www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2021;10(2):e100213
doi: 10.7363/100213
Received: 2021 Mar 29; revised: 2021 May 29; rerevised: 2021 Jun 03; accepted: 2021 Jun 03; published online: 2021 Jul 27

Systematic review

Off-label and unlicensed drug treatments in Neonatal Intensive Care Units: a systematic review

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Abstract

Newborns are particularly susceptible to off-label and unlicensed (OLUL) drug treatments, especially in the intensive care setting, inferring from dosing regimens and indications supported in older populations and built on non-neonatal pathophysiology. This use leads to unpredictable drug effectiveness and safety and, therefore, an increased probability of medication errors and adverse drug reactions. An extensive literature search was conducted in MEDLINE, Scopus, and Web of Science for papers published from 2011 to 2020 considering OLUL drug use in Neonatal Intensive Care Units (NICUs). Of the 902 studies retrieved, 618 after duplicates were removed, 74 full texts were carefully assessed for eligibility and, in the end, 23 published studies were included, representing a total of 6,762 patients in 80 NICUs worldwide. Considering overall prescriptions, 43.5% were OL and 11.1% were UL. Most studies found that more than 50% of the newborns were exposed to at least 1 OLUL drug and 10 of them reported a rate higher than 90%. Most prescribed drug classes in an OL manner were anti-infectives for systemic use drugs, including ampicillin and gentamicin, followed by nervous system drugs such as fentanyl. The most prescribed drug class in a UL manner was nervous system drugs, being caffeine the most prescribed one. The main reasons for OL prescribing included age and dose, and for UL prescribing, modifications of licensed drugs, extemporaneous preparations, or changes in the pharmaceutical forms. Very preterm, lower birth weight, disease severity, and longer length of stay in the NICU were associated with higher OLUL prescribing. These findings show that despite recent attempts by international regulatory authorities to develop more clinical trials in the pediatric population, OLUL drug use is still widespread, particularly among newborns in NICUs.

More efforts must be made by these regulatory entities to ensure the development of safer drugs for the neonatal period.

Keywords

Newborn, off-label, unlicensed, prescribing, drug, Neonatal Intensive Care Unit.

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How to cite

Reis F, Pissarra R, Soares H, Soares P, Guimarães H. Off-label and unlicensed drug treatments in Neonatal Intensive Care Units: a systematic review. J Pediatr Neonat Individual Med. 2021;10(2):e100213. doi: 10.7363/100213.

Introduction

The course of licensing a new drug by regulatory authorities, such as the European Medicines Agency (EMA) or Food and Drug Administration (FDA), is grounded on the quality of manufacture, safety, and efficacy of the intended indications. Only if the products have been accessed by a regulatory agency and the manufacturer satisfies these criteria, the drug can be granted a marketing authorization [1, 2]. The marketing authorization includes the Summary of Product Characteristics (SmPC) that describes essential information for the use of a drug, including pharmacological properties, authorized indications, qualitative and quantitative information on benefits and harms, information for individualized care, and other pharmaceutical information [1].

In the nomenclature of non-labeled drug use, there are two different entities. Off-label (OL) refers to a drug used outside of the terms of the SmPC for unapproved age group, indication, dose, frequency regimen, or route of administration [1, 2]. On the other hand, unlicensed (UL) relates to a drug used without a marketing authorization, including formulation modifications of previously licensed drugs or imported drugs, licensed in other countries [1, 3, 4]. This type of drug use is neither illegal nor incorrect, and it is supported by long-term clinical experience, being acceptable, or even recommended in clinical guidelines, when there is no suitable alternative. This freedom of prescription can be problematic for health care professionals and must be in accordance with the most recent medicine postulates, aiming for the patient's well-being and best care [5, 6].

The pediatric population is particularly susceptible to OLUL drug treatments, especially in the neonatal age and intensive care settings, inferring from dosing regimens and indications supported in older populations and built on non-neonatal pathophysiology. This insufficient evidence-based prescribing is due to the lack of clinical trials in this vulnerable population [1, 2, 7-9]. Traditionally, protecting vulnerable research participants from harm practically meant excluding neonates from drug trials and research, because of their frailty and unique physiology. However, this exclusion creates an ethical dilemma, with the risk of being harmful in a long-term perspective, leading to compromised drug effectiveness and safety, with increased probability of medication errors and adverse drug reactions (ADR) as previously reported in Neonatal Intensive Care Units (NICUs) worldwide [4, 10, 11]. Accordingly, neonatal clinical trials require expensive and time-consuming processes, usually with limited financial rewards, making them less appealing to the pharmaceutical industry. To counter this problem, there is the need to establish legal obligations and financial incentives to promote appropriate studies in this underexplored field [12].

