

# Extemporaneous product use in paediatric patients: a systematic review

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## REZUMAT

**Obiectiv:** Identificarea extinderii relative a produselor preparate raportate la populația pediatrică și implicațiile lor în practica farmaceutică.

**Metoda:** Un studiu extensiv din literatura de specialitate a fost luat în calcul pentru a identifica prevalența produselor preparate, în tratamentele pediatrice, incluzând acele studii care examinează atât produsele „off-label”, cât și medicamentele fără licență, dintre care au fost identificate separat produsele preparate, fiind comparate cu medicamentele cu licență.

**Ce a reieșit din acest studiu:** Au fost identificate și evaluate douăzeci de studii în care au putut fi identificate produse preparate în farmacia sau de un producător licențiat. Deși prescrierea medicamentelor fără licență sau „off-label” apare mai des la copiii mici și la afecțiuni mai grave, totuși, produsele preparate sunt întâlnite în terapia tuturor grupelor de vârstă și în toate ariile terapeutice. Studiile referitoare la înregistrările rețetelor au identificat detaliile produselor preparate mai bine decât pe celelate. În ciuda eforturilor de a îmbunătăți disponibilitatea produselor cu licență destinate copiilor, produsele preparate în farmacii sunt încă necesare pentru a asigura o terapie medicamentoasă optimă pentru copiii în doze eficiente și optime pentru fiecare individ în parte.

**Concluzii:** Pacienții din pediatrie au o nevoie continuă de medicamente preparate în farmacie atunci când dozele potrivite din acel medicament nu sunt disponibile. Farmaciștii au nevoie în aceste cazuri de acces la informații despre stabilitatea, compatibilitatea și formulele medicamentoase, precum și la o instruire corespunzătoare, pentru ca pacienții să fie asigurați că primesc preparate de înaltă calitate, sigure și eficiente.

## ABSTRACT

**Objective:** To identify the relative extent of extemporaneous product use reported in the paediatric population and the implications for pharmacy practice.

**Method:** A systematic literature review was undertaken to identify the prevalence of extemporaneous product use in paediatric patients including those studies examining both ‘off-label’ and unlicensed medicine use from which extemporaneous products were separately identified and compared to licensed drug use.

**Key findings:** Twenty studies were identified and evaluated in which extemporaneous products prepared by a pharmacy or licensed manufacturer could be identified. Although prescribing of unlicensed drugs and licensed drugs used ‘off-label’ occurs more frequently in younger children and for more serious conditions, the use of extemporaneous products is consistent across all age groups and therapeutic areas. Studies using pharmacy dispensing records identified details of extemporaneous products more accurately than studies using prescribing records. Despite efforts to improve the availability of suitable licensed medicine products for children, extemporaneously prepared products are still needed to ensure that optimal drug therapy is available to children in accurate and effective doses and dosage forms.

**Conclusions:** Paediatric patients have a continuing need for extemporaneously prepared medicines when suitable dose forms are unavailable from manufacturers. Pharmacists require access to stability, compatibility and formulation information, as well as appropriate training to ensure patients are supplied with high-quality, safe and effective preparations.

## INTRODUCTION

Extemporaneous or compounded pharmaceutical products are prepared specifically for an individual patient for immediate use and may include modifications to commercially manufactured products such as the preparation of a suspension from tablets or preparation of a product from the individual raw materials. The use and manufacture of medicinal products is controlled in most countries, and medicines must be granted a licence in the UK, marketing authorisation in the EU, approval in the US, and registration in Australia. However, in many countries extemporaneously prepared pharmaceutical products are exempt from this process and have

been broadly defined as ‘unlicensed’, unauthorised, unapproved or unregistered. (1–4) In the context of this review the term ‘unlicensed’ will be used for clarity. In Australia, the Therapeutic Goods Administration (TGA) administers the Therapeutic Goods Act 1990, which controls the availability of medicines and devices. Therapeutic goods must be entered onto the Australian Register of Therapeutic Goods (ARTG) before they can be supplied, and may be required to undergo an evaluation of the synthesis of active constituents, data from animal and human clinical trials and details of pharmacology, toxicology, quality, safety, efficacy and the manufacturing processes employed. (5)

