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USE OF MEDICINES IN CHILDREN

- **Many medicines have not undergone extensive evaluation in children and the "off-label or unlicensed" use of medicines in children is common**
- **Children are particularly susceptible to adverse drug reactions and medication errors**
- **The dose of a medicine, based on age and/or weight, needs to be individualised to the child using a reliable paediatric medicines information resource**
- **Good communication is important between all healthcare professionals involved in the child's treatment and with the parents/carers**

INTRODUCTION

Children experience many of the same diseases as adults, and are sometimes treated with the same medicines.[1] However, the prescribing of medicines in children presents specific challenges.[2-4] For example, the developmental changes that occur throughout childhood affect the response to medicines.[5-7] **Children are particularly susceptible to adverse drug reactions (ADRs) and medication errors.[8]** Medicines require a licence (marketing authorisation [MA]) before they can be marketed,[9,10] which means that they have undergone appropriate clinical evaluation to confirm an acceptable benefit/risk balance for the proposed indication. **Many medicines, currently used to treat the paediatric population, may not have been evaluated, to the same extent, for use in children compared to use in adults.[1]** Therefore, many medicines that are prescribed in children are used "off-label" or are unlicensed for the indication for which they have been prescribed (see later section on "off-label or unlicensed" prescribing).[11] This bulletin reviews some of the factors to consider when prescribing medicines in children.

MEDICINES INFORMATION RESOURCES TO SUPPORT PRESCRIBING OF MEDICINES IN CHILDREN

Table 1 below details the key medicines information resources to support the prescribing of medicines in children.

Table 1: Medicines information resources to support prescribing in children

Health Products Regulatory Authority • The SmPC* may provide information on dosing in children for some medicines www.hpra.ie
HSE Antibiotic Prescribing • Includes general prescribing principles for children and information on prescribing of antimicrobials for children https://www.hse.ie/eng/services/list/2/gp/antibiotic-prescribing/prescribing-for-children/
Children's Health Ireland (CHI) • CHI have a prescribing formulary and also clinical guidelines Available as an app to download; ensure that the most up to date version is being used
British National Formulary for Children (BNFC) • The BNFC is the standard UK paediatric reference source for prescribing in children https://about.medicinescomplete.com/ (subscription required)
Paediatric Formulary UK • This paediatric formulary is produced by the Paediatric Formulary Committee of the Evelina London Children's Hospital Available as an app to download; ensure that the most up to date version is being used
Medicines for Children • This UK website has advice for HCPs and parents, including leaflets on specific medicines and general medicines advice. The website is maintained by the Royal College of Paediatrics and Child Health (RCPCH), the Neonatal and Paediatric Pharmacists Group (NPPG) and the charity "WellChild" https://www.medicinesforchildren.org.uk/

SmPC-Summary of Product Characteristics; HSE-Health Service Executive; HCP-healthcare professionals; *also available on www.medicines.ie

The Summary of Product Characteristics (SmPC) should be consulted initially for licensed information on the use of a specific medicine.[1] Information specifically on the use of medicines in children provided by Irish resources include the HSE antibiotic prescribing website and Children's Health Ireland (CHI) (see table 1). Of note, some resources provide dosing information based on the child's age whereas other resources provide information based on weight. In general, drug dosing in children should be weight based rather than age based (as all children of the same age are not the same size).[1,8] The NMIC can deal with enquiries that prescribers may have that are not addressed in these first line information sources (e-mail: nmic@stjames.ie or phone 01 4730589).

"OFF-LABEL OR UNLICENSED" PRESCRIBING IN CHILDREN

In general, "off-label" use refers to the use of a licensed medicine outside the terms of its SmPC (e.g. outside the licensed indication, age group, dose, frequency and route of administration), while the term "unlicensed medicine" refers to a medicine which is not licensed by the regulatory authority in a particular country.[12-14] As far as possible, medicines should be prescribed within the terms of their MA,[15] however "off-label or unlicensed" use of medicines in children is common (frequently >50%),[15-20] as the MA for many medicines does not include use in children.[18,19,21]

