Use of Extemporaneous Compounding Products in Pediatric Patients: A Systematic Review

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Abstract. The objective of this study to review and identify recent studies related to incidence of the extemporaneous compounding products used for pediatric patients. This systematic literature review was conducted by searching the literature using the PubMed and Google Scholar electronic databases between 2016 and 2021. The literature results were selected, reviewed, and identified in relation to the incidence of extemporaneous compounding product use, including reporting of off-label and unlicensed drug use in children. Five articles according to the inclusion criteria were identified and evaluated related to reporting of extemporaneous compounding product use. The majority of the findings from several countries such as Indonesia, Vietnam, and Africa disclosed that there was still the use of extemporaneous compounding products and even off-label and unlicensed drugs in pediatric patients with the prevalence from 7.9% to 76.37%. Compared with adult patients, the use of extemporaneous compounding products in children is rather a common practice. The general reason is the limited availability of commercial drugs in the market and the different conditions of pediatric patient individually (age, dose, indication, weight, contraindications) are used as the basis for choosing blended or off-label, or unlicensed drug preparations. For this reason, extemporaneous compounding products remain the first alternative in optimizing therapy for children, regardless of efforts that have been made to develop licensed preparations for children. Demand for extemporaneous compounding product prescriptions will continue to occur among pediatric patients, either by formulating or by manipulating dose and adjusting dose due to the lack of commercial drugs available from the manufacturers, specifically for children. Pharmacists, apart from having significant role in perceiving stability information, compatibility of formulas for extemporaneous drugs, conduct training and education, and appropriate communication are essential to ensure the quality of drugs prescribed to patients so they are safe, effective, and guaranteed.

Keywords: "Extemporaneous compounding products" · "Unlicensed" · "Off-label" · "Pediatric"

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1 Introduction

Extemporaneously prepared drugs remain widely used, specially prepared or modified for pediatric patients when the individual dose or dosage form is not available on the market, such as compounding oral suspensions of tablets. [1, 2]. Availability of drugs on the market is generally evaluated for their efficacy and safety through clinical trials for selected populations but is not systematically representative of the pediatric population. [3]. Extemporaneous compounding is a technique for preparing therapeutic preparations by mixing or combining medicinal ingredients used for individual patients with identified special needs. [4]. Extemporaneous compounding is an activity that can pose high risk. It is considered at risk because in several occasions it combines several unlicensed drugs with the inherent risks associated with the pharmaceutical compounding process [5]. The advantage is that extemporaneous compounding is a practical option for providing medicines when there is no alternative, for instance, when a patient requires a special dose or dosage form that is not commercially available, if the patient requires individual doses, those who are difficult to swallow solid drugs or special patients for neonates, children, and elderly patients [1].

The practice of extemporaneous compounding is rather frequent in the treatment of pediatric patients. In extemporaneous compounding specifically for children, it is usually based on individual drug dosage based on prescription requests with a certain and smaller scale, yet most of the available drug forms in the market are formulated in solid drugs, such as tablets or capsules. [6, 7]. The administration of extemporaneous products to children embraces manipulation or modification of the prescribed labeling indication, for instance by manipulating the drug formulation to obtain the correct dose (splitting or cutting a tablet into pieces), or by changing the route of administration to suit the child patient. The use of prescribed drugs outside of the permitted indications by making adjustment to the dose, dosage form, therapeutic indication, route of administration or formulation modified for a particular patient population, and all drug ingredients in the licensing process, as well as licensed products used outside these parameters are referred to as ‘off-label’, or defined as ‘unlicensed’ [2, 8].

Off-label prescriptions are rated as risky or harmful due to a lack of information about drug safety, efficacy, and appropriate use in pediatric patients. Studies conducted by the Food and Drug Administration or FDA revealed that 1–10% of all prescriptions that practiced compounding were not supported by concrete evidence data. The unavailability of research data, especially in children, makes drug licensing for pediatric patients difficult. Previous research suggested that 0.3% to 35% of therapy occurred using unlicensed drugs and 9% to 78.7% of off-label drugs were prescribed for the treatment of pediatric patients. The proportion of unlicensed and/or off-label prescriptions resulting in adverse drug reactions ranges from 23 to 60%. Another study in the US reported that 79% of pediatric hospitalized patients received tertiary care, i.e., a prescription at an off-label location. Another study at the West Australia Hospital unraveled that there were 1,160 prescription drugs for hospitalized pediatric patients and 54% of them were off-label prescriptions. The use of off-label drugs is reported to be used mainly in the genitourinary system and sex hormones, respiratory system drugs, systemic and gastrointestinal hormonal preparations, and metabolic drugs. To overcome these issues,

government health agencies in various countries have begun to restrict their regulations in the drug development process [7], [9, 10].

