

# Off-label drug use in pediatric patients: a comparative analysis with nationwide routine prescription data

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## ABSTRACT

**Background.** Children constitute a special population for off-label drug use (OLDU), yet limited drug-focused data exist regarding pediatric OLDU in clinical practice. This study aimed to investigate pediatric OLDU practice and compare it with pediatric drug utilization patterns of routine prescribing data.

**Methods.** This cross-sectional study examined all approved pediatric OLDU applications, compared with electronic prescription data on national Prescription Information System of Turkish Medicines and Medical Devices Agency in 2015. OLDU applications and prescriptions were analyzed for demographic characteristics, healthcare/socioeconomic indices as well as details of drugs and diagnoses.

**Results.** We found 7,896 OLDU applications and 7,029,512 prescriptions for the pediatric population in 2015. OLDU applications and prescriptions were mostly practiced for “2-11-year-old” children (52.7% vs. 63.4%, respectively;  $p < 0.01$ ). OLDU applications and prescriptions were detected to have a positive correlation with socio-economic development index ( $r = 0.45$ ,  $p < 0.0001$  and  $r = 0.40$ ,  $p = 0.0002$ ; respectively) and the physician density ( $r = 0.66$ ,  $p < 0.0001$  and  $r = 0.43$ ,  $p < 0.0001$ ; respectively). In addition, OLDU was also positively correlated with the number of hospital beds per province ( $r = 0.39$ ,  $p = 0.0003$ ). Antineoplastic/immunomodulating agents were the most commonly applied drug category in OLDU (47.0%), compared with respiratory system drugs (36.6%) in routine prescribing. Eculizumab (6.5%), mycophenolate (5.6%), and canakinumab (4.4%) were the top drugs used as off-label. OLDU applications and routine prescription data revealed the most frequent diagnosis as “I27-other pulmonary heart diseases” (7.4%) and “J06-acute upper respiratory infections” (12.6%), respectively.

**Conclusions.** This is the first nationwide study to show indication- and drug-centered aspects of pediatric OLDU and prescribing practice. Though OLDU applications is overall consistent with routine clinical practice in terms of demographics and institutional capacity, substantial variations exist regarding main drug classes and diseases. Our findings are expected to shed light on interventions focused on improving “indicated” pediatric use of drugs currently applied as off-label.

**Key words:** off-label drug use, children, prescribing, antineoplastic, immunomodulating.

New drug development is a long-term and costly path that requires pre-clinical and clinical efficacy and safety studies. Incorporating all potential indications and target age groups that could benefit from the investigational

new drug poses additional burden, further increasing the expenditure and duration.<sup>1</sup> Therefore, restricting approved indications and age groups of potential novel drug is attempted by conducting clinical trials on somehow standardized populations of healthy/patient volunteers beside ethical, legal, or economic concerns. This pragmatism approach, however, results in limited data of drug use in special groups, such as fragile elderly or children.<sup>2,3</sup>

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Received 1st October 2019, revised 25th April 2020,  
accepted 26th April 2020.

Use of drugs for other than their approved indications, doses, way of administration, age group, or special populations etc. is defined as "off-label drug use (OLDU)".<sup>4,5</sup> It is more common in several branches of clinical practice, including oncology (85%), gynecology and obstetrics (25%), and pediatrics (3% to 90%).<sup>6-10</sup> An important reason for increased rate of OLDU in pediatrics is that children are usually excluded from clinical phase studies due to above-mentioned reasons.<sup>2,11,12</sup> In order to make pediatric pharmacotherapy more labelled, further clinical studies need to be performed with designs overcoming potential difficulties pertaining to children. This could be preceded by comprehensive assessments of routine drug utilization patterns. In addition, age group-specific indications require being reviewed through the evidence arising from systematic evaluation of OLDU experiences in children.

The literature on OLDU seems to be based on rather general off-label use or is focused on special patient subsets, lacking descriptions of a nationwide pediatric OLDU practice compared to routine prescription data.<sup>8-10,13-15</sup> This study aimed to investigate pediatric OLDU practice and compare it with pediatric drug utilization patterns in routine prescribed data.