Therapeutic indications, dose, specific patient population, route of administration, dosage form and all ingredients are subject to the licensing process, and use of a licensed product outside these parameters is deemed to be 'off-label', or a product that has not been subject to this evaluation process may be defined as 'unlicensed'. (1)

The use of licensed drugs in an off-label manner and of unlicensed extemporaneous medicinal products is an important part of patient management in the paediatric population, since many medicines licensed for use in adults are not licensed for use in children even though their use may be accepted as the current standard of care. When a drug is licensed only for adult use, a suitable dosage form for children is unlikely to be available and it may therefore need to be modified to assist patient compliance. It has been estimated that three-quarters of the US Food and Drug Administration (FDA)-approved drugs available in the US are not licensed, or have only partial licensing, for use in children. (6) This is similar to the results of a review of product information for licensed medicines contained in a compendium of Australian Approved Product Information published by the Australian Monthly Index of Medical Specialties (MIMS) that found between 70% and 80% of the 1497 products reviewed had inadequate or lacked dosing information for children. (7) Younger children had significantly less dosing information available. For licensed products that did have specific dosage information for use in children, between 22% and 27% were only available as tablets or capsules which typically require extemporaneous modification into a dose form acceptable to children. (7) The proportion of drugs in this study with paediatric dosage information but without a suitable dosage form was even higher when specific therapeutic classes were analysed. For example, over 40% of medicines licensed for use in children for cardiovascular disease did not have a suitable paediatric dosage form. Similarly, 30–40% of products for endocrine and metabolic disorders, infections and infestations, or central nervous system disorders did not have paediatric dosage forms available even though they had documented dosage information for children. (7)

Difficulties with evaluating the safety and efficacy of medicines in children are a reason cited for the absence of approved prescribing information and specific dosage forms for children. (8) Other reasons include problems with recruiting children for studies and the ethical issues involved with trials which may often involve invasive procedures. (9) There may also be significant financial influences on any

decisions to trial drugs in children. Clinical trials involving children are perceived as expensive to conduct and may be required for several different age groups to include relevant results for patients from neonatal to adolescent children. Suitable paediatric formulations in a variety of doses suitable for a wide range of ages and weights would require further formulation development (and associated testing). The increase in drug-development expenditure may be difficult for a sponsor to recover, as in many cases the expected use in paediatric populations is much less than that in adults. (6) The potential sales of a drug or particular formulation in relatively small markets like Australia appears to significantly impact commercial decisions about registering products that may be available in other countries. (10)

This lack of suitable dosage forms for use in paediatric patients is a contributor to the significant and widespread use of extemporaneous preparations reported in this patient population. This prescribing practice should not be considered unprofessional or illegal, as legislation in most countries including Europe, the US and Australia allows the prescription, dispensing and administration of unlicensed and off-label medicines. (8) The Royal College of Paediatrics and Child Health issued a statement regarding unlicensed drug use noting that 'The use of unlicensed medicines or of licensed medicine for unlicensed applications is necessary in paediatric practice'. (11) Use of extemporaneously prepared medicines is one of the ways that patients and prescribers are able to overcome the problems associated with the lack of approved products for children. (12)

Unlicensed and off-label use of medicines in children has been reviewed by others; (1,6,8,10,13–20) however, in almost all studies, extemporaneous products are included only as a component of unlicensed drug use (which may also include imported drugs licensed in another country, or products used just prior to licensing), which in turn is usually examined in combination with off-label use of licensed drugs. Although the FDA and the TGA have expressed concerns about increasing use of extemporaneously compounded products, there are few data on the extent and nature of their use in children. (21,22) Since compounded drug products are usually prepared in a pharmacy or under a special manufacturing licence that exempts the product from the usual regulatory processes required for licensed drugs, their use presents different areas of concern to off-label use of approved manufactured products. For example, formulation stability, safety and efficacy studies and adverse reactions monitoring systems may not be available for extemporaneous

products, so an accurate understanding of compounded product use is important.