Off-label or unlicensed drug prescription is very commonly found and frequently uses pharmaceutical practice because it is a more practical treatment option for pediatric patient handling which is not commercially available and always accounts several circumstances in combination preparations. [2, 11]. This literature study focuses on the use of extemporaneous compounding products in pharmaceutical setting by pharmacists in pediatric patients as a special category and it separates from unlicensed or off-label use. This review aimed to systematically examine the prevalence of the extemporaneous use involving all reported prescriptions from several countries.

2 Research Method

This systematic literature review is a study that evaluates and analyzes the use of over-the-counter compounding products and medicinal preparations prepared and intended 'specifically' for pediatric patients, and distributed by pharmacists in pharmacies, hospitals, or other healthcare facilities.

2.1 Article Search

Article searches were carried out using electronic databases, PUBMED and Google Scholar from 2016 to 2021. The search was conducted by including terms "extemporaneous", and "compound*", "magistral", "unlicensed", "off label", "off-label", "unregistered", "unapproved", "unauthorized", "unauthorized", and "paediatric", "pediatric", "child*", "neonate", "neonatal", "infant", and "pharmacy" or "pharmacist". The resulting reference lists were determined based on their relevance to this study.

2.2 Inclusion Criteria

The literature included in the literature review should contain information about the prevalence of the use of extemporaneous products for pediatric patients. Reports on prescribing extemporaneous products are specific to pediatric patients in all prescriptions and allow for comparisons between specific regions and specific countries. Studies are limited to English articles only.

2.3 Exclusion Criteria

Articles are excluded if only certain temporary products or product classes are reported, such as total parenteral nutrition. Studies with the unreported total number of prescriptions, reviews, manuals, editorials, letters, and studies are available only in abstract form.

3 Results and Discussion

A total of 693 articles published in the electronic database were identified and evaluated. As many as 104 were excluded due to the article duplication and 102 articles were excluded as well because title screening was not relevant to the study of pediatric patients. The other 150 articles were eliminated because they consisted of only abstracts and 55 textbooks on pediatric treatment therapy manuals. Another 205 studies were excluded due to further analysis related to dosage modification, chemical-physical stability of drug formulations, and drug design, or only articles review. Meanwhile, 72 studies were also ruled out because there was no reported number of prescriptions and they were studies on off-label drugs or unlicensed drugs alone.

3.1 Study Design

The study design of the literature review included pediatric patients who were hospitalized, comprising four prospective studies with incident reports and recording of extemporaneous, off-label, or unlicensed compounding prescriptions and hospital records, two of them also used a prospective survey model. One review is a retrospective study of incident reports and records of prescribing pediatric patients in hospitals (Fig. 1).

Research collected was limited because of the small number of documentation available. In addition, all compounding manipulation information in a hospital with a 'special' license might have not been recorded in any study analysis such as clinical diagnosis data, weight at admission, or including prescribed dose, formulation, indication, and frequency.

3.2 Setting and Characteristics of Respondents

Characteristics of respondents in this systematic review included infant, neonate, and child patients of 0 days to 18 years of age. Pediatric patients were inpatients in neonatal wards, general pediatric wards, and special pediatric wards of hospitals in several countries. Two studies were conducted in Vietnam and Indonesia, and three other studies were conducted in South Africa, West Africa, and Ghana. These five articles review was conducted within 1 to 4 months. Based on patient's diagnosis from the five articles, there were variations of diseases that were handled from general to specific childhood diseases. The average diagnoses were respiratory disorders, either at birth or in children such as pneumonia, cardiovascular disease,

3.3 Definition of Temporary Product

Extemporaneous compounding is an activity that processes 'preparation', 'mixing', 'assembly', 'packaging', and 'labeling' of medicinal products based on prescriptions written by licensed prescribers, prepared specifically for each patient, including the use of 'unlicensed' and 'off-label' drugs and formulated by pharmacists with pharmaceutical practice standards. The challenges in the face of extemporaneous compounding are the availability of drug formulations on the commercial market and the risk of errors such

