviewer) was changed in: "Due to maturation of phase I (e.g.
12 cytochrome P450 families) and phase II (e.g. glucuronide conjugation)"
13

14
15 8. *glucuronide conjugation rather than glucuronidase*

16 On page 6 glucuronidase was changed in glucuronide conjugation twice.
17

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19 9. P18 L40 *can differ=may differ. I would construct a second sentence rather than use and*
20 *as a link...The minimal alveolar concen...is also higher...*

21 "Can differ" was changed in "may differ" and we split the sentence as suggested by the
22 reviewer. " The minimal alveolar concentration (MAC) for almost all vapours is also higher in
23 infants than neonates or adolescents (28-30)."
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27 10. P19 L 44. *omit "causing a relative increase or decrease in assumed bioavailability"...It is*
28 *dosing that is inaccurate; bioavailability is unchanged..."a paediatric formulation improved*
29 *dosing accuracy of amikacin..."*

30 We agree, of course! On page 7 (P19 for the reviewer) the sentence "causing a relative
31 increase or decrease in assumed bioavailability" was omitted and we added "accuracy"
32 between "dosing" and "of".
33

34
35 11. P21 L14 *the last phrase ...information about the global contents of the excipients may still*
36 *be useful.*

37 We have deleted "if the preparation procedures and the exact amounts of each constituent are
38 not provided companies can still inform properly about the global contents of the excipients."
39 and replaced it by "information about the global contents of the excipients may still be
40 useful."
41

42
43 12. P21 L28 *21% (xx)...no reference provided. Actually I thought the figure was around 50%*
44 *for adults*

45 We apologize for leaving out these references. We are referring to two publications:

46 (41) Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based
47 physicians. *Arch Intern Med* 2006 May 8;**166**(9): 1021-1026.

48 (42) Stafford RS. Regulating off-label drug use--rethinking the role of the FDA. *N Engl J Med*
49 2008 Apr 3;**358**(14): 1427-1429.
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53 We have clarified this part to: "reportedly on average approximately 21% and with extremes
54 for anticonvulsants (74%), antipsychotics (60%) and antibiotics (46%) (41;42)"
55

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58 P22 L47 *effectuated = enacted*

59 Enacted was inserted instead of effectuated.
60

13. P23 L 16 *requires the pharmaceutical industry to carry out...*

We inserted "the pharmaceutical industry".

14. *The BBB is an interesting example of differences between the adult and neonate. Unfortunately, the example you use of morphine to illustrate a leaky BBB is based on a poor paper by Way (Clin Pharmacol Ther 1965;6:454-61). Respiratory depression after morphine was greater than that after meperidine. This difference was attributed to greater brain concentrations of morphine because of the poorly developed BBB in the neonate. It was postulated that BBB permeability to water-soluble drugs such as morphine, change with maturation. However, the neonatal respiratory depression observed after morphine could have been explained by pharmacokinetic age-related changes. For example, the volume of distribution of morphine in term neonates 1-4 days (1.3 L/kg) is reduced compared with that in infants 8-60 days of age (1.8 L/kg) and in adults (2.8 L/kg). Meperidine V is increased in neonates. Consequently, we might expect greater initial concentrations of morphine in neonates than in adults (or from meperidine), resulting in more pronounced respiratory depression in the former. Respiratory depression, measured by carbon dioxide response curves or by arterial oxygen tension are similar from 2 to 570 days of age at the same morphine blood concentration. The BBB theory in this particular circumstance lacks strong evidence. It is more likely that the increased neonatal respiratory depression after morphine is due to pharmacokinetic age-related changes.*

The BBB may have impact however, in other ways. Small molecules are thought to access foetal and neonatal brains more readily than in adults. BBB function improves gradually, possibly reaching maturity by full-term age. Kernicterus, for example, is more common in preterm neonates than in full-term neonates. In contrast to drugs bound to plasma proteins, unbound lipophilic drugs passively diffuse across the BBB equilibrating very quickly. This may contribute to bupivacaine's propensity for seizures in neonates. Decreased protein binding, as in the neonate, results in a greater proportion of unbound drug that is available for passive diffusion.

In addition to passive diffusion, there are specific transport systems that mediate active transport. Pathological CNS conditions can cause BBB breakdown and alter these transport systems. Fentanyl is actively transported across the BBB by a saturable ATP-dependent process, while ATP-binding cassette proteins such as P-glycoprotein actively pump out opioids such as fentanyl and morphine. P-glycoprotein modulation significantly influences opioid brain distribution and onset time, magnitude and duration of analgesic response. Modulation may occur during disease processes, fever, or in the presence of other drugs (e.g. verapamil, magnesium). Genetic polymorphisms that affect P-glycoprotein-related genes may explain differences in CNS-active drug sensitivity.

It may be simpler to say that the BBB changes with age and use kernicterus as an example.

The reviewer provides detailed knowledge and examples on the immature aspects of the BBB in neonates and children, but subsequently suggests not to incorporate that information in the manuscript. We agree with that suggestion and only replaced:

"However, the underdeveloped blood brain barrier in neonates should also be taken into account with these compounds, because lipid insoluble compounds such as morphine as compared to fentanyl more easily pass the underdeveloped blood brain barrier and should therefore be reduced in dosage."

into:

"Another factor is the blood brain barrier function, which improves gradually with age, possibly only reaching maturity by full-term age and with small molecules thought to access

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3 foetal and neonatal brains more readily than adult brains. Kernicterus, for example, is more
4 common in preterm neonates than in full-term neonates."
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7 *I think this a very useful paper that readers will find helpful and I appreciate all the efforts*
8 *the authors have undertaken.*
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For Peer Review