In the last years, supported by the international medical community, global policies for prescribing medicines in the pediatric population have been changing with focus also at this particular stage of life [13]. In this matter, the European Union regulatory authorities issued a new pediatric regulation, i.e. Regulation (EC) No. 1901/2006 of the European Parliament and the Council of 12 December 2006, which came into force on 26 January 2007. This regulation intended to collect data on the use of drugs in the pediatric population in all European Union member states, accessing current situation in order to identify within which therapeutic areas there is the need for additional care and studies, without subjecting children or newborns to unnecessary clinical trials [14, 15]. In the European Commission's 10-year report, it was found a positive impact of the pediatric regulation on the development of pediatric medicines in the European Union, resulting in more conducted clinical studies in this population. This was true particularly to new immunology-based therapies, antiviral drugs, and drugs for congenital metabolism diseases. However, this regulation has had little impact on the development of older OLUL drugs [14, 16, 17]. Even if this becomes less urgent

due to the introduction of new drugs with the same indication, it should be considered the impact that can be achieved here. These positive results would not have been accomplished without specific legislation, which becomes clear from the comparison between regions with specific legislation, including the European Union and the United States of America, opposing to countries without this legislation such as Japan and Canada [14, 16].

Although previous studies have tackled this issue, the authors were unable to locate any systematic review evaluating the impact of OLUL drugs currently prescribed in newborns, particularly in intensive care settings. Therefore, this systematic review aims to analyze recent literature assessing the extent of OLUL prescriptions in NICUs and thereby identify therapeutic areas requiring more targeted pharmaceutical research.

Material and methods

Protocol

This review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [18].

Eligibility criteria

Prospective and retrospective studies on the OLUL drug use in newborns (< 28 days of life) at NICUs, published from January 2011 to December 2020, were included. The search strategy was restricted to studies concerning human subjects, with no language restriction. Papers with data concerning the use of OLUL drugs in the neonatal population in NICU were included. Studies concerning OLUL drug use in newborns only in intermediate care or neonatal wards, studies focused only on a single drug or specific disease, studies reporting procedures, drug use in auxiliary diagnostic tests or medical devices were excluded. Studies with patients included in larger studies were excluded to avoid duplicate results, as well as duplicate articles, comments, literature or systematic reviews, editorial letters, opinion papers and those not related to the purpose of the study.

Search strategy and search terms

On 15 January 2021, an extensive literature research was made of papers published in 3 electronic databases, including MEDLINE (through PubMed), Scopus, and Web of Science. The search strategy included the following search terms in Scopus and Web of Science databases: “infant” OR “newborn” OR “neonate” AND “off-label use” OR “off-label prescribing” OR “unlabeled indication”, and in MEDLINE the following Mesh Terms: “Infant, Newborn” AND “Off-Label Use”.

Study selection and risk of bias assessment

The first analysis included a screening of all article titles and abstracts to identify relevant studies. References were cross-checked to identify articles missed in the initial search with the previously referred inclusion and exclusion criteria. The second analysis included a full-text screening of the previous selected studies. Eligibility assessment was done by 2 authors (F.R. and R.P.) in all potentially relevant articles, in an unblinded, standardized manner. Disagreements between the reviewers were resolved by discussion and consensus.

The risk of bias was assessed for all eligible studies according to the National Institutes of Health reporting guideline using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Possible item rankings were “yes”, “no” or “not applicable”. An overall risk of bias was independently assigned to each eligible study by 2 researchers (F.R. and R.P.) and classified into “good”, “fair” and “poor”.

Data collection process and variables

Data extraction was performed by the 2 authors (F.R. and R.P.) in an independent manner using a standardized data extraction sheet followed by cross-checking and discussion of final results. Study variables included OLUL definition used, demographic data (including preterm and low birth weight frequency), NICU prescription and diagnosis characteristics (with the frequency of OLUL drug use, newborns receiving at least 1 OLUL drug, and reasons for OLUL use), most frequent OLUL drugs prescribed, and ADR associated. Drug classes were pooled and categorized according to the Anatomical Therapeutic Chemical (ATC) classification system [19].

Synthesis of results

Categorical variables were presented as absolute and relative frequencies of the total number of OLUL drug prescriptions. When a specific outcome of interest was not reported in all studies, frequencies

were evaluated considering only the patients included in the studies where it was reported.

Results

Study selection

The initial database search resulted in the retrieval of 902 articles; 177 records were identified in MEDLINE, 368 in Scopus and 357 in Web of Science. After duplicates were removed, 618 records were included in the first analysis: screening of the reference list based on their titles and abstracts. This step was cross-checked between the 2 authors, excluding a total of 544 articles. Then, 74 full texts were carefully assessed for eligibility. In this second phase, 51 articles were excluded based on previously defined exclusion criteria: 12 for study design (comments, literature or systematic reviews, editorial letters, opinion papers), 8 studies for insufficient data on the variables of interest, 14 studies reported data from non-NICU settings, 10 studies did not isolate NICU data from intermediate care units or neonatal wards, and 7 studies included patients older than 28 days. In the end, 23 published studies were included in this systematic review and submitted to data extraction, reporting a total of 80 NICUs, 6,762 newborns, and more than 57,000 prescriptions [20-42]. A detailed flow diagram of the study design is presented in **Fig. 1**.