## Material and Methods

This cross-sectional study examined approved pediatric OLDU applications and electronic prescription data registered on national Prescription Information System (PIS). OLDU applications were made to Turkish Medicines and Medical Devices Agency (TMMDA) of the Ministry of Health. The agency reviews the applications and records main medical data and its final status on its electronic medium.<sup>4</sup> PIS, used for examining routine prescription data, mediates several analyses and assessments about electronic prescriptions submitted to the national prescription database.<sup>16</sup> In this study, all pediatric OLDU applications with the final status of "approved" during year 2015 were analyzed. Routine prescribing was evaluated by

the prescriptions in PIS, which were delivered by pediatricians or subspecialists of pediatrics for 18-year-old children. In 2015, the universe of our study, i.e. children, constituted 29.0% of the total population of 78.7 million inhabitants in Turkey.<sup>17</sup>

OLDU applications/prescriptions were examined with respect to patients' demographics, drugs' Anatomical Therapeutic Chemical (ATC) classification, and International Statistical Classification of Diseases (ICD) category. The latter also included applications/prescriptions with multiple diagnoses. Pediatric population were stratified as three groups: infants (<2 years old), children (2-11 years old), and adolescents ( $\geq 12$  years old). These groups were compared in terms of the number of applications/prescriptions, sex, and the mean age. Furthermore, OLDU applications and prescriptions were analyzed with respect to several regional healthcare utilization parameters (number of hospital beds, number of physicians per 100,000 inhabitants, percentage of child population, number of health service applications to secondary/tertiary centers) and socio-economic development index (SEDI). While data on regional healthcare utilization was obtained from Health Statistics Yearbook 2015 of Turkish Ministry of Health and Turkish Statistics Institute<sup>17,18</sup>, SEDI has 61 items indicating various domains (demographics, employment, health, finance, and quality of life, etc.) that were used for scoring and ranking the provinces, as rigorously calculated by the Turkish Ministry of Development.<sup>19</sup>

The drugs at OLDU applications were compared by age groups at the ATC-1 level. Furthermore, the top 15 most commonly applied drugs were examined at ATC-5 level. These drugs were also assessed as to whether they fell into a biotechnological or licensed category.

The top three commonly encountered diagnoses in OLDU applications were examined with their top three applied drugs and the applying physicians' specialty. Beside this indication-focused approach, a drug-focused approach was

also undertaken to show diagnostic distribution: most frequent three diagnoses and total number of different diagnoses were determined for each of the top ten drugs in OLDU applications. This analysis was performed using applications with only a single diagnosis.

### Statistical analysis

Statistical analyses were made through SPSS 25.0 software. Categorical and continuous variables were expressed as number/percentage and mean/standard deviation, respectively. The comparisons between groups were analyzed via chi-square for categorical and t-test for continuous variables. The associations of number of OLDU applications and prescriptions to regional healthcare utilization parameters and SEDI was tested using Spearman's rank correlation. An overall 5% type-I error level was used to infer statistical significance.

The data were collected after the study was approved by the Ethics Committee of Institute of Health Science of Marmara University (Approval Date/No: 11.09.2017/171).

### Results

A total of 7,896 pediatric OLDU applications were detected in the one-year study period,

during which the number of prescriptions in PIS generated for pediatric population was 7,029,512 as routine prescribing. The majority of applications/prescriptions in OLDU and routine PIS practice were for the "children" subgroup (52.7% vs 63.4%, respectively;  $p < 0.01$ ); followed by adolescents in OLDU (36.1%) and infants in PIS practice (24.9%). All comparisons between the age groups in terms of percentage of applications/prescriptions significantly differed from each other ( $p < 0.01$ , Fig. 1). The mean age of the "age groups" was significantly higher in OLDU applications than that in PIS ( $p < 0.01$  for all age groups). The applications/prescriptions were more likely to be generated for boys over girls in all age groups in both OLDU and PIS database with a tendency to be balanced with increasing age: girls constituted 45.5% and 45.0% in infants and 48.4% and 49.4% among adolescence in OLDU and PIS database, respectively.

The number of OLDU applications and prescriptions were found to be positively correlated with SEDI ( $r = 0.45$ ,  $p < 0.0001$  and  $r = 0.40$ ,  $p = 0.0002$ ; respectively), the number of physicians per 100,000 inhabitants ( $r = 0.66$ ,  $p < 0.0001$  and  $r = 0.43$ ,  $p < 0.0001$ ; respectively). In addition, OLDU applications were also positively correlated with the number of hospital beds per province ( $r = 0.39$ ,  $p = 0.0003$ ).