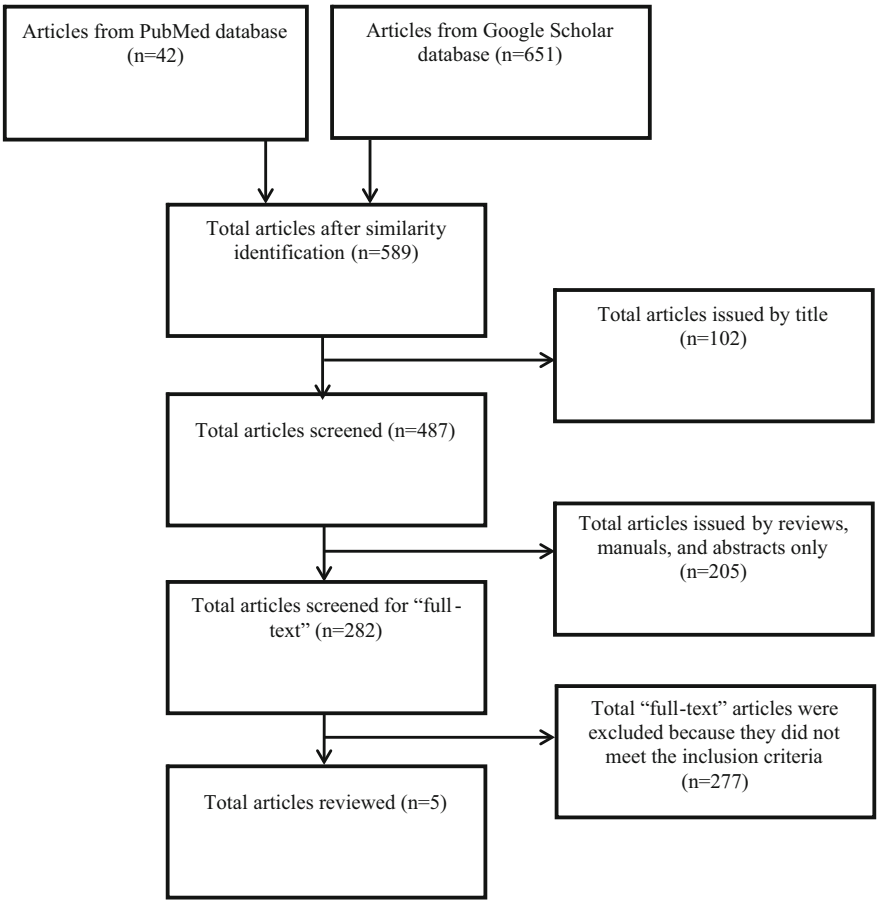

Fig. 1. Article review identification

as information related to drug compatibility, stability, and bioavailability. Insufficient information may lead to problems for pharmacists in the event requests for individual patient's extemporaneous compounding should be prepared [12, 13]. Therefore, it can be concluded that the process of compounding extemporaneous products and unlicensed or off-label drugs is one of the perilous action in pharmacies, clinics, hospitals or other health facilities because the information is mainly related to the compatibility, stability, bioavailability of the drug, and substance/drug to be formulated [13]. The use of 'unlicensed' or 'off-label' drugs is arduous journey to eliminate since those categories are widely used in pharmacies or hospitals and are often prescribed to newborns at a young age who are in vulnerable conditions [14]. Research by Conroy et al. state that almost 93% of infant patients received drug therapy at least one 'unlicensed' or 'off-label' drug during their stay in the intensive care unit. [15]. Studies conducted by Jong, GW., et al. in the UK and Europe found that a large proportion of prescriptions containing various 'unlicensed' and 'off-label' drugs were prescribed to pediatric patients in care centres.

Even in Dutchcentersals, 92% of patients received one or more variations of an 'unlicensed' or 'off-label' prescription. [15, 16]. The use of extemporaneous compounding products from the five articles is presented in Table 1.

Table 1. The term of extemporaneous compounding

Term	Definition	Adopted from
Extemporaneous Compounding	"products that make life easier for patients and their caregivers without compromising safety"	[21]
	"manipulation or modification of the compounding of a commercial drug resulting in a change in the form or properties of a drug, or the manufacture of a drug from a raw product by a manufacturing pharmacist"	[23]
Off-label drugs	"drugs prescribed outside the terms and conditions of the product license"	[23]
	"the use of an authorized drug for purposes other than those specified in the product characteristics or as approved by the drug regulatory board or national authority"	[24]
	"all drugs whose prescription does not comply with the license issued by the Drug Administration of Vietnam"	[9]
Unlicensed drug	"most unlicensed drugs are temporary preparations manufactured from capsules or tablets to obtain a lower dose that is not available in the listed product"	[25]
	"Popular products are called 'specialty' or 'special demand products'."	[21]
	"formulations produced under a special license, and drugs without a prescribed dose for certain age groups"	[23]
	"drugs that have not been approved for medicinal use in certain countries"	[24]
Pediatric patient	"children who should not be considered 'little adults' because their pharmacokinetics and pharmacodynamics vary throughout childhood"	[25]
	"among the most vulnerable people in society"	[21]
	"pediatric patients aged 2–11 years"	[23]

