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Off-Label Use of Medicines in Children Attending a Secondary Healthcare Facility in Federal Capital Territory

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ABSTRACT

Before a new drug is approved for marketing in any country, it must have undergone three phases of clinical trials designed to assess its efficacy and safety when used according to an approved recommendation. After a drug has been tested and approved by the regulatory authorities, the drug is usually given a 'label' or 'license' which is a report describing the drug intended use and dosage. This study aimed at evaluating the use of medicines outside the terms stated in the label. The study was conducted using a data collection form to obtain information from patients' case file. Data were analysed using Statistical Package for Social Sciences. The case notes of 449 patients were included in the study. The ages of the patients ranged from 4 days to 16 years. Females constituted 51.7% (232) and males 48.3% (217). A total of 1866 drugs were administered to patients, of which 469 (25.13%) were off-label prescriptions. The highest category of off-label drug was indication (45%). This study has revealed a considerable prevalence of off-label use of medicines, there is however need for proper pharmaceutical care to be emplaced in healthcare facilities so as to minimize off-label drug use and prevent adverse effect of drugs as a result of inappropriate use of medicines.

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Introduction

When a drug is approved for sale, the approval stipulates, among other things; the population for whom it can be prescribed, the indication for use, and the dosage which the drug can be administered. When a medicine is used beyond the criteria set out in the product approval, it is referred to as off-label use [1]. Several medications use to treat children in hospital are prescribed as off-label [2]. The use of off-label and unlicensed drugs to treat children is widespread and occurs in medical and surgical wards, as well as in critically ill children [3]. Drugs are being used in children at ages for which they have not been licensed, doses greater than that recommended by manufacturers as well as for indications outside the terms of the product license. It is not clear whether the use of medicines in terms outside their use is appropriate [4].

The use of off-label medicines for children present serious ethical concerns. Children often receive several prescriptions when they fall ill. Most of these medications received by children have not been properly tested in controlled clinical trials for them [5]. The metabolism and excretion of medicines in children may differ from that of an adult and may predispose them to harmful effects [6]. Research has shown that for some medicines, hepatic glucuronidation is lower in children of aged thirteen to twenty-four months than adults [7].

Paediatric doses are commonly estimated from approved adult doses with an average body weight of 60kg [6]. Therefore, calculating paediatric doses from this basis without acknowledging the physiological and metabolic differences between adults and children may lead to either therapeutic failure as a result of too little of the drug being given or toxicity as a result of excess drug administration [8]. Due to the fact that children are rarely included in clinical trials before drugs are licensed, many medicines given to children have no suitable paediatric dosage form. Adult medicines are therefore frequently formulated for children, this include crushing tablets or capsule to obtain liquid preparations. This situation has left children as therapeutic orphans [9]. Prescribing of medicines for children is largely empirical rather than evidence-based and clinicians commonly make educated guesses about doses and efficacy rather than rely on data from paediatric clinical trials. Conducting clinical trials in children presents moral, ethical, and legal problems, and this issue has generated much interest and debate among health care researchers, parents, and policy makers [10].

Nahata [5] reported that the problem of off-label use of medicines in children has engaged the interest of many health care professionals and researchers. The practice of using off-label drug in children is not illegal in many countries, but it is not free of risk. The prescribing of off-label medicines poses significant challenge of maintaining the delicate balance between risks and benefits of medication therapy in children that has generated much interest and debate. Problems associated with off-label use of drugs have been documented by several studies [11, 12].

There is increased awareness that the majority of medications used in children have not been labeled for such use and have not been tested to define safety, efficacy, and appropriate dosing in children population [13,14,15,16]. Many drugs prescribed for children are used outside the specifications in the license. The concern for efficacy, incidence of adverse events, appropriateness of dosage form and approved/unapproved indications raises ethical and safety concerns about use of drugs in children.

