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Original Research Article

## Use of off-label drugs in the neonatal intensive care unit in India

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### ABSTRACT

**Background:** Off-label use of drugs is widespread in pediatrics and almost all neonates hospitalized in NICU are affected by the use of off-label drugs regardless of gestational age and birth weight. This is because of the lack of regulation for medications in the neonatal population and the delays in updating drug instructions. This is mainly due to the ethical difficulty in the research and difficulties in conducting clinical trials in this vulnerable population. Hence, the study was planned to assess the extent of the use of off-label drugs in the NICU.

**Methods:** An observational study was carried out in the NICU of a tertiary care center from May 2021 to Oct 2022 and case records of neonates admitted to the NICU were evaluated.

**Results:** Among 1745 drug prescriptions in 360 neonates, 1208 (69.22%) were off-label. Anti-infectives were the most commonly used off-label class of drug, Piperacillin+tazobactam was the most commonly used off-label drug and most common reason for off-label prescriptions was indication and administration. It was found that 79.44% of neonates received at least one off-label drug.

**Conclusions:** Off-label use of drugs, specifically anti-infective drugs, is common in NICUs of India as in other countries. So, more research should be done to generate evidence-based guidelines for the rational use of drugs in neonates.

**Keywords:** Neonates, Neonatal intensive care unit, Off-label drug use, Prescription

### INTRODUCTION

Neonatal intensive care unit (NICU) is a highly specialized place that focuses on the main human and material resources needed to provide never-ending support to newborns (NB), especially to ill newborns, including preterm and low birth weight babies who require Intensive Care.<sup>1,2</sup> Such care almost always involves the use of numerous drugs, many of which are without the proper drug description leaflet for use in the first month of life.<sup>2</sup> Neonates are a special part of the patient population with special concerns regarding drug therapy because prematurity and low birth weight may have a significant effect on the pharmacokinetics and pharmacodynamics of drugs which makes the administration of drugs more

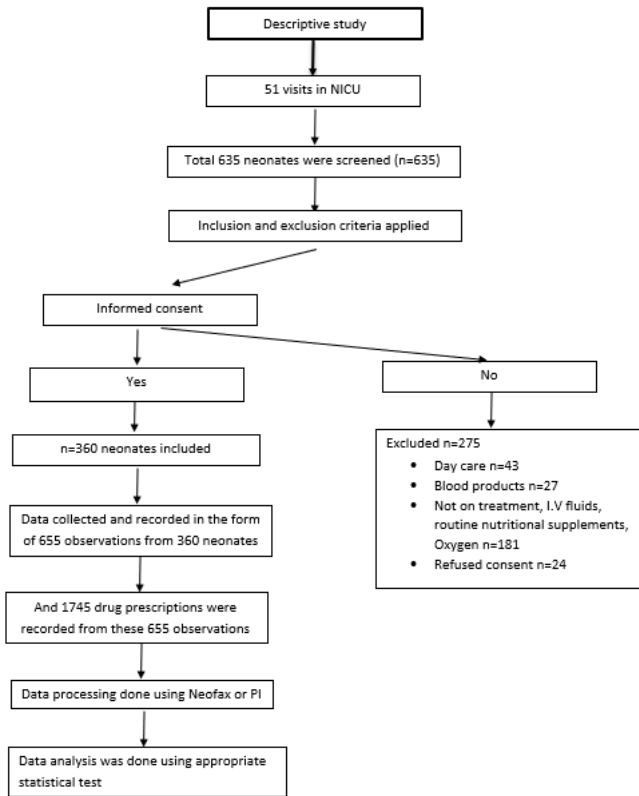
delicate.<sup>3</sup> However, despite many advances in neonatal care, there are, yet, no guidelines that are universally standardized for the rational use of drugs in a NICU. Most of the drugs today have not included neonates for safety and efficacy during their clinical trials.<sup>1</sup> Most such drugs are prescribed to them by extrapolating adult data in off-label conditions.<sup>4</sup> Off-label use of drugs is legal and common practice and can be beneficial, especially in situations where approved treatment fails to correct the condition of a sick neonate.<sup>5</sup> Almost all neonates hospitalized in NICU are affected by the use of off-label medicines regardless of gestational age and birth weight.<sup>3</sup> Off-label use of drugs is widespread in pediatrics due to the delays in updating drug instructions, the absence of standard prescribing information about the medicine and therapeutic options might get restricted without off-label