In most cases, modifications to the formulation of a licensed drug product or formulation from raw materials is carried out in a pharmacy; however pharmacists may also engage a licensed manufacturer (a so-called, 'specials' manufacturer) to prepare an unlicensed product for a specific patient. (23) The manipulation of licensed products may also take place in the ward by nurses or at home by parents and carers. (24) This review will focus on the relative use of extemporaneously prepared products in paediatric practice as a specific and separate category from unlicensed or off-label use.

## Aim

The off-label use of medicines and use of unlicensed products for children is recognised as being particularly prevalent in paediatric practice (11,25,26) and the two groups are usually considered in combination, with the focus primarily on off-label drug use. The aim of this review is to systematically examine the extent of extemporaneous product use in relation to all prescriptions and the implications for pharmacy practice.

## Methods

A systematic review of studies that analysed the use of extemporaneously prepared medicines and unlicensed medicines prepared by a 'specials' manufacturer for paediatric patients, and dispensed by hospital or community pharmacies was undertaken.

## Literature Retrieval

Searches were conducted of the following electronic databases; EMBASE (1974 to July 2007), MEDLINE (1966 to July 2007), International Pharmaceutical Abstracts (1970 to July 2007) and MEDTEXT (1968 to July 2007). Search terms included extemporaneous (or compounded, compounding, magistral, unlicensed, off label, off-label, unregistered, unapproved, unauthorized, unauthorised) and paediatric (or pediatric, child, children, neonate, neonatal, infant, baby) and pharmacy (or pharmacist).

Reference lists of retrieved studies were also scanned for other relevant reports.

## Inclusion Criteria

Articles were included in the review if they met the following criteria: primary reports of prescribing of extemporaneous or 'special' products for paediatric patients relative to all prescriptions to enable

comparisons between specialty areas and countries to be made. The review was not restricted by the country in which the study was conducted but was restricted to English language papers. Studies that included only off-label drug use were excluded from this review.

## Exclusion Criteria

Articles were excluded if: the number of extemporaneous products dispensed was not reported separately from off-label use; the total number of prescriptions was not reported; only a specific extemporaneous product or class of products was reported (e.g. total parenteral nutrition or only oral liquids). Reviews, editorials, letters, and studies only available in abstract form were also excluded.

## Results

Twenty-six published studies were identified, (26–51) and six were excluded. Four studies were excluded because unlicensed drug use was reported as an aggregated number combined with off-label drugs only, (30,33,50,51) and a further two studies were excluded because they involved a subsequent analysis of the same dataset as one of the included studies. (48,49) Although these studies analysed off-label and unlicensed drug use in paediatric patients, the treatment settings and severity of illness and ages of patients varied and hence were divided into five groups: neonatal ward patients, intensive care patients, specialty paediatric ward patients, general medical and surgical ward patients and paediatric patients in the community. Interestingly, no studies examined the use of extemporaneous products alone but studies tended to only include these as a category of unlicensed and off-label drug use. Table 1 summarises the studies included in this review.

## Extemporaneous Product Definition

Collating the results of published studies presents some difficulties because the definition of an unlicensed product can vary and extemporaneous products are often considered only as part of the larger grouping of 'unlicensed and off-label' medicines. The extemporaneously prepared product group is rarely considered separately. A number of studies have adopted the definition of 'unlicensed' medicines first used in a review of off-label and unlicensed product use in children in the UK by Turner et al. (1) The categories of unlicensed drug use included:

- modifications to a licensed product – for example, crushing tablets and suspending the powder to produce an oral liquid suspension

- licensed medicines required as a different dose or dosage form and produced by a manufacturer licensed to make such products ('specials' manufacturer) – for example, a lower concentration of an adult-strength, existing parenteral product
- unlicensed drugs made by a licensed manufacturer – for example, medicines whose sales could not justify the expense of registration and general release
- a chemical used as a medicine when no licensed product or pharmaceutical-grade material is available
- drugs used prior to granting of a licence, which may be supplied by the manufacturer on provision of the individual patient details
- imported unlicensed drugs, licensed in the country of origin.