3.4 Incidence Rate of Use of Temporary Products

The practice of extemporaneous compounding is still carried out in several countries, especially for pediatric patients [17, 18]. This occurs due to the unavailability or limited suitable commercial preparations for pediatric patients and other considerations. This gives rise to a variety of unlicensed products and off-label products which are often considered 'unlicensed' and 'off-label' drugs. The group of products prepared for an extemporaneous basis is rarely separated. Some studies have adopted the definition of 'unlicensed' drug that was first used in a review of the use of off-label and unlicensed products in children in several countries. [2]. This study classified respondents into three groups: neonatal ward patients, general ward patients, and special pediatric ward patients (see Table 2).

In the neonatal ward, there is one study involving hospitalized patients in the neonatal ward [19]. Off-label use is a common problem in pediatric care, with an incidence rate of up to 85% of the 810 prescriptions reported for the neonatal intensive care unit and included a relatively high incidence of off-label use while the use of unlicensed drugs was reported at 1.5% [19]. The results of this study agree with Las jan, et al., conducted in Estonia which reported 87% of all drugs were prescribed off-label to neonates out of 490 identified neonates. [20]. The number of prescriptions prescribed in this study was low compared to some of the studies conducted worldwide [20].

General children's ward. Two articles reviewing the co-administration of unlicensed and off-label drugs in general pediatric wards yielded 51.9% [9] and 71.5% [18] of reported prescriptions. The results of the literature review that we carried out on the two articles included a fairly high incidence and it occurred mostly in children under 2 years compared to children over 2 years. Meanwhile, the use of products produced on an extemporarily or 'special' basis from 3 studies involving general pediatric wards was reported at 17.8%. [9], 7.9% [18], 76.37% [21]. A study conducted in the Netherlands showed that a significantly higher percentage of children under six months of age than older children used one or more unlicensed or off-label prescriptions. [16]. Another study in Malaysia noted that children aged 2 years on average and greater number of drugs prescribed were more likely to receive drugs for unlicensed administration. [22].

Special wards for children, no different from other wards, still have off-label and unlicensed drug prescriptions for hospitalized pediatric patients. A study was conducted in a specialized ward of oncology, cardiology, neurology, immunology, infectious diseases, and gastroenterology. It found that almost half of the prescriptions served (49%) were unlicensed, off-label, and temporary products, yielding 20%, 29%, and 15%, respectively and 24% was a combination of the use of unlicensed and off-label drugs. [26]. According to research reports, the incidence of using unlicensed and off-label drugs is rather high in the cardiology specialty, gastroenterologist, followed by the oncology ward. [2]. The use of off-label and unlicensed drugs in pediatrics is evenly practiced worldwide [8].

Incidents of using unlicensed and off-label drugs for the treatment of pediatric patients generally occur in many countries, it can be in pharmacies, hospitals, or community. Studies generally investigate the use of unlicensed drugs or what is referred to as temporary compounding in children, which can be combined with the use of licensed

Table 2. Literature regarding the use of temporary drugs in pediatric patients

Author	Country	Method	Setting	Duration	Prescribing	Patient	Off-label and non-licensed recipes	Unlicensed recipe	Extemporaneous
[9]	Vietnamese	prospective	General children's ward	1 month	320	104	54 (51.9%)	57 (17.8%)	57 (17.8%)
[18]	Indonesia	retrospective	General children's ward	3 months	1961	200	1403 (71.5%)	154 (7.9%)	154 (7.9%)
[21]	Ghana, West Africa	prospective	General children's ward	4 months	622	622	-	52 (0.08%)	475 (76.37%)*
[19]	south Africa	prospective	Neonatal ward	3 months	810	168	85%	1.5%	0
[26]	south Africa	prospective	Special children's ward	3 months	1514	199	24%	20%	23%

* calculated from the most frequently prescribed drug formulations

drugs off-label. [2]. The use of this drug is very accessible for pediatric patients, especially if the preparation is made unlicensed. Behind these advantages, the risks that will occur are bad reactions, poor stability, decreased effectiveness, and other disadvantages compared to commercial preparations on the market. The reasons and considerations that should be considered in the use of unlicensed and off-label drugs are the patient's age and weight, the appropriate indication, the dose and frequency of administration, the route of administration of the drug, and the contraindication of unlicensed or off-label drugs used especially for pediatric patients [18]. From findings, it can be concluded that the incidence of drug use is very common and even (licensed/unlicensed) drugs. Therefore, the role of health workers is required, especially pharmacists due to their crucial role. If the drugs prescribed are compounded or manipulated or modified, "commercial" drugs can be used on a smaller scale and specifically for pediatric patients. With the role of pharmacists, the use of unlicensed and/or off-label drugs should be informed in terms of usage, information related to drugs, monitoring therapy, and quicker and more appropriate action if unwanted reactions occur.