The extent of prescribing of "off-label or unlicensed medicines" in children varies between 11-90%,[14,20,22,23] with more "off-label" prescribing occurring in younger age groups (i.e. <2 years),[13,14] those receiving care from paediatricians, and in the hospital setting.[20,24] The prescribing of an "off-label or unlicensed medicine" often reflects the lack of a suitable licensed medicine for children.[3,14,20,23] **It is important to consider that an "off-label or unlicensed medicine" may not have been studied for its intended use in children.[15] Such use potentially exposes children to ADRs or may result in**

lack of efficacy due to under-dosing of the medicine.[19,23] "Off-label or unlicensed" prescribing presents a dilemma for prescribers who may have to balance clinical experience with a lack of suitable data on paediatric indications and formulations.[6,7,20,23] Prescribing "off-label or unlicensed medicines" alters (and probably increases) the prescriber's professional responsibility and potential liability.[15,25] "Off-label" prescribing is considered appropriate if 1) it is justified by best available evidence (e.g. mentioned in a professional guideline and/or prescribing formulae), 2) it occurs as part of a formal research protocol, or 3) is due to exceptional use (justified by individual circumstances).[23] The prescriber should be able to justify and feel competent in using such medicines and inform the patient (dependent on the child's age and understanding) and their parent/carer that the prescribed medicine is being used for an unapproved indication.[15,23,25,26] It is important to be aware that the use of over the counter medicines may also be "off-label" in children.[13]

Various jurisdictions including the US (2002) and the EU (2007) have introduced legislation to encourage the development of medicines for use in children.[24,27] In the EU, a 10-year review of medicines for children reported that 260 new medicines for use in children were authorised from 2007 to 2016; there was an increase in the number of medicines for children in certain areas e.g. rheumatology and anti-infective agents, however there was less progress in diseases that are largely confined to children.[19] While these regulatory initiatives resulted in more medicines with paediatric indications and a decrease in "off-label" use of medicines,[19,28,29] there is still a need for more paediatric indications.[22]

CHILDHOOD DEVELOPMENTAL STAGES

More physiological changes occur in the first 15-20 years of life than in the next three to four decades, so children are not just "small adults".[2] Several classifications are used to define the age ranges in childhood,[30,31] one of which is described in table 2.

Table 2: Age ranges and definitions of paediatric populations[31]

Pre-term newborn	<37-week gestation
Term newborn	0 to 27 days
Infants and toddlers	28 days to 23 months
Children	2 to 11 years
Adolescents	12 to 16/18 years (dependent on region e.g. EU, USA)

Pre-term infants may vary from a 25-week gestation newborn weighing 500 gram to a 37-week gestation newborn weighing 2,500 grams. Factors to consider when prescribing include gestational age, renal and hepatic immaturity, immature blood brain barrier and rapidly changing developmental processes, all of which can result in the need to alter the dosing regimen of some medicines frequently with ongoing exposure.[31]

Term newborn infants or neonates (age <28 days) are also subject to many of the factors which apply to pre-term infants. Increased susceptibility to toxic effects of medicines can result from immature clearance systems in these patients (e.g. chloramphenicol is associated with "grey baby syndrome").[31]

Infants and toddlers undergo a period of rapid central nervous system (CNS) maturation, immune system development and total body growth. Hepatic and renal clearance continues to mature rapidly so that by the age of 1 to 2 years the clearance of many medicines may exceed adults.[31]

Children: Most pathways of drug clearance are mature in this age group, with clearance often exceeding adult values (e.g. carbamazepine). CNS-active medicines may also adversely affect a child's developmental milestones. The onset of puberty is highly variable, which can affect the activity of enzymes that metabolise medicines, and the dose requirements of some medicines may decrease (e.g. theophylline).[31]

Adolescents: This group experience a period of rapid growth, continued neurocognitive development and sexual maturation. Medicines and diseases that delay or accelerate the onset of puberty can have a profound effect on the pubertal growth spurt e.g. sex hormones, chemotherapy. Many diseases are also influenced by the hormonal changes around puberty (e.g. increases in insulin resistance in diabetes, changes in the frequency and severity of migraine attacks).[31]

The safe and effective medication treatment for children requires an understanding of the wide variability and constant changes in the pharmacokinetics of medicines, which occur from birth to adulthood (see table 3).[1,5-7] **In particular, care is needed when prescribing in neonates who are most at risk of ADRs and from medication errors.**[1,15,22]

Table 3: Pharmacokinetics of medicines in infants and children[1]