Unlicensed medicine use in most studies has mainly involved the first four categories, with drugs used in clinical trials and imported drugs involved infrequently. In the reviewed studies, extemporaneously prepared pharmaceutical products are usually included as a subcategory of medicines that are unlicensed for use in children. There was some variability in the definition of an unlicensed drug although the one first proposed by Turner et al (1) is used in almost half of the included studies. (26–28,34,36–40,42) One study classified modifications to an existing formulation as 'off-label' use. (41)

In two studies, unlicensed products were defined as either products extemporaneously prepared in a pharmacy or under a 'special' licence by a manufacturer. (29,47) In four studies, unlicensed products were defined solely as pharmacy-prepared or modified drugs, (31,35,43,45) without including other categories used by Turner et al. (1)

In most cases, there were standard exclusions from the unlicensed drug category (for example, standard intravenous replacement solutions, saline flushes, blood products, heparin to maintain intravenous lines, topical anaesthetics and oxygen), and although there was some variation in the exclusions, the differences were not likely to have significantly affected the reported results.

## STUDY DESIGN

The majority of the included studies of children admitted to hospital wards were prospective reviews of prescribing records, (26–29,31,34,35,38–42) and four were retrospective reviews of hospital prescribing records. (32,36,37,43) For the four studies involving paediatric patients in the community, there was a

single day, prospective survey of prescribing records, (44) a retrospective analysis of prescribing records, (47) a cross-sectional study of pharmacy dispensing records, (45) and a population-based cohort study. (46) Modifications to licensed drugs or compounding in the pharmacy or under 'special' licence may not be recorded in prescribing records, and retrospective analysis may not capture all of this information.

Although prescribing records usually provide patient characteristic information and diagnosis and are more suited for assessment of the licensing status of commercially manufactured drugs, pharmacy dispensing records are likely to be a better indicator of extemporaneous preparation or 'specials' manufacture.

## SETTING AND PATIENT CHARACTERISATION

Three studies were set in intensive care neonatal wards, (27–29) two in paediatric intensive care wards, (31,32) five in specialty paediatric hospital wards, (34–37) eight in general paediatric medical or surgical wards, (26,30,31,38,40–43) and four involved paediatric patients receiving treatment in community-based settings. (44–47) It is important to consider these groups separately as the defined ages of paediatric patients can be from 0 to 18 years with a variable upper limit, and it has been shown that there are fewer suitable drugs and dosage forms for younger children. (7,49) Patients in the intensive care neonatal wards were premature to full-term infants, while the age range of patients in the other included studies was between 0 and 12, 0 and 15, 0 and 16 or 0 and 18 years. In some studies, the use of extemporaneous products was further analysed by age group. (34,35,45) Similarly, suitable licensed drug products may not be available for children suffering from severe, rare or uncommon diseases, and the requirement for extemporaneously prepared products may be greater than for treatment of more common illnesses.

The durations of the reviewed prospective studies were most often between 1 and 8 months although one cross-sectional study analysed prescriptions written on a single day, which may not have been a representative sample. (44) Four studies analysed results for a period of 1 or 2 years. (35,45–47) Study periods between 2 and 4 months were most common and should adequately capture typical extemporaneous product use.

Six studies were set in the UK, two in Australia, three in Israel, one each in Serbia, Germany, Italy and Ireland, three in the Netherlands and one analysed prescribing of unlicensed and off-label drugs concurrently in five European countries. Prescribing of extemporaneous drugs was evident in all countries involved and indicates that the problem of insufficient, suitable paediatric dosage forms is widespread.