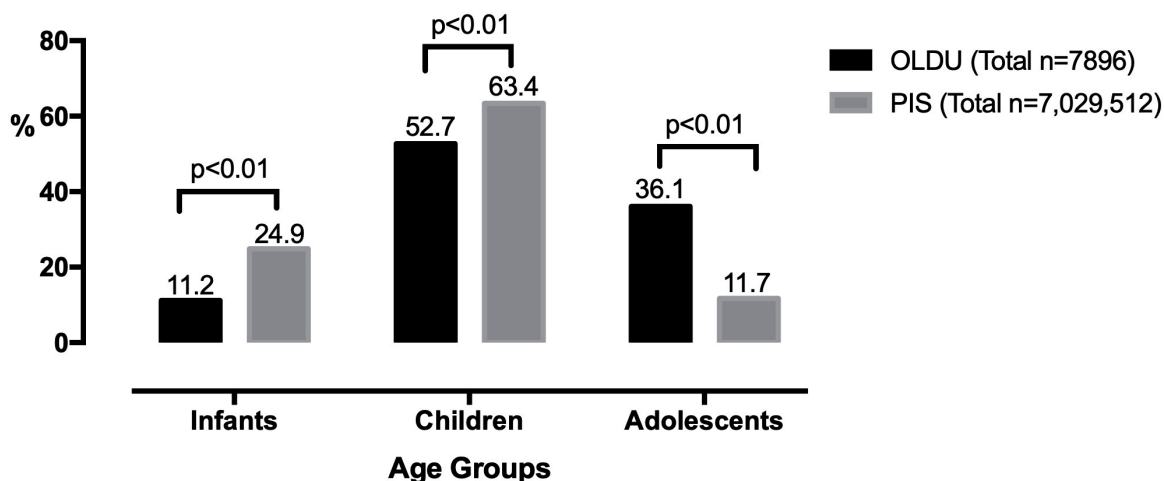


Fig. 1. Comparison of OLDU applications and routine prescribing data on PIS based on the age groups (OLDU, off-label drug use; PIS, Prescription Information System).

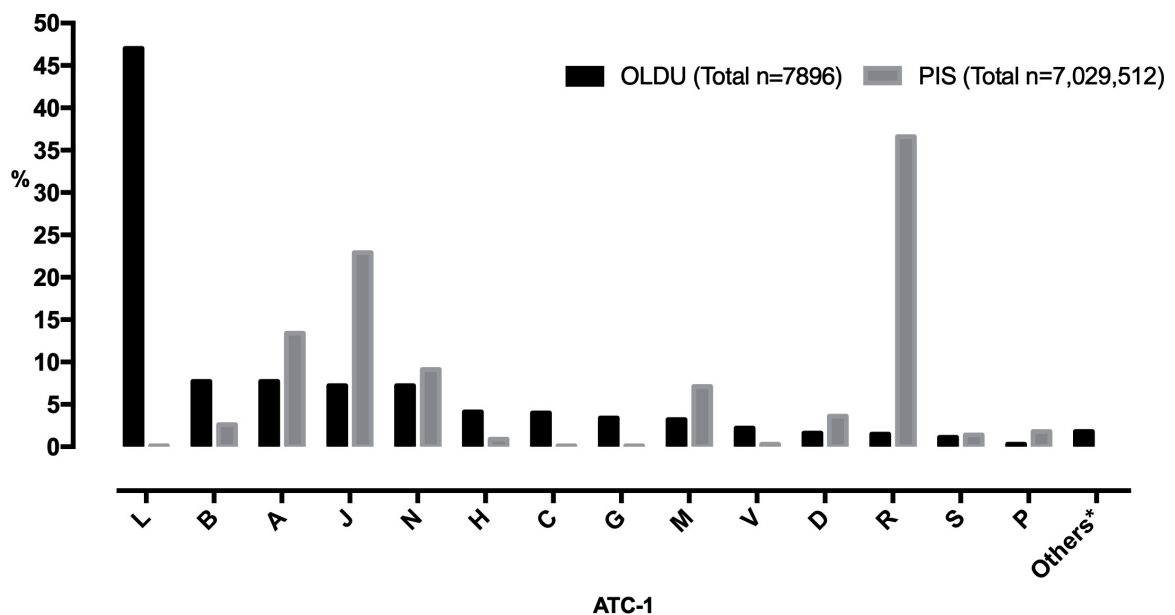
The number of health service applications or the percentage of child population was not correlated with OLDU applications or routine prescriptions ( $p > 0.05$  for each).

OLDU applications showed the most common drug group at ATC-1 level as “antineoplastic and immunomodulating agents” (47.0%), followed by “blood and blood forming organs” (7.7%) and “alimentary tract and metabolism” (7.7%). On the other hand, the most commonly prescribed drug group in routine practice belonged to “respiratory system” (36.6%), “anti-infectives for systemic use” (22.9%) and “alimentary tract and metabolism” (13.4%), (Fig. 2).

The distribution of drug categories in OLDU applications revealed significant differences between infants, children and adolescents ( $p < 0.05$ ), except “blood and blood forming organs” and “systemic hormonal preparations, excluding sex hormones and insulins” ATC-1 categories (Table I).