prescribing which forces pediatricians to prescribe medicines in off-label means.<sup>6-14</sup> Therefore, it is usual to use drugs in neonates approved for older children and adults, as well as the pharmaceutical forms' adaptation to specific situations.<sup>15</sup> The WHO has estimated that all medicines used worldwide in neonates are prescribed or dispensed inappropriately i.e., in off-label conditions.<sup>16</sup> This is due to the lack of regulation for medications in the pediatric population, the difference in scientific studies on the action of drugs in pediatrics, and the lack of knowledge by some professionals, promoting the use, with increasing frequency of off-label medicines, especially in the neonatal period. This is mainly because of the ethical difficulty in the research, difficulties in conducting clinical trials, and lack of interest and financial incentive for the pharmaceutical industry to develop suitable formulations for neonates and the biological effect that drugs can bring to this vulnerable population.<sup>3,17-24</sup> Literature shows that in neonates drugs are extensively prescribed off-label ranging from 26% to 95%.<sup>25,26</sup> This historical picture of the use of off-label drugs in newborns is a common worldwide occurrence.<sup>26</sup> According to WHO, off-label use of drugs is the use of licensed medicines for indications that have not been approved by a national medicine regulatory authority is considered off-label use, that is when a drug is prescribed differently from those recommended in the drug prescription leaflet, regarding therapeutic indication, dosage, route and frequency of administration and patient's age;<sup>27,28</sup> According to the American Academy of Pediatrics, off-label use is "use of a drug that is not included in the package insert (FDA approved labelling) and does not imply improper, illegal, contraindicated or investigational use". This statement also highlights that off-label use does not necessarily require prescribers to obtain informed consent if the decision to use the medication is supported by scientific or anecdotal evidence and is not investigational in nature.<sup>29</sup> The definition of off-label varies according to the regulatory agencies of the countries. According to a systematic review done in one of the USA studies which included 31 studies describes that use of medication outside the package insert recommendations for indication, patients age, route, dose and frequency is the most common definition of off-label use and stated that approximately all infants admitted to NICU receive at least one off-label drug. In NICUs of India, US and Europe, the use of off-label drugs is 12.3% to 61.9%, 60% to 75% & 23% to 98.6%, respectively.<sup>20,30-33</sup> The application of pharmacotherapy is complex in hospitalized newborns, with factors of vulnerability including developmental immaturity and limited evidence-based dosing information.<sup>34,35</sup> Considering the scarcity of controlled clinical trials due to a lack of interest by pharmaceutical companies and ethical issues related to the recruitment of neonates in clinical trials, neonatologists are forced to use drugs in an off-label manner to provide maximum benefit from available drug therapies.<sup>36</sup> The purpose of off-label use is to benefit a neonatal population. Off-label use may provide the best available treatment for a patient, as well as the standard of care for a specific problem for which,

there is no relief from standard drugs which are primarily indicated for its management.<sup>29</sup> The main advantage does not deny children the potential to benefit from new medicines. Such use may be clinically appropriate when there are no alternatives and if employed judiciously, the benefits of off-label use far outweigh the risks.<sup>14,37</sup> When scientific and medical evidence justifies off-label uses, clinicians help neonate patients by prescribing off-label drugs.<sup>38-40</sup> Clinicians' freedom to prescribe off-label medicines conveys important advantages. It allows revolution in clinical practice, especially when approved treatments have failed. It offers patients and physicians an earlier approach to potentially valuable medicines and permits physicians to adopt new practices based on emerging evidence.<sup>37</sup> So off-label use of drugs has numerous advantages, and therefore, the government in close association with DCGI should look at ways and means to update the off-label practice to provide maximum benefits to sick newborns.<sup>14</sup> Off-label use is sometimes inevitable as most of the marketed prescription drugs have no labelling indications for children.<sup>41</sup> At present, there are gaps in reporting and evidence of off-label drug recommendations in pediatric guidelines and there is often extensive variation in the information reported between different guidelines that recommend the same drug for off-label use. Children and adolescents are not seen as an isolated patient group, but as an essential part of the whole population who deserve "equity" compared with the standard patient and therefore have the right to receive drugs of appropriate quality and safety.<sup>42,43</sup> As a result, there is a need to better clarify the current evidence for pediatric off-label usage of drugs in pediatric guidelines to support the judicious use of drugs and for pediatricians to guide the off-label prescription of drugs. Most of the studies related to off-label use of drugs have been done outside India and there are only a few studies are available from India, and no study has been done in our Malwa region, in Punjab. That's why this study was planned to collect data in a tertiary-level NICU to determine the extent of the use of off-label drugs in this region and it will help us to make the policy for the drugs being used in NICU.