**Table 1** Systematic review of published studies of extemporaneous drug use in children

Country	Reference	Setting	Method	Duration	Prescriptions	Patients	Unlicensed and off-label prescriptions (%)	Unlicensed prescriptions (%)	Extemporaneous (%)
Neonatal ward									
Israel	29	1 neonatal ICU	Prospective	4 months	525	105	397(75)	87(16) <sup>a</sup>	26(5)
UK	27	1 neonatal ICU	Prospective	13 weeks	455	70	294(65)	45(10)	45(10)
Australia	28	1 neonatal ICU	Prospective	10 weeks	1442	97	833(58)	152(11)	152(11)
Paediatric intensive care ward									
Netherlands	31	3 ICU, 1 medium care	Prospective	5 weeks	1234	237	1414(66)	664(54) <sup>b</sup>	521(42)
Israel	32	2 paediatric ICU	Retrospective	4 months	905	116	243(42)	360(40)	239(26)
			Prospective	3 months	586	42	118(41)	14(2)	2(0.3)
					288			0(0)	0(0)
Paediatric specialty ward									
UK	34	1 paediatric oncology unit	Prospective	4 weeks	569	51	273(45)	106(19)	106(19)
Serbia	35	1 paediatric cardiology ward	Prospective	2 years	2037	544	1179(58)	236(11)	236(11)
Germany	36	1 paediatric isolation ward	Prospective	8 months	740	178	198(27)	3(0.4) <sup>c</sup>	3(0.4)
UK	37	Paediatric gastroenterology inpatients and outpatients	Retrospective	6 months	777	308	384(49)	93(12) <sup>d</sup>	37(5)
Paediatric general medical and surgical ward									
Europe	26	5 paediatric medical wards	Prospective	4 weeks	2262	624	1036(46)	164(7)	164(7)
Netherlands	31	3 ICU, 1 medium care	Prospective	5 weeks	1234	237	884(72)	664(54) <sup>b</sup>	521(42)
					905		450(59)	360(40)	239(26)
UK	38	1 medical, 1 surgical paediatric ward	Prospective	13 weeks	2013	609	506(25)	139(7)	130(7)
Australia	39	1 medical, 1 surgical ward	Prospective	4 weeks, 5 weeks	735	200	32(16)	Not noted	44(6)
UK	40	1 medical, 1 surgical paediatric ward	Prospective	4 weeks	715	Not noted	235(33)	0(0) <sup>e</sup>	0(0)
Italy	41	9 general paediatric wards	Prospective	3 months	4265	1461	2559(60)	137(3)	137(3)
Ireland	42	1 paediatric general ward	Prospective	2 months	237	74	54(23)	8(3) <sup>f</sup>	5(2)
Israel	43	1 paediatric ambulatory ward	Retrospective	2 months	222	132	76(34)	18(8)	18(8)
Paediatric patients treated in the community									
France	44	95 paediatrician offices	Prospective	1 day	2522	989	844(33)	99(4) <sup>g</sup>	99(4)
UK	47	Prescribing records of 1 general practice	Retrospective	1 year	3347	1175	361(11)	10(0.3) <sup>h</sup>	10(0.3)
Netherlands	45	Pharmacy dispensing data	Cross sectional	1 year	68 019	19 283	26741(39)	11288(17) <sup>i</sup>	11288(17)
Netherlands	46	150 general practitioners' records	Population based cohort	1 year	17 453	6141	5048(29)	2667(15)	1062(6)

ICU, intensive care unit.

<sup>a</sup>Included 61 instances of theophylline, unlicensed for infants <6 months and defined as unlicensed.

<sup>b</sup>Modified commercial preparation or made completely in the pharmacy.

<sup>c</sup>Database generated may not have detected modifications to licensed drugs or those made under a special license in an unlicensed dosage form.

<sup>d</sup>Included imported medicines and drugs awaiting licensing.

<sup>e</sup>Does not include modified commercial preparations.

<sup>f</sup>Unlicensed products included drugs licensed only in adults.

<sup>g</sup>Probably underestimated due to 1 day survey outside winter and rotavirus seasons.

<sup>h</sup>158 (4.7%) of scripts had insufficient information to determine licensing status.

<sup>i</sup>Unlicensed defined as extemporaneous.

## EXTENT OF EXTEMPORANEOUS PRODUCT USE

Pharmacy or licensed manufacturer-prepared extemporaneous products are used in all paediatric settings. Studies were classified into five groups: neonatal ward patients, intensive care patients, specialty paediatric ward patients, general medical and surgical ward patients and paediatric patients in the community, since younger patients and those treated for more serious conditions have been noted to utilise a greater proportion of unlicensed drugs and drugs prescribed for unapproved indications. (8,27–29) However, when extemporaneous products are considered alone, they appear to be used fairly consistently across all age groups and conditions.