A total of 336 different drugs were detected in OLDU applications. The most commonly applied drug was eculizumab (6.5%), followed by mycophenolate (5.6%) and canakinumab (4.4%). The most commonly applied off-label drug by age groups was determined as sapropterin (16.6%) in infants, eculizumab (6.7%) in children, and mycophenolate (8.0%) in adolescents. The top 15 drugs in OLDU applications were found to constitute 50.0% ( $n = 3937$ ). While eight of these (53.3%) were biotechnological drugs overall, stratification by age group showed three (20.0%) in infants and eight (53.3%) in both children and adolescents. In addition, only two (13.3%) of these top 15 drugs were found to be unlicensed in Turkey (Table II).

The distribution of diagnoses in OLDU applications revealed 548 different diagnoses with the most frequent group as “I27-other pulmonary heart diseases” (7.4%), as compared to that in PIS-based routine prescribing as “J06-acute upper respiratory infections”



**Fig. 2.** Distribution of the drugs at OLDU applications and routine prescribing data on PIS by ATC-1 category. (OLDU, off-label drug use; PIS, Prescription Information System; A, Alimentary tract and metabolism; B, Blood and blood forming organs; C, Cardiovascular system; D, Dermatological; G, Genitourinary system and sex hormones; H, Systemic hormonal preparations, excl. sex hormones and insulins; J, Anti-infectives for systemic use; L, Antineoplastic and immunomodulating agents; M, Musculoskeletal system; N, Nervous system; P, Antiparasitic products, insecticides and repellents; R, Respiratory system; S, Sensory organs; V, Various; \*, Products with no ATC code).

**Table I.** Comparison of drugs at ATC-1 level in OLDU applications based on age groups.

ATC-1 codes	Infants n (%)	Children n (%)	Adolescents n (%)	P-value
L-Antineoplastic and immunomodulating agents	248 (28.2)	1894 (45.5)*	1566 (54.9) <sup>#</sup>	<0.05
B-Blood and blood forming organs	66 (7.5)	325 (7.8)	220 (7.8)	>0.05
A-Alimentary tract and metabolism	188 (21.3)	338 (8.1)*	84 (2.9) <sup>#</sup>	<0.05
J-Anti-infectives for systemic use	80 (9.1)	301 (7.2)	189 (6.7)	<0.05
N-Nervous system	24 (2.7)	382 (9.2)*	160 (5.6) <sup>#</sup>	<0.05
H-Systemic hormonal preparations, excl. sex hormones and insulins	23 (2.6)	182 (4.4)	121 (4.2)	>0.05
C-Cardiovascular system	61 (6.9)	151 (3.6)*	102 (3.6)*	<0.05
G-Genitourinary system and sex hormones	41 (4.6)	103 (2.5) <sup>§</sup>	122 (4.3)	<0.05
M-Musculoskeletal system	6 (0.7)	148 (3.6)*	98 (3.4)*	<0.05
V-Variou	40 (4.5)	88 (2.1)*	42 (1.5)*	<0.05
D-Dermatologicals	18 (2.0)	82 (2.0)	28 (1.0) <sup>#</sup>	<0.05
R-Respiratory system	31 (3.5)	43 (1.0)*	45 (1.6) <sup>#</sup>	<0.05
S-Sensory organs	23 (2.6)	27 (0.6)*	38 (1.3) <sup>#</sup>	<0.05
P-Antiparasitic products, insecticides and repellents	11 (1.2)	8 (0.2)*	7 (0.2)*	<0.05
Products with no ATC code	23 (2.6)	91 (2.2)	28 (1.0) <sup>#</sup>	<0.05
Total	883 (100.0)	4163 (100.0)	2850 (100.0)	

\*p<0.05 vs. infants; <sup>#</sup>p<0.05 vs. both infants and children; <sup>§</sup>p<0.05 vs. both infants and adolescents  
OLDU: off-label drug use.