Age-related trend	Clinical implications
ABSORPTION	
Gastrointestinal	
Neonates – in the first few days of life the intestine is highly permeable (especially in premature neonates); there is reduced gastrointestinal motility; gastric pH is increased **Infants** – increased gastric motility	Absorption of medicines varies widely, especially in younger children Potential for ↑ absorption of carbamazepine, diazepam and digoxin Potential for ↑ concentration of acid-labile medicines (e.g. penicillin) and ↓ concentration of weak acids e.g. phenytoin Potential for ↓ absorption of sustained-release formulations; potential for ↓ absorption of rectally administered medicines
Skin	
Neonates and young infants - ↑ hydration and ↑ permeability	A potential for ↑ absorption of topical preparations (e.g. corticosteroids) through the skin especially if an occlusive dressing is used
DISTRIBUTION	
Neonates have a higher proportion of body weight in water form (70%) than adults (50% to 60%); may be ↑ up to 85% in premature neonates	Water-soluble drugs such as gentamicin will be distributed more widely in the body resulting in lower serum levels (may require a higher dosage)
Premature infants have ↓ percentage of fat (1%) compared to 15% in normal full-term infants	May result in ↑ concentrations of lipid soluble drugs (e.g. vitamin A and E)
Neonates – reduced plasma protein binding	May result in more free drug in the bloodstream
METABOLISM	
Neonates and infants - Drug metabolising enzymes (DME) in infants are only 50% to 70% of adult values. **Children** - ↑ production of all DME until aged 3 to 4 years. May result in ↑ metabolic activity compared to adults	Neonates may be at increased risk of adverse effects because of slow plasma clearance rates and prolonged half-lives, especially medicines given over long periods Certain medicines may need to be given in higher doses on a per unit weight basis or more often compared to adults (e.g. theophylline)
EXCRETION	
Neonates and young children - ↓ glomerular filtration rate in neonates and young infants (may reach adult value by age 6 months)	Implications for clearance of some common medicines (e.g. penicillin, aminoglycosides and digoxin; clearance rates may fall to 17% to 34% of the adult clearance rate) May require adjustments in dose and dosing schedules, and closer monitoring

In addition, obesity results in physiological changes that can affect the volume of distribution and the clearance of drugs;[32] useful UK guidance on this issue is available on

how medicines should be dosed in children who are obese.[32]

PAEDIATRIC PRESCRIBING

The rational prescribing of medicines requires the use of medicines appropriate to clinical needs, in appropriate doses, for an adequate duration of time and at a reasonable cost.[33] In some conditions, the use of non-pharmacological therapy as first-line may be the most rational approach (e.g. reflux and viral infections).[8,34,35] While the rational or appropriate use of medicines in adults has been extensively studied,[36] there is a lack of evidence on the appropriate use of medicines in children.[37-40] A number of prescribing tools for potentially inappropriate prescribing (PIP) in children have recently been developed and used in research;[38-40] possible indicators for assessment of PIP in primary care include 1) children <12 years who are prescribed a pressurised metered-dose inhaler should be prescribed a spacer device at least every 12 months, 2) an emollient should be prescribed to children who are prescribed more than one topical corticosteroid/year, and 3) codeine/dihydrocodeine medications should not be prescribed to children <12 years.[39]

Evidence suggests that the percentage of children in the community who receive at least one medicine is up to 70%.[21,41] Studies report that the prevalence of prescribing is higher in those aged <6 years,[41] and that a minority of children (20%) (e.g. those with conditions including cancer and asthma) account for the majority of medicine use (70%).[42] Conditions that commonly affect children include asthma, infections, allergy and also attention deficit hyperactivity disorder (ADHD).[43] In the UK from 1998 to 2018, an increase in the prescribing of medicines in primary care for ADHD, gastro-oesophageal reflux, and anxiolytics and hypnotics, and a decrease in the prescribing rates for cough preparations and analgesics was reported.[11] It is important to consider the possibility of over diagnosis and overtreatment in the paediatric population.[34,44] Table 4 lists the 10 most commonly prescribed medicines in children on the General Medical Services (GMS) schemes in Ireland.[45]

Table 4: The 10 most commonly prescribed medicines in children (by age range) in 2020[45]

	<2 years	2 to 5 years	6 to 11 years	12 to 17 years
1	amoxicillin	amoxicillin	salbutamol	salbutamol
2	nutrient combinations**	salbutamol	beclometasone	beclometasone
3	omeprazole	beclometasone	amoxicillin	LNG and EE
4	hydrocortisone	macrogol combinations	montelukast	amoxicillin
5	prednisolone	prednisolone	macrogol combinations	methylphenidate
6	imidazoles/triazoles combined with corticosteroids	amoxicillin and beta-lactamase inhibitor	prednisolone	montelukast
7	amoxicillin and beta-lactamase inhibitor	montelukast	amoxicillin and beta-lactamase inhibitor	benzoyl peroxide combinations
8	macrogol combinations		desloratadine	amoxicillin and beta-lactamase inhibitor
9	emollients and protectives	desloratadine	methylphenidate	cetirizine
10	salbutamol	phenoxymethylpenicillin	levocetirizine	sertraline