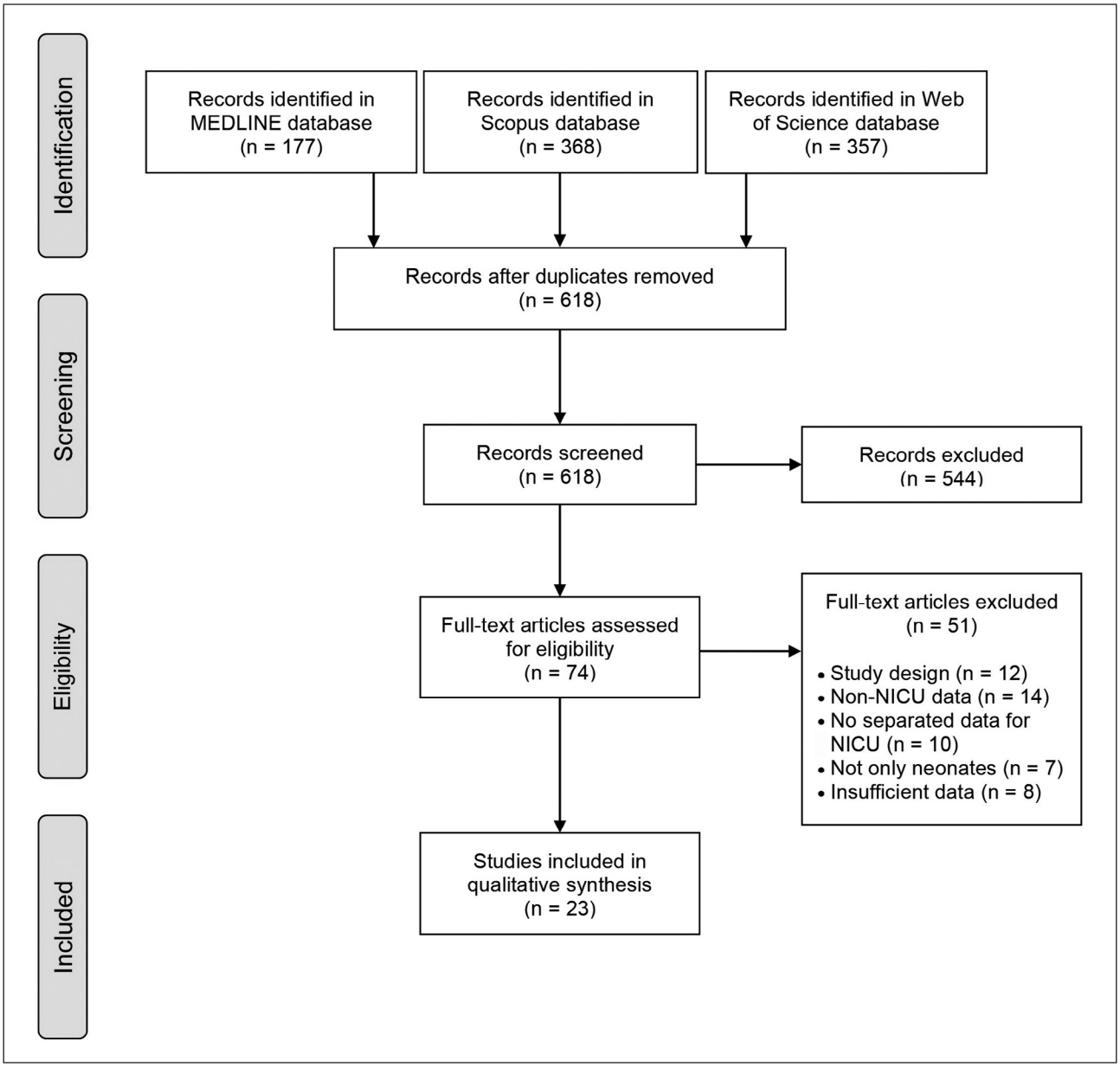

Figure 1. Flow diagram of study selection.
NICU: Neonatal Intensive Care Unit.

All eligible studies were rated as "good" after the risk of bias assessment, as detailed in **Annex 1**.

Characteristics of selected studies

Characteristics of selected papers are summarized in **Tab. 1**.

The included studies have representation in 15 different countries and 4 continents: the majority from Europe, but also South America (Brazil), Africa (Ethiopia), and Asia (India, Iran, Turkey, Malaysia, and Israel). The most represented countries were Brazil and India, with 4 studies each. Six studies were performed in more than 1 NICU, 1 of them with 17 and another with 36 different NICUs [21, 23, 26, 28, 36, 39]. Most reports included a study period of at least 3 months, ranging from 2 weeks to 60 months and including data from 2009 to 2019 [30, 31, 33, 35-40, 42]. This review included 14 prospective studies [20-26, 28, 31, 32, 35, 37, 38, 40], 4 cross-sectional studies [27, 33, 39, 42], and 5 retrospective studies [29, 30, 34, 36, 41].

Results of individual studies

Demographic and Neonatal Intensive Care Units' characteristics

Demographic and NICUs' characteristics are summarized in **Tab. 2**.