## METHODS

This was a prospective observational study conducted in the NICU of a tertiary care hospital in, Guru Gobind Singh Medical College and Hospital, Faridkot (Northern India) from May 2021 to October 2022. Informed consent were taken from the parents of the enrolled patients. All neonates (pre-term and term) admitted to the NICU and who had received at least one drug were included in the study. Patients were selected based on inclusion-exclusion criteria. Neonates who were under observation only or were not receiving any drugs or receiving intravenous fluids, routine nutritional supplements, vitamin K, vaccines, blood products, or oxygen therapy and whose parents refused to give consent were excluded from the study. This study was carried out by evaluating case sheets of neonates.



**Figure 1: Study procedure summary.**

All data including demographic details, diagnoses, and drug prescription details (dose, administration, route of administration, frequency, and indication) were recorded in a self-designed form. All this data was checked for off-label status by using Neofax 2020 as a reference source and package insert as an alternative source. Descriptive statistics were used to describe baseline variables. Categorical outcome variables were analyzed by Chi-square test. All Statistical Analysis was done using statistical software packages IBM SPSS version 23 (SPSS Inc. New York, USA).

**RESULTS**

Out of 635 neonates screened, 360 were included in the study and 275 were excluded according to exclusion criteria. Data was collected in the form of 655 observations from 360 neonates. On further analysis of the 655 observations, a total of 1745 drug prescriptions were recorded from 28 different drugs. Among 360 neonates, 198 (55%) were males and 162 (45%) were females, 228 (63.3%) were Preterm and 132 (36.6%) were term, 270 (75%) were low birth weight neonates and 90 (25%) were normal birth weight neonates, 185 (51.3%) were inborn and 175 (48.6%) were outborn, 318 (88.3%) were medical patients and 42 (11.6%) were surgical patients (Table 1). The mean birth weight and gestational age were 1940±645 (SD) grams and 34.17±3.49 (SD) weeks respectively. Common clinical conditions were respiratory distress,

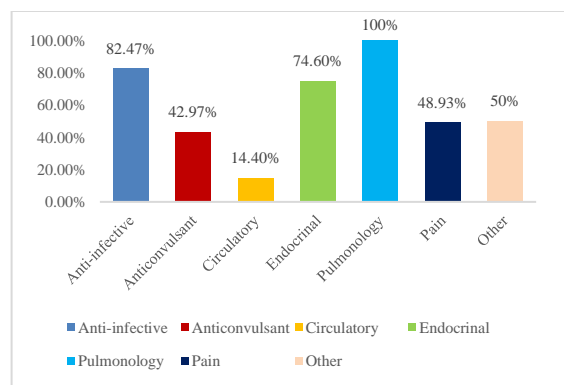
septic shock, birth asphyxia, apnoea of prematurity, TTNB, and neonatal Seizures.

**Table 1: demographic data distribution (n=360).**

Parameters	Patients	
	N	%
<b>Gender</b>		
Male	198	55
Female	162	45
<b>Gestational age (weeks)</b>		
Term	132	36.6
Preterm	228	63.6
<b>Birth weight (grams)</b>		
Normal birth weight	90	25
Low birth weight	270	75
<b>Place of birth</b>		
Inborn	185	51.3
Outborn	175	48.6
<b>Type of patient</b>		
Medical	318	88.3
Surgical	42	11.6