## NEONATAL WARDS

Three studies involved neonatal inpatients. (27–29) The combined grouping of off-label and unlicensed products comprised 75%, 65% and 58% of all prescriptions with just extemporaneous or ‘specials’ manufactured products dispensed in 5%, 9.9% and 11% of prescriptions respectively. Although Barr et al noted that 87 of the 525 (16%) prescriptions analysed were unlicensed, (29) this figure included 61 instances of theophylline which was classed as unlicensed because it was not approved for use in this age group. In this study, a special approval was obtained to administer the drug to patients and so extemporaneous drugs actually numbered 26 (5%) in total. Barr et al and O’Donnell et al found that the most common reason for using an unlicensed product was that modification was required by the pharmacy. (28,29) These studies were set in Israel and Australia where the use of ‘specials’ manufacturers is less common than in the UK, where Conroy et al reported that of the 45 (9.9%) extemporaneous products prescribed, 21 (4.6%) unlicensed drugs were prepared extemporaneously by a pharmacy with the remaining 24 items (5.3%) prepared by ‘specials’ manufacturers. (27)

## INTENSIVE CARE WARDS

Patients admitted to paediatric intensive care wards in two studies were prescribed unlicensed and off-label drugs in total in 66% and 42% of prescriptions. (31,32) When only extemporaneous or ‘specials’ manufactured medicines are considered in these two studies, they comprised 42% and 0.3% of prescriptions. Gavrillov et al (42% off-label or unlicensed with 0.3% extemporaneous) relied on analysis of prescribing records which may not indicate modification of dosage forms. (32) The level of extemporaneous product dispensing reported by

’t Jong et al (66% off-label or unlicensed with 34% extemporaneous) was determined from pharmacy dispensing records and may reflect the ready availability of pharmacy compounding services in countries like the Netherlands. (31)

## SPECIALTY WARDS

Off-label and unlicensed drugs were prescribed for children admitted to hospital in four studies set in specialised oncology, cardiology, isolation and gastroenterology wards in 45%, 58%, 27% and 49% of prescriptions, with extemporaneous products used in 19%, 11%, 0.4% and 5% of prescriptions, respectively. (34–37) Unlicensed drug use in the isolation ward (0.4%) was considered to be underestimated since data to determine if modifications to a commercial product took place were incomplete. (36)

## GENERAL MEDICAL/SURGICAL WARDS

Unlicensed and off-label use of medicines in the eight studies set in general medical and surgical wards ranged from 16% to 60% (median: 34%) of prescriptions. (26,31,38–43) Extemporaneous or ‘specials’ manufactured product use in the seven of the eight studies involving general medical and surgical wards was reported to range from 2% to 26% (median: 7%). The eighth study analysed prescriptions written for pain management in a medical and surgical ward of a paediatric hospital. (40) Although no extemporaneously prepared products were prescribed, the authors noted that due to the lack of suitable doses and dosage forms for children, manipulation of the available adult products commonly took place when administering doses. Nursing staff were required to divide solid dose forms and dissolve tablets in water, administering fractions of the liquid to children. The inherent problems of inaccuracy and potential error due to the lack of appropriate dosage forms and doses were noted.

## COMMUNITY-BASED PATIENTS

Total unlicensed and off-label drug use in paediatric patients in community settings was approximately 30%; however, the use of extemporaneously prepared or ‘specials’ manufactured products alone was reported to range from 0.3% to 16% (median 5%) in the four included studies. (44–47) The two studies reporting the highest rates of extemporaneous product use (16% and 6%) were set in the Netherlands. (45,46) These results possibly, once again, reflect the ready availability of pharmacy compounding services and the study method, which

analysed pharmacy dispensing records. In comparison, the study set in the UK (which identified 0.3% extemporaneous product use) employed prescribing records which may not accurately indicate extemporaneous modification or preparation. (47)

Although the total use of unlicensed medicines and drugs used 'off-label' for unapproved indications is greater in younger age groups or in the treatment of more serious conditions, when the use of extemporaneous products and those manufactured under a 'special' licence is considered alone, it was similar across all paediatric ages and conditions.