Regarding patient's sex 57% were male, with a male:female ratio of 1.3:1. Mean gestational age was between 34 and 36 weeks in 10 studies [24, 26, 27, 29, 30, 32, 33, 37, 39, 41] and between 32 and 33 weeks in 4 studies [21, 23, 35, 36], including 2 studies evaluating only preterm [33, 34]. Most neonates were preterm, representing 67.9% of the study population [20, 21, 25-42]. Nine studies reported the number of very premature (< 32 weeks of gestational age), ranging from 5% to 65% [20, 24, 26, 28, 35-39]. Only 10 studies characterized birth weight in some extension, with a percentage of very low birth weight ranging from 5% to 84% [20, 28-32, 34-36, 39]. Median or media length of stay in the NICU was reported in 15 studies, ranging from 6 to 20 days [20, 23, 26, 27, 29-31, 33, 35-37,

Table 1. Studies characteristics.

Study reference	Year of publication	Country	Study design	Time period (months)	NICU, n	Newborns, n	Newborns receiving at least 1 drug prescription, n
20	2012	Brazil	PS, cohort	2	1	129	61
21	2012	Turkey	PS, cohort	1	17	464	NS
22	2013	Malaysia	PS	2	1	86	86
23	2014	India	PS, cohort	3	2	156	156
24	2014	Ireland	PS, cohort	2	1	110	110
25	2014	Finland	PS	2 weeks	1	25	NS
26	2015	France	PS, cohort	12	2	910	NS
27	2015	Portugal	CSS	6	1	218	NS
28	2016	Italy	PS, cohort	3	36	220	220
29	2016	Brazil	RS, cohort	6	1	201	192
30	2017	Spain	RS	3	1	41	NS
31	2017	India	PS, cohort	9	1	1,080	460
32	2017	Brazil	PS	6	1	157	NS
33	2017	India	CSS	6	1	154	NS
34	2017	Finland	RS, cohort	60	1	282	NS
35	2018	Brazil	PS, cohort	12	1	220	NS
36	2018	Netherlands	RS, cohort	12	4	1,491	NS
37	2018	Israel	PS	2	1	134	134
38	2019	Spain	PS	6	1	84	84
39	2019	Iran	CSS	3	2	193	NS
40	2019	India	PS	3	1	81	NS
41	2020	Germany	RS, cohort	12	1	204	NS
42	2020	Ethiopia	CSS	2	1	122	NS

NICU: Neonatal Intensive Care Unit; PS: prospective study; NS: not specified, CSS: cross-sectional study; RS: retrospective study.

Table 2. Demographic and Neonatal Intensive Care Units (NICUs) characteristics.

Study reference	Gender male, n (%)	Gestational age weeks, mean (± SD)	Term, n (%)	Preterm, n (%)	Very preterm, n (%)	LBW, n (%)	VLBW, n (%)	ELBW, n (%)	Length of stay days, median (min-max)	Most frequent causes of admission	Most frequent drug classes[d]	Drugs needed per newborn, median (range)
20	76 (59)	NS	77 (60)	52 (40)	7 (5.4)	26 (20.2)	7 (5.4)	NS	10 (1-31)	Jaundice, RDS, prematurity	J, A, N	5[b]
21	NR	32.5 ± 4.7	114 (24.6)	350 (75.4)	NR	NR	NR	NR	NR	NR	J, A, R	3 (1-11)[c]
22	48 (56)	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR	NR
23	NR	32 (30-35)[a]	NR	NR	NR	NR	NR	NR	8 (5-18)[a]	NR	J, R, N	3 (1-6)
24	NR	35 ± 5	NS	NS	43 (39.1)	NR	NR	NR	NR	Prematurity, RDS	NS	4 (3-11)
25	NR	NR	11 (44)	14 (56)	NR	NR	NR	NR	NR	NR	N, A, J	NS
26	522 (57)	34 (31-37)[a]	236 (26)	671 (73.7)	246 (27)	NR	NR	NR	18 (8-38.75)[a]	NR	J, B	8 (5-13)[c]
27	121 (55.5)	36 ± 4	124 (57)	94 (43)	NR	NR	NR	NR	7 (1-210)	NR	J, N, A	3 (0-34)
28	131 (59.5)	NS	29 (13.2)	191 (86.8)	144 (65)	49 (22.3)	47 (21.4)	93 (42)	NR	Prematurity, RDS, infections	J, R, B	4 (1-9)[a]
29	100 (52.1)	33.3 ± 4.3	48 (25)	144 (75)	NS	NS	70 (36.5)	NR	18.8 ± 18.1[b]	Jaundice, RDS, sepsis	J, B, A	8.8 ± 6.1[b]
30	28 (68)	35.9 ± 4.2	22 (53.7)	19 (46.3)	NR	6 (15)	NR	NR	8 (1-38)	NR	J	6.65 ± 3.28[b]
31	273 (59.3)	NR	208 (45.2)	252 (54.8)	NR	197 (42.8)	NR	NR	10 (2-78)	RDS, sepsis, pneumonia	J	5.7[b]
32	89 (56.7)	36 (33-38)[a]	65 (41.4)	88 (56)	NS	91 (58)	23 (14.6)	6 (3.8)	NR	Congenital malformations, respiratory, cardiovascular	J, N, A	7.6 ± 7.9[b]
33	83 (53.9)	34 ± 2.75	0	154 (100)	NS	NR	NR	NR	17 ± 16.5[b]	RDS, sepsis, jaundice	J, R, N	7 (0-17)[c]
34	NR	NR	0	282 (100)	NR	282 (100)	236 (84)	113 (40)	NR	NA	NA	NR
35	111 (53.7)	32.5 ± 4.4	43 (19.5)	177 (80.5)	43 (19.5)	79 (35.9)	50 (22.7)	37 (16.8)	12 (1-106)	Respiratory, prematurity, infections	J, A, N	7 (1-31)[c]
36	865 (58)	32.7 (29.9-37.9)[a]	465 (31.2)	1,026 (68.8)	662 (44.4)	NS	NS	216 (14.5)	12 (5-32)[a]	NR	J, N, B	5 (3-10)
37	69 (51)	35 (33-38)[a]	54 (40)	61 (45.5)	18 (13)	NS	NS	NR	11.5 (6-24.5)[a]	NR	NR	6 (5-10)
38	52 (61.9)	NS	37 (44)	47 (56)	17 (20.2)	NR	NR	NR	NS	Prematurity, RDS, congenital cardiopathy	A, J, N	4 (1-43)[c]
39	114 (59.1)	34 ± 4.4	89 (46)	104 (54)	47 (22)	77 (40)	29 (15)	NR	10.6 ± 9.8[b]	Jaundice, RDS, sepsis	J, R, A	4.5 ± 3[b]
40	54 (66.7)	NR	58 (71.6)	23 (28.4)	NR	NR	NR	NR	6[b]	RDS, sepsis, meconium aspiration syndrome	J, A, N	7 (1-14)[c]
41	118 (58)	34.1 ± 4.3	74 (36.3)	130 (64.7)	NR	NR	NR	NR	20.8 (1-252)	NR	J, N, C	11.1 ± 10.7
42	72 (59)	NR	77 (63.1)	45 (36.9)	NR	NR	NR	NR	6 (1-32)	RDS, sepsis	J, M, N	NR