**Table 2: Distribution of various drug categories used Off-label and most commonly used off-label drugs.**

Drug category	Commonly used off-label drugs	N (%)
<b>Anti-infective</b>	Pipracillin+Tazobactam, Ciprofloxacin, Fluconazole, Tigicycline, Meropenem, Vancomycin, Metro-nidazole, Amikacin, Linzolid	82.47
<b>Anti-convulsant</b>	Levetiracetam, Phenytoin	42.97
<b>Circulatory</b>	Milrinone, Adrenaline	14.40
<b>Endocrinal</b>	Dexamethasone, Hydrocortisone	74.60
<b>Pulmonology</b>	Caffeine Citrate	100
<b>Pain</b>	Paracetamol	48.93
<b>Other</b>	Sildenafil, Furosemide	50
<b>Total</b>		69.22



**Figure 2: Distribution of various drug categories used Off-label and most commonly used off-label drugs.**

**Table 3: List of 15 most frequently used off-label medications in NICU during the study period.**

Medicines	Total Prescriptions	Number of off-label Prescriptions	% age	Reason for off-label
Piperacillin+tazobactam	157	157	100	Indication
Caffeine Citrate	133	133	100	Administration
Ciprofloxacin	131	131	100	Indication
Fluconazole	74	74	100	Administration
Meropenem	67	67	100	Indication
Tigicycline	65	65	100	Indication
Paracetamol	44	44	100	Dose
Metronidazole	33	33	100	Indication
Phenytoin	14	14	100	Administration
Amikacin	11	11	100	Administration
Milrinone	11	11	100	Dose
Levetiracetam	10	10	100	Indication
Linzolid	10	10	100	Administration
Dexamethasone	9	9	100	Frequency
Vancomycin	231	226	97.83	Administration

**Table 4: comparison of total drug use and off-label use according to gestational age.**

Total drug use	According to Gestational age on delivery						P value
	Term			Preterm			
	Number of babies on drugs	Number of babies on Off-label drugs	% age	Number of babies on drugs	Number of babies on off-label drugs	% age	
	132	108	81.81	228	178	78.07	0.396

**Table 5: Comparison of total drugs use and off-label use among different weight categories.**

Total drug use	According to birth weight						P value
	LBW			Normal birth weight			
	Number of babies on drugs	Number of babies on Off-label drugs	% age	Number of babies on drugs	Number of babies on off-label drugs	% age	
	270	214	79.25	90	74	82.22	0.542

During the study period, among 1745 drug prescriptions, 1208 (69.22%) were found off-label and each admitted neonate received 2.67 drugs per day and out of these, 2.30 neonates were off-label. It was found that 79.44% of neonates received at least one off-label drug. Most of the medications were administered through the parenteral route. The most frequently prescribed class of drug was Anti-infectives (61.6%) and the ten most commonly used drugs were colistin, vancomycin, piperacillin+tazobactam, caffeine citrate, ciprofloxacin, dopamine, phenobarbitone, dobutamine, fluconazole, and meropenem. As shown in (Table 2), Anti-infectives (82.47%, 887/1075) was the most commonly used off-label class of drug followed by anticonvulsants and others. All the drugs used in Pulmonology (133/133) were used as off-label drugs, but they comprised only a small portion of the total number of prescriptions. Piperacillin+tazobactam was the most frequently used off-label drug followed by caffeine citrate, ciprofloxacin, vancomycin, and others (Table 3). The most

common reason for the off-label use of these drugs. The comparison of total drug use and off-label use according to gestational age on delivery is shown in tabl. It shows that in preterm neonates, the total number of prescriptions was 228, and off-label prescriptions were 178 (78.07%), and among term neonates, total prescriptions were 132, and off-label prescriptions were 108 (81.08%). However, no significant difference was found (p=0.396) in off-label drug exposure between preterm and term neonates. On comparison of total drug use and off-label drug use among different weight categories, it was found that in neonates with LBW, the total number of prescriptions was 270 and off-label prescriptions were 214 (79.25%) and among neonates with normal birth weight, total prescriptions were 90 and off-label prescriptions were 74 (82.22%). However, we did not find a significant difference (p=0.542) in off-label drug exposure between neonates of low birth weight and normal birth weight (Table 5).