**Table II.** Distribution of drugs at ATC-5 level in OLDU applications based on age groups.

Rank	All age groups, (%)	Infants, (%)	Children, (%)	Adolescents, (%)
1	Ecuzumab*, (6.5)	Sapropterin, (16.6)	Ecuzumab*, (6.7)	Mycophenolate, (8.0)
2	Mycophenolate, (5.6)	Ecuzumab*, (11.3)	Mycophenolate, (5.0)	Rituximab*, (6.1)
3	Canakinumab*, (4.4)	Sirolimus, (4.0)	Iloprost, (4.5)	Canakinumab*, (5.6)
4	Iloprost, (4.3)	Valganciclovir, (3.3)	Sirolimus, (4.3)	Ecuzumab*, (4.7)
5	Rituximab*, (4.1)	Dextromethorphan, (2.9)	Canakinumab*, (4.2)	Iloprost, (4.5)
6	Sirolimus, (3.8)	Sildenafil, (2.8)	Lacosamide, (3.9)	IVIg*, (3.3)
7	Sapropterin, (3.4)	Bosentan, (2.7)	Adalimumab*, (3.3)	Anakinra*#, (3.3)
8	Lacosamide, (2.9)	Iloprost, (2.6)	Rituximab*, (3.2)	Sirolimus, (3.1)
9	IVIg*, (2.8)	Ranibizumab*, (2.4)	Somatropin*, (3.1)	Adalimumab*, (2.6)
10	Anakinra*#, (2.7)	Propranolol, (2.3)	Sapropterin, (2.8)	Somatropin*, (2.3)
11	Adalimumab*, (2.7)	Calcium folinate, (2.3)	IVIg*, (2.7)	Infliximab*, (2.1)
12	Somatropin*, (2.6)	Isotretinoin, (1.9)	Anakinra*#, (2.6)	Lacosamide, (1.9)
13	Sildenafil, (1.4)	Imatinib, (1.8)	Elosulfase alfa*#, (2.0)	Tacrolimus, (1.7)
14	Tacrolimus, (1.4)	IVIg*, (1.7)	Botulinum toxin, (1.4)	Botulinum toxin, (1.6)
15	Elosulfase alfa*#, (1.4)	Foscarnet#, (1.6)	Tacrolimus, (1.4)	Testosterone, (1.6)
Others n, (%)	3959, (50.0)	578, (39.8)	2029, (48.9)	1353, (47.6)
Total n, (%)	7896, (100.0)	883, (100.0)	4163, (100.0)	2850, (100.0)

\*Biotechnological drugs; # Unlicensed drugs in Turkey.  
OLDU: off-label drug use, IVIG: intravenous immunoglobulin.

(12.6%). Among the top 15 diagnoses of OLDU applications, three belonged to “E-endocrine, nutritional and metabolic diseases” (22.2%) and other three belonged to “D-diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism” (18.8%) main ICD categories. On the other hand, ten out of 15 top diagnosis belonged to “J-diseases of

respiratory system” (82.4%) category in routine prescribing (Table III).

The most commonly applied diagnosis for pediatric OLDU was epilepsy (G40), for which the most commonly requested off-label drug was lacosamide (42.4%) by mostly pediatric neurologists (92.4%). The second most common

**Table III.** Distribution of diagnoses in OLDU applications and routine prescribing on PIS.

Rank	OLDU applications		PIS prescriptions	
	Diagnosis	n (%)	Diagnosis	n (%)
1	I27_Other pulmonary heart diseases	592 (7.4)	J06_Acute upper respiratory infections of multiple and unspecified sites	1,105,753 (12.6)
2	G40_Epilepsy	537 (6.7)	J02_Acute pharyngitis	887,111 (10.1)
3	D59_Acquired haemolytic anaemia	496 (6.2)	J03_Acute tonsillitis	832,465 (9.5)
4	N04_Nephrotic syndrome	390 (4.9)	J20_Acute bronchitis	408,156 (4.6)
5	E85_Amyloidosis	388 (4.8)	J00_Acute nasopharyngitis [common cold]	406,688 (4.6)
6	E70_Disorders of aromatic amino-acid metabolism	349 (4.3)	K52_Other noninfective gastroenteritis and colitis	297,534 (3.4)
7	M08_Juvenile arthritis	319 (4.0)	J21_Acute bronchiolitis	291,426 (3.3)
8	E23_Hypofunction and other disorders of pituitary gland,	221 (2.8)	J45_Asthma	254,218 (2.9)
9	D69_Purpura and other haemorrhagic conditions	166 (2.1)	J39_Other diseases of upper respiratory tract	240,556 (2.7)
10	T86_Failure and rejection of transplanted organs and tissues	164 (2.0)	J30_Vasomotor and allergic rhinitis	232,309 (2.6)
11	C91_Lymphoid leukaemia	146 (1.8)	J01_Acute sinusitis	218,139 (2.5)
12	D18_Haemangioma and lymphangioma, any site	146 (1.8)	L30_Other dermatitis	216,021 (2.5)
13	B25_Cytomegaloviral disease	142 (1.8)	R10_Abdominal and pelvic pain	202,737 (2.3)
14	C74_Malignant neoplasm of adrenal gland	139 (1.7)	D64_Other anaemias	173,984 (2.0)
15	G80_Cerebral palsy	112 (1.4)	Z00_General examination and investigation of persons without complaint and reported diagnosis	153,660 (1.7)
	Others	3718 (46.3)	Others	2,886,872 (32.8)
	Total	8025 (100.0)	Total	8,807,629 (100.0)