SD: standard deviation; LBW: low birth weight; VLBW: very low birth weight; ELBW: extreme low birth weight; NR: not reported; NS: not specified, NA: not applicable; RDS: respiratory distress syndrome.

[a] Result presented as median (interquartile range); [b] result presented as mean (± standard deviation); [c] result presented as median (minimum-maximum values); [d] drug classes according to Anatomical Therapeutic Chemical (ATC) classification system: A – alimentary tract and metabolism, B – blood and blood-forming organs, C – cardiovascular system, J – anti-infectives for systemic use, M – musculo-skeletal system, N – nervous system, R – respiratory system.

39-42]. Most frequent causes of admission included respiratory distress syndrome or other respiratory conditions [20, 24, 28, 29, 31-33, 35, 38-40, 42], sepsis or other suspected or proven infections [28, 29, 31, 33, 35, 39, 40, 42], prematurity [20, 24, 28, 35, 38] and newborn jaundice [20, 29, 33, 39]. One study only analyzed the pattern of prescription of antibiotics, so no other diagnoses rather than infections were reported in that study [34]. Most prescribed drug classes in NICUs, according to the ATC classification system, were anti-infective for systemic use (J), reported in all studies that specified drug class prescription pattern [20, 21, 23, 25-33, 35, 36, 38-42], followed by nervous system (N) drugs [20, 23, 25, 27, 32, 33, 35, 36, 38, 40-42], alimentary tract and metabolism (A) drugs [20, 25, 27, 29, 32, 35, 38-40], respiratory system (R) drugs [21, 23, 28, 33, 39] and blood and blood forming organs (B) drugs [26, 28, 29, 36]. Number of drugs needed per newborn was reported in 16 studies, all of them with a median or mean of at least 3 drugs [20, 21, 23, 24, 26, 27, 29, 30, 32, 33, 35-40].

Off-label and unlicensed prescriptions

OLUL prescriptions pattern is summarized in **Tab. 3**.

A total of 57,683 prescriptions were included in this review, with 86.6% of newborns receiving at least 1 OLUL drug. Considering OLUL definition, most studies based their criteria on national entities for medicine and health products or health surveillance, with only 5 studies reporting to international entities like FDA or EMA. Five studies did not evaluate UL prescriptions [23, 31, 33, 34, 40] and 1 considered them as OL [36]. One study performed in Brazil presented their results accordingly to their national health surveillance agency (ANVISA) and FDA

Table 3. Off-label and unlicensed (OLUL) prescriptions.