3.5 Types of Compound Preparations

The types of preparations studied in this literature study are mostly oral dosage forms, such as oral suspensions, syrups, and powder forms which are formulated from several medicinal substances. Huu et al. found that from 320 prescriptions, the entire prescriptions were oral preparations, either solid with 45.3% (pulverize/powder and granule reconstitution) or compounding oral liquid preparations, totaling 64.7%. [9]. Another study, Ankrah et al., state that prescription oral suspensions and syrups were in the top five alternatives and dominated the types of preparations formulated for pediatric patients in their study. Ankrah et al. also mention that the preparations often used for pediatric patients include powders or granules for suspensions, solutions, syrups, and suspensions, which are different from the usual preparations for adult patients, including tablets, capsules, and caplet preparations [21]. The results of a study from Kooblal, Yajna., showed similar results that pediatric patients appeared to use oral compound preparations. From the results of the research, antimicrobial-bacterial drugs had a fairly large incidence, in this case, drugs for tuberculosis (isoniazid, ethambutol, pyrazinamide, ethionamide, and sometimes rifampicin) of 77% in pediatric patients who have a drug compounding process followed by oral compound preparations such as food supplements (potassium chloride and potassium phosphate), heart medications such as spironolactone and morphine painkillers [26]. The last two studies did not specify the use of solid or liquid oral formulation.

3.6 Reasons for Using Extemporaneous Compound Drugs

Referring to four out of five papers that have been reviewed and presented in the previous table, it can be determined that there are special requests due to special needs, such as certain doses or indications for pediatric patients, for instance, the pharmaceutical industry cannot prepare different and even special variations so that the availability in the market is only commercial preparations. The rest of the prescriptions are customized or manipulated at the request of a special recipe. In the results of this research paper, the

reasons of the extemporaneous compounding drug use for pediatric patients included; the dosage for individual, the demand for temporary drug preparations, age, lack of pediatric data, or lack specified and detailed drug formulations, suitability route of administration, and dosage frequency,

Table 3. Types of drug preparations and reasons for compounding drugs

Author	Country	Settings	Patient	Type of medicine	Causes of doing compounding drugs (or not doing compounding drugs)
[9]	Vietnamese	General children's ward	104	Use of solid and liquid oral preparations	Age is not allowed and dosage is not allowed, and access is limited to special drug formulations for pediatric patients
[18]	Indonesia	General children's ward	200	Not recorded/unspecified	The most frequent reason was indication (34.6%)
[21]	Ghana, West Africa	General children's ward	622	Average oral suspension and syrup	Not recorded
[19]	south Africa	Neonatal ward	168	Not recorded/unspecified	Off-label prescriptions 48% for age, 44% for frequency, 37% for body weight and 29% for indication, < 2% for routes and <1% for drugs contraindicated in neonates
[23]	south Africa	Special children's ward	199	Average oral preparation with compounding process	The incidence rate for the category of neonates is 26.7%, extemporaneous 17.4%, age 5.8%, child data less 1.2%, Route 1.2%, Frequency 1.2%, Contraindications 1.2%

Table 3 [9, 18, 19, 21, 26]. From the research above, the reasons imply that the selection of compounded drugs for pediatric patients is categorized as either 'unlicensed drugs' or 'off-label drugs' or special drugs, the practice is in pharmacies, hospitals, or other health facilities. This practice is still happening and will continue to happen as the world of health and drug compounding develops and as long special demand for treatment exists. It is our duty and role as health workers, especially pharmacists, to monitor and conduct learning related to the development of treatment, especially for children, to obtain maximum results and minimal unwanted risks.

4 Conclusion

The limited variety of commercial and licensed drugs available in the market, both in form and route of preparation which is often not suitable for pediatric patients, is a global problem. Thus, this will still be an alternative reason for prescribing extemporaneous compounding for "special" patients which is currently acceptable. Requests for prescriptions with extemporaneous compounding products will continue to occur among pediatric patients. It can be formulation or manipulation of dosage forms and adjusted dosages, in which the availability of commercial drugs for children is still very limited. Therefore, pharmacists (in preparing compounded drugs) should understand the appropriate and uniform standards that can be applied.

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