OLDU: off-label drug use, PIS: Prescription Information System.

diagnosis was “other secondary pulmonary hypertension (I27.2)” where more than half (56.2%) included iloprost for OLDU near always by pediatric cardiologists (99.6%). “Hemolytic uremic syndrome (HUS) (D59.3)” was the third indication, for which eculizumab constituted near all applications (99.1%) by mostly pediatric rheumatologists/nephrologists (93.1%), (Table IV).

Drug-centered analysis for diagnoses in OLDU applications showed eculizumab to be mostly requested for HUS (86.4%), mycophenolate for nephrotic syndrome (35.8%), and canakinumab for amyloidosis (66.2%), (Table V).

### Discussion

This study examined an exclusive practice of drug use in pediatrics, as off-label, and we described close to eight thousand OLDU applications all over the country, compared to routine prescribing from several aspects. It appears that OLDU shared several characteristics of routine prescribing practice such as sex, health/socio-economic indicators, or partially age group distribution, however it substantially differed in terms of drug and disease spectrum.

A major contribution to OLDU applications came from the children (2 to 11-year-old) group

in routine prescribing. Though lower than the latter, the percentage of this age group in all pediatric OLDU applications (52.7%) seemed to comparably reflect the share of this age group (49.6%) within the pediatric population in 2015.<sup>20</sup> The distinguishing feature of OLDU in terms of age distribution was that adolescents dominated infants, which was the inverse in routine prescribing. This brings the possibility of delayed recognition of conditions that could require OLDU in early periods of life. In fact, OLDU practice was reported to be more frequent at younger ages, including newborns.<sup>14,21</sup> However, the distribution of OLDU applications by age groups in our study appears to be very similar to that of the corresponding age groups reported in the normal population.<sup>20</sup> Therefore, the difference between OLDU and routine prescription in terms of age groups is likely to result from the nature of the latter. While OLDU is a physician-driven practice, the key trigger in routine prescribing is patients’ health-seeking behavior, which may account for increased representation of infants. In fact, health-seeking behavior in parents of <1-year-old children was reported to be about seven-fold of that in parents of 1 to 5-year old children.<sup>22</sup>

OLDU applications or routine prescribing were reported to be influenced by several factors, including regional variations, inhabitant’s distribution, and institutional

**Table IV.** Distribution of mostly encountered diagnoses in OLDU applications with requested drugs and applying physician specialties.

Drugs	Epilepsy (G40), n (%)	Other secondary pulmonary hypertension (I27.2), n (%)	Haemolytic-uremic syndrome (D59.3), n (%)
1	Lacosamide, 228 (42.4)	Iloprost, 267 (56.2)	Eculizumab, 445 (99.1)
Most commonly applied drugs 2	Zonisamide, 57 (10.6)	Sildenafil, 77 (16.2)	Mycophenolate, 2 (0.4)
3	IVIg, 43 (8.0)	Bosentan, 68 (14.3)	Rituximab, 1 (0.2)
Major applying specialty	Paediatric neurology, 496 (92.4)	Paediatric cardiology, 473 (99.6)	Paediatric rheumatology & nephrology, 418 (93.1)

OLDU: off-label drug use, IVIG: intravenous immunoglobulin.