## DISCUSSION

In this prospective study, we observed that more than half (69.22%) of the prescribed drugs in the NICU were off-label. Similar findings were observed in the study done in south India, which comes out to be 61.9%.<sup>30</sup> Another study done in north India found fifty percent of off-label use of drugs in the NICU.<sup>13</sup> One more similar north Indian study done in Uttar Pradesh found four out of ten drugs used in NICU were off-label.<sup>1</sup> The reason behind the variability in the number of off-label use drugs is differences in neonatal conditions, the availability of drugs, and drug resources. Whereas, a systematic review of 31 studies done in the US in 2018, reported overall off-label drug use in neonates ranging from 26-95%.<sup>26</sup> The variation in results might be attributed to the different geographical conditions, different definitions of off-label, and different resource materials (formularies and package insert) referred to determine the off-label status and duration of hospitalization. From the total number of neonates included in this study, eight out of ten were exposed to at least one off-label drug. The study done in Pakistan also concluded that eight out of ten neonates received at least one off-label drug.<sup>44</sup> Even though studies done in developed nations like Germany and Netherlands, showed similar results (seven out of ten).<sup>32,45</sup> But this was even higher in comparison to this study. It was reported that a study done in south India showed 96.6%, in Brazil (96-99%), and in China, (92%) of neonates received at least one off-label drug.<sup>3,30,46</sup> The reason behind the off-label use of drugs is majorly due to the lack of evidence-based guidelines, as the neonatal population comes under the vulnerable special group, there are worldwide ethical issues related to neonatal clinical trials that lead to the use of prescription drugs as off-label in both developed and developing nations. In the present study, anti-infectives (eight out of ten) were the most commonly used off-label class of drug followed by Endocrinal drugs (seven out of ten). All the drugs used in Pulmonology were used as off-label drugs, but they comprised only a small portion of the total number of prescriptions. A study done in south India (seven out of ten), China (nearly three-fourths), and Spain (five out of ten) also reported a similar finding that anti-infectives were the most frequently used off-label class of drugs.<sup>21,30,46</sup> This is not unexpected as the burden of infections remains high in the developing world as compared to the developed world. This is the reason for the more frequent use of off-label antibiotics. It is usual practice to initiate antibiotic therapy empirically considering the seriousness of the illness. Sepsis and neonatal prematurity are one of the most common causes of neonatal morbidity and mortality in India. Therefore, a high prevalence of off-label use of anti-infectives is expected in India. However, another study done in Brazil found the respiratory group was the most commonly used off-label. The reason behind this could be due to the apnoea of prematurity and hyaline membrane diseases as most of the study population was predominately pre-terms.<sup>3</sup> Another study carried out in Italy reported the drugs used in cardiovascular diseases were most

commonly used as off-label drugs.<sup>47</sup> Differences in an off-label class of drug uses in different countries can be explained by the type of morbidities observed in hospitals i.e., differences in neonatal conditions, a combination of genetic factors, environmental factors, nutritional status, and health status of the mother Geographical variation also exists in the class of drug being used off-label. The most commonly used off-label drugs in this study were piperacillin+tazobactam followed by caffeine citrate, ciprofloxacin, and vancomycin. The most common reason for off-label use of these drugs was administration followed by indication (age). Studies conducted in PGI Chandigarh in north India reported that ciprofloxacin and vancomycin were the most commonly used off-label drugs;<sup>13</sup> cefotaxime, piperacillin+tazobactam in Uttar Pradesh;<sup>1</sup> amikacin and gentamicin in another south Indian study.<sup>30</sup> However, the most common reason for off-label use of drugs in above mentioned studies was dose followed by frequency and age (indication). In another study conducted in Spain, the researcher found that ampicillin and gentamicin were the most commonly used off-label drugs;<sup>21</sup> gentamicin and albuterol in Iran;<sup>48</sup> Fentanyl and Gentamicin in Brazil;<sup>3</sup> ampicillin and cefotaxime in Pakistan were most commonly used off-label drugs.<sup>44</sup> The most common reason for off-label use in the studies mentioned above was dose followed by age or indication and frequency. According to study done on a review of drug utilization patterns in NICUs worldwide, which was conducted in Australia including 19 studies, reported the most commonly administered off-label drugs as benzylpenicillin, furosemide, ranitidine, fentanyl, theophylline, and gentamicin and the most frequent reason shown by this study was frequency, age, and indication.<sup>34</sup> As discussed, earlier, the reason for the variability in these results may be due to the lack of evidence-based guidelines specifically for neonates. As we have observed worldwide anti-infectives are the most commonly used off-label drugs and even there is variability in antibiotic use in different countries. The heterogeneity in the use of drugs is indicated that empirical treatments with these drugs are different between countries and even between the NICUs of the same country. The variation in reports of common off-label use of different drugs can be due to newborn characteristics, gestational age, specific diseases, and differences in the count of medical and surgical patients. This is not a new finding, because there is no consensus based on clinical trials in favor of specific antibiotic treatment for the prophylaxis and treatment of sepsis in newborns. Consequently, the selection of antibiotics or other drugs will depend on the experience of different physicians, disease epidemiology, the difference in availability of medicines approved for neonatal use, and hospital guidelines rather than on comparative clinical trials. Another reason for the variant antibiotic use is the existence of different bacterial resistances between countries. It should be noticed that off-label use can be recorded in different ways and in addition, the off-label classification may vary from study to study or country to country, making a direct comparison between our results and the existing literature difficult.