Children are very vital, and it is important that the medication being given to children are the right medication for the appropriate ailment. Inappropriate prescribing can lead to wastage of resources and health hazards. Several studies have shown varying degrees of inappropriate prescription mostly characterized by polypharmacy, overuse of antibiotics and injections [17,18,19]. Periodic assessment of prescribing patterns will help in identifying specific drug use problems and provide policy makers with relevant information that could be useful in review and implementation of rational drug prescribing. This study therefore aimed to determine the extent of use of off label medicine prescribed to outpatients in a secondary health facility in Abuja.

Methods

Data Collection Procedure

The study was undertaken with the aid of a data collection form, which was used to collect data from the case files of paediatric in and out patients who visited the health facility where this study was undertaken between 1st of March to 30th April 2021. Convenience sampling strategy was adopted. Inclusion criteria involves out patient children who were 16 years and below. Paediatric patients whose prescriptions requires the use of standard intravenous product replacement solution, flushes of sodium chloride 0.9%, blood products and oxygen therapy were excluded.

Data were collected from the case files and case notes of patients using the data collection form that was already designed for the study. All medicines prescribed were reviewed and categorized as off-label based on deviation from the recommended dose (lower or higher than the recommendation in their product label), age (medicines not recommended for patients below certain age), formulation (medicines not available in paediatric formulation) and indication (medicine prescribed outside those listed in the product label).

The British National formulary for children, Paediatric formulary, EMDEX, WHO hospital care for children and the drug leaflets were used as references to determine off-label medicines prescribed.

Data Analysis

The data collected were coded, sorted and grouped according to the study variable after which the data were entered into Microsoft excel. The data were cross checked, inspected and scrutinized so as to ensure accuracy, relevance, consistency and uniformity. The data were then transferred into Statistical Package for Social Sciences (SPSS) for descriptive statistical analysis.

Ethical Consideration

Ethical Approval was obtained from the Federal Capital Territory Health Ethics Committee prior to the commencement of data collection. Confidentiality was maintained by not including the names of the patients in the data collection form.

Results

The case notes of 449 patients who met the inclusion criteria were analyzed for this study. The ages of the patients ranged from 4 days to 16 years. Females constituted 51.7% (232) and males 48.3% (217). A total of 1866 drugs were administered to patients of which 469 (25.13%) were off-label prescriptions. Patients received between 0 - 21 different drugs. The patients were mostly young children of 1 to 5 years (206, 45.9%) and infants (158, 35.2%). Neonates were 35 (7.8%), whilst older children of 5 to 12 years were 39 (8.7%). Adolescents of 12 to 16 years were in minority (11, 2.4%). Figure 1 below gives an overview of medicines prescribed and off-label medicines prescribed according age group.

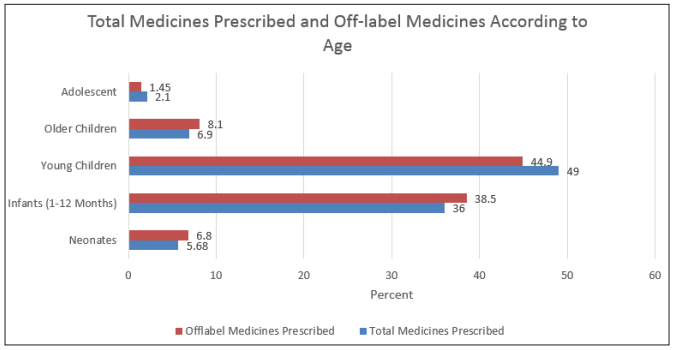

Figure 1: Medicines Prescribed and Off-label Medicines Use According to Age

Findings from this study shows that close to half of the off-label use of medicines were attributed to indication. Further details relating to category of off-label use of medicines are presented in table 1 below.