**Table V.** Distribution of top ten drugs used as off-label with their frequent diagnoses and diagnostic variation.

Drug, (n)	Most frequent diagnosis, n (%)	Second most frequent diagnosis, n (%)	Third most frequent diagnosis, n (%)	Total number of different diagnoses, n
Eculizumab, (515)	Haemolytic-uremic syndrome, 445 (86.4)	Unspecified nephritic syndrome: diffuse mesangiocapillary glomerulonephritis, 27 (5.2)	Paroxysmal nocturnal haemoglobinuria, 19 (3.7)	10
Mycophenolate, (439)	Nephrotic syndrome, 157 (35.8)	Systemic lupus erythematosus, 42 (9.6)	Idiopathic thrombocytopenic purpura, 38 (8.7)	42
Canakinumab, (347)	Amyloidosis, 230 (66.3)	Juvenile arthritis with systemic onset, 83 (24.0)	Juvenile rheumatoid arthritis, 12 (3.5)	8
Iloprost, (336)	Other secondary pulmonary hypertension, 267 (79.5)	Primary pulmonary hypertension, 64 (19.0)	Dilated cardiomyopathy, 3 (0.9)	5
Rituximab, (318)	Nephrotic syndrome, 74 (23.3)	Idiopathic thrombocytopenic purpura, 28 (8.8)	Systemic lupus erythematosus, 18 (5.7)	57
Sirolimus, (303)	Haemangioma, any site, 55 (18.2)	Other congenital malformations of circulatory system, 48 (15.2)	Lymphangioma, any site, 45 (14.9)	37
Sapropterin, (266)	Classical phenylketonuria, 198 (74.4)	Other hyperphenylalaninaemias, 65 (24.4)	Disorders of aromatic amino-acid metabolism, 2 (0.8)	4
Lacosamide, (228)	Epilepsy, 227 (99.6)	Other generalized epilepsy and epileptic syndromes, 1 (0.4)	-	2
IVIg, (221)	Epilepsy, 43 (19.5)	Immunodeficiency with predominantly antibody defects, 31 (14.0)	Kidney transplant failure and rejection, 26 (11.8)	49
Anakinra, (217)	Amyloidosis, 130 (59.9)	Juvenile arthritis with systemic onset, 62 (28.6)	Juvenile rheumatoid arthritis, 15 (6.9)	10

OLDU: off-label drug use, IVIG: intravenous immunoglobulin.

infrastructure.<sup>23-25</sup> OLDU practice was reported as more common in the provinces with high numbers of physicians and secondary/tertiary institutions.<sup>24</sup> On the other hand, prescribing studies reported association of drug utilization to some regional characteristics such as socio-economic indicators, number of physicians, or percentage of young population.<sup>23,25</sup> These seem to be consistent with our findings, showing positive correlation of OLDU applications and routine prescriptions to regional healthcare utilization and socio-economic indicators. The mere difference between OLDU and prescribing

practice was the positive association between OLDU and the number of hospital beds. This might be attributed to the fact that OLDU is more likely to be applied from secondary/tertiary healthcare institutions, as a recent nationwide study in Turkey reported that 81% of all applications for OLDU were submitted from university hospitals.<sup>26</sup>

Our study showed comparably lower rates of off-label biotechnological drugs in infants. While efficacy/safety data on biotechnological drugs is already scarce in the overall pediatric population, this difference between the age



groups might be explained by increased recognizability of some diseases with increasing age. For instance, several chronic inflammatory conditions such as juvenile idiopathic arthritis, inflammatory bowel diseases, or endemic familial Mediterranean fever was reported to be more prevalent with increasing age in children.<sup>27,28</sup> This was further supported by our findings that showed higher off-label use for canakinumab, adalimumab, rituximab, anakinra, and infliximab -typical biologicals for the abovementioned conditions- in children and adolescent age groups compared to that in infants.

Routine prescribing demonstrated predominance of respiratory diseases along with drugs of respiratory system and systemic anti-infectives, consistent with the literature.<sup>29-32</sup> On the contrary, near half of the drugs (47.0%) applied for pediatric OLDU was antineoplastic/immunomodulating agents. The most frequently applied drug, eculizumab, is a monoclonal complement C5 antibody,<sup>33</sup> and the first novel anti-complement therapy in HUS characterized by complement alternative pathway dysregulation.<sup>34</sup> A recent study in France reported close to 80% of off-label eculizumab use was due to hemolytic anemias including HUS.<sup>35</sup> In our study, it was also the third most common diagnosis among OLDU applications and responsible for >85% of off-label eculizumab use. Meanwhile, the drug acquired approval towards the end of this study period in October 2015 and started to be used as labelled.<sup>36</sup>

Mycophenolate, the second most common reason for our pediatric OLDU applications, is an immunosuppressive approved in post-transplant patients in many countries including Turkey.<sup>37,38</sup> In our study, being among the top two applied drugs particularly in children and adolescent groups, mycophenolate was used for nephrotic syndrome over one-third of applications. A systematic review regarding off-label use of mycophenolate reported that nephrotic syndrome constituted ten out of 41 studies with beneficial effects.<sup>39</sup> Off-label

use in this indication might be attributed to its comparably lesser toxicity over other currently used immunosuppressive agents like cyclosporin A or cyclophosphamide.<sup>40,41</sup> Furthermore, the fact that its off-label use was requested for 42 different diagnoses including systemic lupus and thrombocytopenic purpura in our study indicates the need for mycophenolate as an alternative immunosuppressive drug in children. Rituximab was one of such drugs that were applied for a variety of diagnoses (57 out of the 548 different diagnoses in total) in our study, particularly in adolescent and child groups. It was reported to have promising results in children with immunosuppressive-refractory nephrotic syndrome or those suffering from serious adverse effects,<sup>42</sup> which may explain its preference as a therapeutic alternative for different conditions. In fact, a Spanish study performed in adults reported off-label use of rituximab in 17 different autoimmune conditions, 55% of which were systemic lupus erythematosus.<sup>43</sup> In addition, reports from several recent studies on rituximab's efficacy on nephrotic syndrome<sup>44,45</sup> suggest that off-label experience in pediatrics could constitute a base for such use in adults.