In the present study, no statistically significant difference ( $p=0.396$ ) was found in off-label drug exposure in different gestational age groups. The percentage of off-label drugs prescribed to term and preterm neonates were 81.80% and 78% respectively. Similar results were found compared to the study conducted in south India in which 96% of term and 100% of preterm neonates were exposed to off-label drugs, and their results were also statistically non-significant ( $p=0.23$ ).<sup>30</sup> A study done in Brazil found nine out of ten term neonates were on off-label drugs and 100% preterm neonates were on off-label drugs,<sup>3</sup> and nearly five out of ten terms and seven out of ten preterm neonates were exposed to off-label drugs in Iran.<sup>48</sup> The variability in results could be due to differences in the number of term and preterm neonates recruited in different studies and most of the preterm neonates are vulnerable to infections and other various diseases. The other reason can be the antenatal policy and the health facility of that institute at the time of delivery. The number or percentage of low-birth-weight neonates (seventy-five percent) was found higher in our study and the percentage of exposure to off-label drugs was seventy-nine percent but the percentage of off-label drug exposure was almost similar irrespective of birth weight. No statistically significant difference was found ( $p=0.542$ ) in comparison of off-label drug exposure in low birth weight and normal birth weight babies. A study conducted in Italy also had a high number of low-birthweight neonates (eight out of ten)<sup>47</sup> and another study done in Brazil also reported more low-birth-weight neonates in their NICU.<sup>49</sup> On the other hand, Studies conducted in Mumbai and China reported a smaller number of low-birth-weight neonates in their NICUs.<sup>20,46</sup> This is because of variability in the type of admissions in the NICU. Overall, it appears that types of medicines used in NICU worldwide are similar, with the usage of aminoglycosides, penicillin, piperacillin + tazobactam, amikacin, gentamicin, ampicillin, vancomycin, fentanyl, paracetamol, caffeine, and multivitamins. The differences in results detected between our study and other aforementioned studies may be due to differences in the definition of off-label use, licensing properties in different countries, different sample sizes, and different types of hospitals, where the study was performed. The strength of the present study was that it focuses particularly on the rural area of a resource-constrained developing country which is usually untouched to address this gap of the paucity of data. The limitation of this study was that it was a single-center study and the sample size was small. These limitations can be overcome by conducting multicentre studies, researchers can overcome the limitation of small sample sizes and limited diversity in patient populations and generate more robust evidence to guide clinical practices.

## CONCLUSION

Literature shows that drugs are widely prescribed for neonates with a prevalence of up to 95%. The current study has also shown that off-label use of drugs for neonates is a common phenomenon in India (69.22%), as in other

countries. Anti-infectives were the most commonly used class of drug and Piperacillin+tazobactam was the most frequently used off-label drug. The findings of this study highlight the need for a more robust and comprehensive approach to studying the use of drugs in neonates. Developing evidence-based guidelines is of utmost importance for the rational use of drugs for this vulnerable population. The guidelines could serve as a valuable source for neonatal healthcare professionals, helping them to make informed decisions about the use of drugs in neonates based on the latest evidence.

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