Data used: GMS 2020, drugs were extracted at the 5th ATC level; **- this is a milk substitute for cow's milk allergy; LNG – levonorgestrel; EE - ethinylestradiol

FORMULATION ISSUES

It is important that the prescriber is aware of the formulation of the medicine that will be dispensed and that the parent/carer is given instructions on how to use the medicine correctly.[1] Oral paediatric formulations include liquid formulations, tablets for oral suspension (suitable for all age groups), disintegrable tablets (suitable for those aged >2 years), chewable tablets, scored tablets and other solid formulations (suitable for school-age children and teenagers).[22] In general, children aged <5 years (and some older children) find a liquid formulation more acceptable than tablets or capsules,[15] however for long-term treatment it may be possible to teach a child how to take tablets or capsules.[15,46] The Medicines for Children website contains information for parents on how to give tablets to children.[47]

The lack of age-appropriate formulations may result in the modification (e.g. mixing with food, splitting, crushing or dissolution of tablets) of adult formulations by healthcare professionals (HCPs) and parents/carers; this may result in suboptimal adherence due to unpleasant taste, exposure of the patient to unsafe ingredients, under-dosing with loss of efficacy, and overdosing with unintended adverse effects.[22,48] **Some medicines such as modified release formulations or those with an enteric coating should never be crushed.[1]** A medicine should not be mixed with food unless there is information to support this method of administration.[1,15] Some paediatric-related medication issues associated with oral formulations are included in table 5.

Table 5: Paediatric issues with oral formulations[22]

Paediatric medication issues	Possible solutions
Swallowing tablets or capsules; may cause difficulties regardless of age	Some children learn to swallow tablets at a young age; the use of orodispersible tablets may help
Spitting out tablets or liquids; occurs due to unpalatable taste or inability to swallow tablet	Parent/carer training essential; disguising the medicine with food may be possible if information available to support this (need pharmacist input), use of oral syringes
Vomiting – frequently occurs due to taste	Devices such as oral syringes may be helpful; parent/carer requires training
Taste preferences – children may refuse to take medications if the taste or texture is unpleasant	Flavour of some formulations may be masked (by adding/mixing with drink), however the pharmacist should be consulted to ensure compatibility

The correct dosing of liquid formulations depends on the accuracy of the measuring device; this relates to small volumes especially.[48] Oral syringes should be used rather than measuring spoons;[49,50] the measurability of the prescribed dose of medicine should be considered at the time of prescribing.[50-52]

ADVERSE DRUG REACTIONS IN CHILDREN

Adverse Drug Reactions (ADRs) (a reaction to a medicine that is noxious and unintended) in children are associated with morbidity and mortality.[16,21,53] **Children are considered to be at risk of ADRs due to their metabolic and physiological immaturity, the limited availability of paediatric clinical pharmacology studies and due to frequent use of "off-label" medicines.[1,54]** Recent studies estimate that children are at a similar or higher risk of ADRs compared to adults.[43,55-57] The incidence of ADRs is higher in hospitalised children than in those in the community,[1,56-60] where the rates of ADRs reported in the community vary from 0.6 to 11%.[59]

Medicines commonly associated with an increased risk of ADRs in the community include anti-infectives and non-steroidal anti-inflammatory drugs (NSAIDs).[21,59,61,62] Other medicines associated with ADRs in children include methylphenidate, corticosteroids, anti-epileptics, antihistamines, anaesthetic agents, opioids and oncology agents.[16,21,43,60] The most common antibiotics associated with ADRs include amoxicillin and amoxicillin/clavulanic acid,[21] both among the top ten most commonly prescribed medicines for children in Ireland (see table 3). Factors associated with an increased risk of ADRs in children are listed in table 6.