Table 1: Category of Off-label Medicines

SN	Off-label Category	Frequency (%)
1	Dose	177 (37.7)
2	Age	67 (14)
3	Formulation	14 (2.9)
4	Indication	211 (45)

Discussion

Of the case notes evaluated in the study, females were slightly higher than males. This shows that more females received prescription for medicine than males. This is however in contradiction with other similar studies which shows that male children received more prescription for medicine than females [6,20,21,22]. Young children of aged 1 to 5 years were more in the study as they made up close to half of the sample, whilst adolescents of aged 12 to 16 were the least of the entire study sample, and this could be attributed to the fact that younger children are more likely to fall ill due to their low immunity.

Available evidence suggests that there is insufficient data on off-label use of medicines in Nigeria, hence there is need to constantly evaluate off-label use of drugs in children so as to ensure appropriate pharmaceutical care intervention in this

category of patients, as well as prevent adverse drug occurrence [23-25]. In this study, a quarter of the total medicines prescribed were off-label, and this proportion was slightly higher than 21.5% reported by in South East Nigeria during a study among children aged 0-5years who were either on hospital admission or accessing care as outpatients in a tertiary and primary health centers [6]. Also, the proportion of off-label medicines in this study was lower than that reported by in North Central Nigeria during a study regarding off-label and unlicensed drug prescriptions for children living with HIV/AIDS [23]. Available evidence suggests that the proportion of off-label use of drugs varies depending on the level of healthcare, clinic settings, physician's specialty, patient's characteristics, countries [26]. Furthermore, A study undertaken in Australia had reported about one-third of off-label use of medicines among paediatric population, whilst this present study had off-label use of medicines higher than 10.5% reported in United Kingdom among children [27,28]. However, off-label prescriptions in this study was comparable to 26% obtained in paediatric oncology centres involving both in and out patients in United Kingdom, as well as 26.4% recorded in paediatric isolation ward in Germany [29,30].

There were four main forms of off-label prescription classification in this study which include age group, dose, formulation, and indication. Off-label prescription of age group category involved use of drug dosage form in unapproved age group, for example use of cotrimoxazole tablets in children less than twelve years old. Adequate fluid intake is advised for patients taking cotrimoxazole, this may however be difficult to achieve in children who naturally may prefer to chew rather swallow. On the other hand, children may prefer to drink artificial fruit juices instead of water. There is insufficient data on the pharmacokinetics of cotrimoxazole in the presence of different components of such artificial juice. More also, clinical trials of cotrimoxazole tablets did not include paediatrics subjects, the paediatrics patients given solid dosage formulation of cotrimoxazole could have been inadvertently exposed to clinical adverse conditions such as urolithiasis and other drug allergies associated with cotrimoxazole [31-33].

The two groups mostly prescribed with off-label drugs were young children aged 1-5 years and infants aged 1-12 months, this is in agreement with previous Nigerian study reported by [34]. Higher rate of the use of off-label medicines was previously reported among these two age groups [20]. This study is however in contrast to previous studies reported in Netherland Scotland and Finland [35-37]. where the prevalence of off-label medicines was highest in neonates. The main reason for these variations in results may be related to differences in the study population [34].

Indication accounted for close to half of off-label use of medicines in this study. Inappropriate dosing accounted for slightly above a third of the total off-label prescription given to paediatrics in this study and of which this may be characterized by potential health hazards such as sub-optimal treatment from under-dosing and drug toxicity from over-dosing. The low prevalence of off-label prescription as a result of formulation is in contrast with the study reported by Oreagba et al. [34].

Conclusion

One quarter of the medicines prescribed to paediatrics in this study was off-label, and two groups were mostly prescribed with off-label drugs which include young children aged 1-5 years and infants aged 1-12 months. Children in the hospital setting are often treated with drugs not specifically approved for use in children, and drugs are also used outside the terms of the product license that apply to indication, age, dose, and formulation. Off-label prescribing is said to be prevalent from this study. All drugs used to treat children should be subjected to the licensing process to ensure their quality, safety, and efficacy. Appropriate pharmaceutical care intervention is recommended in healthcare facilities as this practice can play critical role in reducing the frequency of off-label use medicines.

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