The only nervous system drug among the top ten OLDU applications was lacosamide, approved by the FDA for partial epilepsy in ≥16-year-old children in 2008 and ≥4-year-old in 2017.<sup>46</sup> In Turkey, it is still only approved for ≥16 years of age and above.<sup>47</sup> Epilepsy was the second most frequent diagnosis in our study, consistent with reports stating the disease as a common condition requiring OLDU.<sup>48</sup> While lacosamide was among the most frequently requested drugs in child and adolescent groups (sixth and twelfth rank, respectively), it was beyond the 15<sup>th</sup> rank in infants. This might suggest that physicians are unlikely to prefer unapproved antiepileptics in younger patients even in the OLDU context. In addition, though a study reported its efficacy for refractory focal epilepsy,<sup>49</sup> two studies in different European countries reported lower prescription rates of newer antiepileptics in infants than that in older children.<sup>50-51</sup>

The main indication for OLDU practice in our study was “other pulmonary heart disease”, encompassing primary and secondary pulmonary hypertension. Beside digoxin, calcium antagonists, anticoagulants, and oxygen therapy, the disease could also be managed with prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors.<sup>52,53</sup> Consistent with these, iloprost, sildenafil, and bosentan were the most commonly applied drugs for secondary pulmonary hypertension in our study. Moreover, a previous OLDU study in Turkey reported that these drug groups were most commonly requested for pulmonary hypertension in pediatric populations.<sup>26</sup> It could be suggested that these drugs were subject to OLDU applications as they had limited clinical trial data on pediatric use.<sup>52</sup> Among these agents, bosentan had been approval in pulmonary hypertensive  $\geq 3$ -year-old children in US,<sup>54</sup> and the summary product of bosentan in Turkey with a statement of limited experience in  $< 2$  years of age.<sup>55</sup> These might explain higher off-label use of bosentan in infants. On the other hand, sildenafil use was common in this age group whereas iloprost was found to dominate child and adolescent groups. In fact, the latter is approved for pulmonary hypertension in Turkey with a warning that stated it had no clinical data on pediatric use.<sup>56</sup> Contrarily, sildenafil is only approved for erectile dysfunction.<sup>57</sup> This difference of indication might partly explain preference of iloprost over sildenafil in older age groups. Another factor could be the warning on sildenafil’s FDA-approved pulmonary hypertension label that recommends against chronic use in pediatric cases due to increased mortality concerns.<sup>58</sup>

Our findings should be interpreted in the light of several limitations. First, we did not have information on medication history regarding the diagnoses that required OLDU or currently used drugs for accompanying diseases. Diminished efficacy or adverse effects due to concomitant medication might have forced physicians toward OLDU practice. In

addition, we did not collect data on how many OLDU applications were made for a particular indication regarding same/different drugs with no further information about OLDU switches for the same indication. Another limitation was the lack of data on duration and posology of off-label drugs. Finally, this study only included OLDU requests that were approved by the health authority, excluding rejected applications and any other OLDU practiced with the physicians’ own discretion.

In conclusion, this study is the first to show indication- and drug-centered aspects of pediatric OLDU at national level, exposing its similar and distinguishing features from routine prescribing practice. Though OLDU applications is overall consistent with routine clinical practice in terms of demographics and institutional capacity, substantial variations exist regarding main drug classes and diseases. Pediatric OLDU practice seems to converge on particular classes of drugs for certain indications that are rather encountered during childhood and usually required alternative pharmacotherapeutic options. Besides, pediatric OLDU appears to differ from that in adults in terms of indications and drugs. Our findings are expected to shed light on interventions focusing on increasing “indicated” use of off-label drugs and contribute to their rational use within the pediatric OLDU context, if inevitable.

### Acknowledgements

The authors thank to Dr. Esra Onal for her contribution to the study design and Dr. Fatma Isli, Esmâ Kadi and other respective staff/consultants of TMMDA for their assistance in data collection.

### Funding

This work was supported by Research Fund of the Marmara University (Project Number: SAG-C-DRP-150218-0034).

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