Table 6: Risk factors for adverse drug reactions in children[56,59,61,63,64]

Prior history of an adverse drug reaction Polypharmacy Impaired renal or hepatic function	"Off-label" use General anaesthetic use Certain genetic polymorphisms

The identification of an ADR can be challenging due to the HCP or parent/carer not recognising whether the child is experiencing an ADR or symptoms of the underlying illness, and/or the inability of the child to communicate.[1,22] This results in the risk of an ADR going unnoticed and progressing to a more severe reaction.[22] The management of an ADR depends on a number of factors such as 1) whether the ADR is dose-related, 2) the severity of the reaction, 3) the importance of the medicine to the child's treatment, 4) the risks of stopping the medicine and 5) the ability to treat the ADR.[43]

It is important that there is communication between all the HCPs involved in the child's treatment and also with the child's parents/carers.[43] The parent/carer should be provided with information e.g. with a patient information leaflet and/or direction to the Medicines for Children website,[47] as to the likely signs and symptoms of an ADR.[15,43] **Regular medication reviews in children with chronic conditions who are taking multiple medicines may also help to identify ADRs and improve the patient's and their parents/carers understanding of their medicines.[43]** It is also important to consider reporting an ADR to the Health Products Regulatory Authority (www.hpra.ie).

MEDICATION ERRORS IN CHILDREN

Medication errors (an error occurring in the prescribing, dispensing or administration of a medicine) are associated with increased morbidity and mortality;[65-67] they are the most common type of errors experienced by paediatric patients.[65,66,68] **Prescribing errors are the most common type of medication errors,[69] and occur more frequently in children than in adults and may be up to 3 times more likely to cause harm.[70,71]** Neonates are particularly vulnerable to the effects of prescribing errors.[71] Errors such as the use of the abbreviation "mcg" for microgram if read incorrectly can have serious consequences.[65,72] **Dosing errors are the most common prescribing error in children;[70,71,73] these include tenfold dosing errors which can be lethal.[74]** Dosing errors include both overdosing (commonly with analgesics) and under-dosing (commonly with anti-epileptics).[68] A common error in calculating a dose for a child is the failure to divide the total daily per-kilogram dose by the number of doses to be given in a day, thereby mistaking it for a single dose that is inadvertently given at time points throughout the day.[1] Prescribing errors occur due to a number of factors as shown in table 7.

There is a lack of evidence on interventions to decrease medication errors in children in the primary care setting,[67,68] however improved training, computerised records and pharmacist review of prescriptions have been shown to reduce prescribing errors in the hospital setting.[75-78]

Table 7: Causes of paediatric prescribing errors[65,72]

Theme	Explanation
Fundamental differences between adults and children	Rapidly changing, highly variable size and weight; physiology and metabolism; pharmacokinetics and pharmacodynamics; disease states and prematurity; development (including puberty) and cognition
Individualised dosing and calculations	Dose adjustments not made or made incorrectly, miscalculation, misplacement of decimal points or confusion around e.g 'mg/kg/day' dosing equations are a major cause of errors
"Off-label or unlicensed" prescribing	Lack of available clear dosing information, miscommunication on dosing between paediatricians, general practitioners and pharmacists
Medication formulations	Lack of paediatric formulations available
Communication with children and parents	Incomplete, misleading or incorrect information coming from parents and carers regarding dose (e.g. millilitres versus milligrams)
Experience working with children	Lack of experience; not recognising differences in prescribing for children
Other causes	Busy workplace environments, fatigue, distractions, interruptions, lack of support and information to assist prescribers

Factors associated with administration errors in primary care include poor communication between HCPs and with parents/carers, transitions of care (e.g. hospital to home), involvement of multiple carers (e.g. parents and school) and the use of a dosing cup/teaspoon rather than an oral syringe.[68,79-81] **Incorrect administration by the parent/carer is the most common preventable medication error in the primary care setting;[68]** studies have found that up to 70% of parents make dosing errors.[82,83] **Interventions to improve medication error rates in the community include medicines reconciliation at transitions of care and improved communication between HCPs and with the parent/carer.[68]** A number of interventions have been shown to reduce parent dosing errors with liquid formulations including the use of oral syringes rather than spoons and the use of pictograms to show parents how to use these syringes.[68,81,83-88] The administration of a medicine during school time should be avoided if possible; medicines should be prescribed for once or twice-daily administration whenever practicable.[15] Medication errors should also be reported to the HPRA.

SUMMARY

Medicines should only be used in children after considering the potential benefits and risks of the medicine.[1,8,15] **Children are particularly susceptible to ADRs and medication errors.[8]** In particular, care is needed in the neonatal period where the risk of toxicity is increased.[1,15] Due to different pharmacokinetics in various age groups, doses of medicines for children cannot be extrapolated from adult doses. The dose of each medicine needs to be individualised to the particular age group and/or weight of the child with information from a reliable paediatric medicines information resource (see the section on useful resources). It is important to discuss the treatment with the child (dependent on the child's age and understanding) and their parent/carer.[15]

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