## DISCUSSION

Unlicensed and off-label use of drugs in paediatric drug therapy occurs in all countries and specialty areas of practice. Research has generally examined unlicensed (including extemporaneous) drug use in children in combination with off-label use of licensed drugs. However, the use of medicines prepared specifically for a patient, whether by extemporaneous compounding in a pharmacy or as an unapproved 'special' made by a licensed manufacturer, presents a range of challenging issues of concern such as quality, ingredient compatibility, stability, efficacy and adverse event monitoring difficulties, when compared to commercially manufactured and registered products which are used outside the licensing conditions. This is the first review of extemporaneous drug use in paediatric patients that has considered these products separately from other categories of unlicensed drugs and off-label use.

The use of extemporaneous preparations in these studies has been measured using either records originating from the prescribing doctors or from the dispensing records of pharmacies. Prescribing records usually contain information on patient history, demographics and diagnoses, so that an assessment can be made about off-label use of drugs. However, prescribing records are less suited to identifying whether a prescribed drug is modified or made by the pharmacy, or made under special licence by a manufacturer. That the numbers of unlicensed drugs reported when dispensing records are analysed are greater than those using prescribing records, probably reflects difficulties in identifying an extemporaneous product using the latter method. For example, if a commercially manufactured product is prescribed but is unavailable or in an unsuitable form, preparation by the pharmacy may not be indicated in the prescribing records. Pharmacy dispensing records should, however, indicate that

the product was made as an extemporaneous product or supplied as an unlicensed product by a manufacturer and are better suited to identifying extemporaneous manufacture.

Although studies examining off-label and unlicensed medicines have shown that younger patients with more serious conditions are more likely to be prescribed these products as a group, when the use of extemporaneous products alone is collated, the frequency of prescribing is similar across all ages and conditions. Extemporaneous products are used most frequently in countries such as the Netherlands where pharmacy compounding services are freely accessible. The level of prescribing of extemporaneous products is usually less than that of off-label use of drugs but indicates that access to suitable drugs and dosage forms for children is a problem affecting all paediatric patients. A small study conducted over two months in England found that just over half of extemporaneous prescriptions prescribed were prepared by the community pharmacy, with the remainder ordered from (so-called) 'specials' manufacturers. (52) Although the cost of extemporaneous products ordered from 'specials' manufacturers has been reported to be much higher than for those prepared in community pharmacies, (53) the 'specials' industry in the UK has been noted to be preparing an 'ever-increasing' number of prescriptions. (54) A study of changes in paediatric drug licensing in the US, UK, Australia and New Zealand found that there has been just a modest improvement in the availability of drugs and suitable dosage forms for use in children since the introduction of legislation and incentives to encourage manufacturers to submit paediatric dosage information and dosage forms for approval. (55–61) The European Regulation on medicines for paediatric use came into force on January 26, 2007, and through a combination of legislated requirements for paediatric clinical trials in exchange for patent extensions for new drugs and a paediatric study programme for off-patent drugs it is hoped that there will be significant improvements in the availability of approved drugs for children in the next few years. (62,63)

The incidence of adverse drug reactions associated with extemporaneous or 'specials' products has not been extensively explored in the literature. However, there is a risk of harm due to measurement or preparation error and therapeutic failure due to instability or incompatibility of ingredients, and pharmacists must be aware of and take steps to minimize these risks.

It may be overly optimistic to expect that all drugs, especially older or less-frequently used drugs and those that are no longer protected by patent, will be available in suitable forms for children. There will be a continuing requirement for extemporaneous preparation by pharmacists, and it is imperative that comprehensive standards to ensure product quality are established. An accreditation process has been implemented in the US and is under discussion in Australia. (64,65) If licensed manufacturers are unable to supply suitable licensed products, pharmacists need to be equipped with the stability, formulation and compatibility information and skills to produce safe, stable and effective preparations.