Study reference	Prescriptions, n	Different drugs, n	OL prescriptions, n (%)	UL prescriptions, n (%)	OLUL prescriptions, n (%)	Newborns receiving at least 1 OLUL drug, n (%)
20	318	57	88 (27.7)	24 (7.4)	112 (35.2)	48 (78.7)
21	1,315	93	441 (33.5)	379 (28.8)	820 (62.3)	NR
22	682	NR	252 (37)	236 (34.6)	488 (71.6)	79 (92.4)
23	568	NR	286 (50.3)	NR	NS	NR
24	900	69	27 (39) [a]	13 (19) [a]	40 (58) [a]	87 (79)
25	263	NR	132 (50)	66 (25)	198 (75)	25 (100)
26	8,891	142	5,287 (59.5)	466 (5.2)	5,753 (64.7)	862 (94.8)
27	1,011	84	533 (52.7)	44 (4.4)	577 (57.1)	152 (69.7)
28	720	79	425 (59)	104 (14.5)	529 (73.5)	193 (87.7)
29	3,291	87	1,359 (41.3)	395 (12)	1,754 (53.5)	191 (99.5)
30	273	48	113 (41.4)	15 (5.5)	128 (46.9)	37 (90.2)
31	2,642	NR	326 (12.3)	NR	NR	175 (38) [d]
32	1,187	127	665 (56) [b] 592 (49.9) [c]	86 (7.2) [b] 84 (7.1) [c]	751 (63.2) [b] 676 (57) [c]	[150 (95.5) [d], 48 (30.6) [e]] [b] [113 (72) [d], 20 (12.7) [e]] [c]
33	1,426	NR	1,082 (75.9)	NR	NR	150 (97.4) [d]
34	NR	NR	NR	NR	NR	51 (18) [d]
35	17,421	NR	8,591 (49.3)	4,278 (24.6)	12,809 (73.9)	212 (96.4) [d], 145 (66.8) [e]
36	10,895	181	2,506 (23)	NS	NS	806 (54) [d]
37	1,069	49	693 (64.8)	63 (5.9)	756 (70.7)	129 (96.3)
38	564	85	127 (22.5)	45 (8)	172 (30.5)	50 (59.5)
39	1,049	59	399 (38.1)	20 (1.9)	419 (40)	164 (85)
40	560	NR	241 (43)	NR	NS	NR
41	2,274	102	892 (39.2)	8 (0.4)	900 (39.6)	128 (62.7)
42	364	NR	246 (67.6)	86 (23.6)	332 (91.2)	114 (93.4) [d], 57 (46.7) [e]
Total, n	57,683	93 [f]	24,682 (43.5)	6,315 (11.1)	30,997 (54.6)	2,145 (86.6) [g]

OL: off-label; UL: unlicensed; NR: not reported; NS: not specified.
[a] Result presented per drug instead prescription; [b] result according to ANVISA criteria; [c] result according to FDA criteria; [d] only for OL drug; [e] only for UL drug; [f] result presented as mean; [g] only studies considering newborns receiving concurrently OLUL prescriptions were considered.

regulations and found a significant disparity in proportions of OL prescription (56% for ANVISA versus 49.9% for FDA) and newborns subjected to OL drugs (95.5% for ANVISA versus 72% for FDA). No differences were found for the use of OL drugs for different age groups, neither for UL prescription. [32]. In another study, in Turkey, the authors reported 62.3% of OLUL prescribing accordingly to their national database (TMMDA), which significantly decreased to 47.6% when following the international pediatric dosage handbook [21]. Besides differences between countries and NICUs, 1 study reported that prescribing habits tended to vary also among physicians [31]. All studies, except 1, presented a percentage of OLUL per prescription and the percentage of newborns receiving at least 1 OLUL. One study presented their results per different number of drugs prescribed instead of prescriptions [24].

Considering overall prescription, 43.5% were OL and 11.1% were UL, with a total of 26,628 and 6,315 prescriptions, respectively. Most studies found that more than 50% of the newborns were exposed to at least 1 OLUL drug, 10 of them reporting a rate higher than 90% [22, 25, 26, 29, 30, 32, 33, 35, 37, 42]. Nine studies reported more than 50% of OL prescription [23, 25-28, 32, 33, 37, 42]. The highest percentage reported (75.9%) was found in a study conducted in India, which included only preterm newborns and considered UL prescriptions as OL. Just 3 studies reported OL rates lower than 30% [20, 36, 38]. Regarding UL prescriptions, all studies reported a proportion of less than 30%, except 1 [22], and most of them less than 15%.

Concerning ADR, despite being discussed as a central concern related to OLUL prescription, none of the studies systematically reported them.

Most frequently prescribed off-label and unlicensed drugs

The detailed pattern of OLUL prescriptions in the studies is summarized in **Tab. 4**.

According to the ATC classification system, the most prescribed OL drug classes matched the most prescribed in the NICUs, namely anti-infective for systemic use (J), followed by nervous system (N), reported in almost all studies, and alimentary tract and metabolism (A) drugs reported in 5 studies [21, 33, 35, 41]. It was also common the OL prescription of respiratory system (R) drugs [21, 33, 35, 41], cardiovascular system (C) [23, 28, 36, 41] and musculo-skeletal system (M) drugs [31, 42]. The most frequently OL drugs prescribed were ampicillin (mentioned in 8 studies [20, 28-30, 33, 37, 39, 42]), gentamicin (reported 6 times [24, 29, 30, 35, 37, 39]), fentanyl (cited in 5 studies) and aminophylline [33, 35, 37] and paracetamol [20, 30, 31] (in 3).

Concerning UL prescribing, nervous system (N) was the main drug class reported, stated in 6 studies [20, 21, 27, 35, 38, 42], followed by cardiovascular system (C) drugs [21, 27, 35, 38]. Most frequently prescribed drugs in a UL manner were caffeine and phenobarbital, reported in 7 [20, 24, 28, 30, 32, 35, 38] and 4 [35, 37, 39, 42] studies respectively.

Reasons and risk factors for off-label and unlicensed prescription

Reasons for OLUL prescribing are listed according to frequency in **Tab. 5** and, when it was reported, the respective percentage was also included.

Regarding reasons for OLUL prescribing, 19 studies reported data on OL categories [20-23, 25-32, 34, 36-40, 42] and 11 studies reported data on UL categories [21, 22, 24, 27, 29, 30, 36, 38-40, 42]. Most commonly stated reasons for OL prescribing included the use of drugs outside the age range permitted in the marketing authorization, reported in 9 studies as the main cause [20, 21, 23, 26, 28-30, 33, 38], and the use of drugs outside the established dose range, also reported in 9 studies as the main reason [22, 24, 27, 31, 32, 35, 37, 40, 42]. Other frequent reasons, reported in a smaller magnitude, included indication, contraindication, route of administration, and frequency. One study found that anti-infectives for systemic use (J) were more often used as OL in dose followed by frequency and age, while nervous system (N) drugs, namely anticonvulsants and sedatives, were mostly used as OL for age [40]. Main reasons identified for UL drug use included modifications of licensed drugs, extemporaneous preparations or changes in the pharmaceutical form, reported in all 11 studies exploring UL reasons [21, 22, 24, 27, 29, 30, 36, 38-40, 42], and imported drugs, reported in 6 studies [21, 22, 29, 30, 36, 42].

Four studies addressed risk factors for OLUL prescription, and 3 of them found a positive association with length of stay [22, 26, 38], 1 of them reporting that each additional day of stay multiplied the risk of OLUL prescription by 1.1 [26]. One study evaluating the Neonatal Therapeutic Intervention Scoring System for disease severity found that the severity of the disease was a risk factor for OLUL prescribing [20]. Concerning gestational age and premature deliveries (< 37 weeks of gestational age): 2 studies found an association between prematurity and an increased risk of OLUL exposure

Table 4. Most frequently prescribed off-label and unlicensed (OLUL) drugs.

Study reference	Most frequent OL drug classes [c]	Most frequent OL drugs	Most frequent UL drug classes [c]	Most frequent UL drugs
20	J, N, A	Ampicillin, paracetamol, hydrocortisone	N	Caffeine, metamizole, chloral hydrate
21	J, N, R	NR	N, C, R	NR
22	NS	NS	NS	NS
23	J, N, C	NS	NR	NR
24	NS	Benzylpenicillin, gentamicin	NS	Caffeine
25	NS	NS	NS	NS
26	NS	Calcium folinate, amikacin sulphate, ferrous fumarate	NS	Glucose monohydrate 10%, norepinephrine, ketamine hydrochloride
27	J, N, A	NS	C, J, N	NS
28	C, N, J	Ampicillin, fluconazole, fentanyl	R, B, A	Caffeine
29	NS	Ampicillin, gentamicin, heparin	NS	Tricalcium phosphate, alprostadil, biotine
30	J, N, A	Ampicillin, gentamicin, paracetamol	NS	Caffein citrate, hydrocortisone suspension, morphine
31	J, M	Meropenem, piperacillin-tazobactam, paracetamol	NR	NR
32	(N, J, A) [a]; (N, J, C) [b]	Fentanyl, multivitamins, midazolam	NS	Caffeine
33	J, R, N	Ampicillin, aminophylline, midazolam	NR	NR
34	NA	Meropenem, rifampicin, levofloxacin	NA	NR
35	J, R, N	Fentanyl, gentamicin, aminophylline	N, A, C	Caffeine, phenobarbital
36	C, N, J	Heparin, fentanyl, propofol	NR	NR
37	NR	Ampicillin, gentamicin, aminophylline	NR	Furosemide, phenobarbital, naloxone
38	A, N, J	Fentanyl, vitamin E, cefazolin	B, N, C	Caffeine, spironolactone, ranitidine
39	J	Ampicillin, gentamicin, albuterol	NS	Phenobarbital, furosemide
40	NR	NR	NR	NR
41	N, R, C	NS	NS	NS
42	J, M, N	Ampicillin, vancomycin, ceftazidime	J, M, N	Paracetamol, phenobarbital, aminophylline

OL: off-label; UL: unlicensed; OLUL: off-label and/or unlicensed; NR: not reported; NS: not specified.
[a] Result according to ANVISA criteria; [b] result according to FDA criteria; [c] drug classes according to Anatomical Therapeutic Chemical (ATC) classification system: A – alimentary tract and metabolism, B – blood and blood-forming organs, C – cardiovascular system, J – anti-infectives for systemic use, M – musculo-skeletal system, N – nervous system, R – respiratory system.