To meet appropriate quality standards for compounding, pharmacists need to be able to access information relevant to extemporaneous dispensing as well as suitable equipment, skills and ingredients

for what may become a specialised area of pharmacy practice.

## CONCLUSION

The lack of available licensed medicines and dosage forms suitable for paediatric patients is a widespread problem, and the prescribing of extemporaneous products to meet this unmet medical need is an accepted part of paediatric practice. Despite the efforts of drug regulatory agencies, not every medicine will be available in a suitable dose and dosage form, and it seems likely that pharmacists will continue to be required to prepare extemporaneous products. Appropriate standards need to be uniformly implemented, and pharmacists need to have access to stability, compatibility and formulation information as well as appropriate training to ensure patients are supplied with high-quality, safe and effective preparations.

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## Revista presei

## Un nou medicament care ajută la dezintoxicarea tinerilor dependenți de droguri

Cercetătorii din SUA au descoperit că utilizarea pe termen lung a unui medicament care ajută la ameliorarea simptomelor de abstenență poate fi un real sprijin pentru tinerii care beneficiază de tratamente pentru dependența de heroină sau de medicamente împotriva durerilor precum Oxycontin.

Tinerii dependenți cărora li s-a administrat medicamentul Suboxone de la Reckitt Benckser timp de 12 săptămâni au fost mai puțin tentați să ia droguri în această perioadă și au continuat tratamentul de dezintoxicare mai mult timp decât restul.

Există, așa cum a subliniat Dr. George Woody de la Universitatea din Pennsylvania, Philadelphia, foarte multe tratamente, în toate țările lumii, care ajută dezintoxicarea și consiliază pe termen scurt tinerii dependenți de drogurile opioide, dar acest tratament medicamentos poate deveni mai eficient. Același specialist, Dr. George Woody, subliniază că există de multe ori ezitări în utilizarea unor tratamente medicamentoase în aceste cazuri. Problema programelor lipsite de suport medicamentos este rata mare

de recăderi, subliniază acesta pentru prestigioasa revistă *Journal of the American Medical Association*.

Suboxone, cunoscut generic drept buprenorphine-naloxone, combină de fapt două medicamente. Buprenorphine ușurează simptomele de abstenență, în timp ce naloxone împiedică abuzul de droguri prin amplificarea rapidă a simptomelor de abstenență în cazul în care se administrează în același timp cu un consum de droguri, mai ales pe cale rapidă, prin injecție.

Cercetătorii au studiat 152 de persoane dependente de opioide cu vârste între 15 și 21 de ani, pe o perioadă de 12 săptămâni. Pacienții din grupul Suboxone au primit medicamentul pe parcursul a 9 săptămâni și apoi a început să li se scadă doza până a fost întreruptă în săptămâna a 12-a. Al doilea grup a primit o doză mai mică din acest medicament, doar pe termen foarte scurt, și a fost întrerupt gradat în săptămâna a 2-a. Toți pacienții, din ambele grupuri, au fost permanent consiliați individual și în grup.

Până în a 8-a săptămână, 23% dintre pacienții cărora li se administra

tratamentul medicamentos au avut rezultate de urină pozitive față de 54% dintre pacienții care nu beneficiau de acest tratament. Dr. George Woody a afirmat, în concluzia acestor teste, că cei din grupul tratat medicamentos consumau mai puține opioide decât ceilalți pacienți, și nu au fost depistate efecte secundare.

Opioidele includ heroina, morfina și anumite medicamente împotriva durerii precum Vicodin și Oxycontin.

Ca urmare a acestor experimente, se poate trage concluzia că tinerii care continuă tratamentul cu Suboxone sunt mai puțin predispuși să ia droguri precum opioidele, cocaina sau marijuana, sau să-și injecteze alte droguri, decât cei care beneficiază doar de dezintoxicare pe termen scurt și consiliere.

„Aceste descoperiri ar trebui să asigure și să încurajeze furnizorii care au ezitat până acum să ofere un tratament mai extins cu Suboxone populației”, afirmă Dr. Nora Volkow, director al Institutului Național pentru Abuzul de Droguri din SUA, care face parte din Institutul Național al Sănătății din SUA.