[22, 42], opposing to 2 other studies that found no association [30, 31]. For very premature delivery, 8 studies reported a higher risk of exposure to OLUL prescriptions [20, 24, 26, 29, 32, 33, 35, 38], with 5 of them reporting that 100% of these newborns received at least 1 OLUL drug [20, 32, 33, 35, 38], and 1 study reporting that this group was at more than 10-fold higher risk of exposure to OLUL prescribing, when compared to preterm newborns [26]. Concerning birth weight, 1 study found that an increase in birth weight decreased the probability of OL usage in general and anti-infectives for systemic use (J) [34], and another 1 reported a higher risk of OLUL exposure in extremely low birth weight newborns (< 1,000 g), with all of them receiving at least 1 OLUL drug [35].

Table 5. Reasons for off-label and unlicensed (OLUL) prescribing.

Study reference	Main reasons of OL prescribing (%)[a]	Main reasons of UL prescribing (%)[a]
20	Age (70.4), dose (14.8), indication (8), frequency (6.9)	NR
21	Age (50.1), dose + frequency (13.5), indication + contraindication (8.1)	Extemporaneous preparation (20.5), formulation manufactured under special license (12.4), imported drugs (8.3)
22	Dose (38,4), age (34), indication (21,3), frequency (0.8)	Extemporaneous preparation (71.1), unregistered product (28.9)
23	Age (74), dose + indication + route of administration + frequency (26)	NR
24	Dose, age	Extemporaneous preparation
25	NS	NS
26	Age (58.8)	NR
27	Dose + frequency (50.3), age (33.6), indication (0.8), route of administration (0.4)	Extemporaneous preparation, formulation manufactured under special license
28	Age (34.4), dose + frequency (20.6)	NR
29	Age, dose, route of administration, formulation, indication	Extemporaneous preparation, imported drugs
30	Age (42.5), dose (31.0), frequency (16.8), dose + frequency (8.8), indication (0.9)	Extemporaneous preparation, imported drugs
31	Dose (52), age (21)	NR
32	Dose, indication, route of administration, age	NR
33	Age (55), dose (41)	NR
34	NR	NR
35	Dose (38.5), indication (16.2), age (25), route of administration (11.9), frequency (40)	Extemporaneous preparation
36	NR	NR
37	Dose, indication, frequency, age, route of administration	Extemporaneous preparation, imported drugs
38	Age (55.1), indication (41.8), dose (2.2), route of administration (0.9)	Extemporaneous preparation
39	Frequency (48.3), dose (44.9), age (5.2), route of administration (1.6)	Extemporaneous preparation
40	Dose, age, frequency, indication, route of administration	NR
41	NR	NR
42	Dose, frequency, age, contraindication	Extemporaneous preparation, imported drugs

[a] Reasons of OL or UL prescribing, in frequency order (percentage of total OL or UL prescriptions when specified in papers).
OL: off-label; UL: unlicensed; NR: not reported; NS: not specified.

Discussion

OLUL prescription plays an important role in neonates, particularly in the intensive care setting. This is hampered by several factors, such as the lack of evidence-based trials for efficacy and safety, resulting in a shortage of information in SmPC for this age group as lack of licensed formulations or information about actual ADR [43]. Although it has been noticed an outbreak of attention in this field, as shown in the growing amount of research investigating the use of drugs in newborns, a lot remains unknown and inapplicable to clinical practice [43, 44].

This systematic review of OLUL drug treatments in a neonatal intensive care setting summarizes available data from 23 published studies representing a significant number of newborns (6,762 patients) in 80 NICUs worldwide, including European, Asian, South American, and African ones. Besides this large representation, most studies were restricted to 1 NICU and included a limited sample size, highlighting the need to perform wider studies.

In more than 57,000 prescriptions considered in this review, 43.5% and 11.1% of them were given in an OL or UL manner, respectively. Most of the studies, all from the last 10 years, reported exposure to OLUL drugs higher than 90%, reinforcing that OLUL prescription is still a widespread problem nowadays and particularly in this population. Nevertheless, a lack of agreement on a common definition for OL or UL was notable, with most studies using national authorities' criteria not allowing a straightforward comparison between studies. In fact, a Brazilian study that analyzed OLUL prescriptions according to the different definitions of their national authority and FDA, in the same population and period, verified a significant difference between them, when referring to OL prescriptions [32], and another study, in Turkey, when comparing their results to the international pediatric dosage handbook, found equally a significant difference in both OL and UL prescribing rates [21]. In general, most studies assumed as OL when a drug was prescribed outside the terms of the marketing authorization for age, administration route, frequency, dose, or indication. Though, for other authors, different formulations or contraindications were regarded both as OL or UL. These prescribing habits tended to vary not only between countries and hospitals but also among physicians, reflecting differences in NICU conditions, duration of hospitalization and drug availability. This discloses the need to perform not

only wider studies but with an international basis and with the same criteria definition.

Most prescribed OL drug classes reflected the most generally prescribed drugs in NICUs, namely anti-infective for systemic use (J), nervous system (N), and alimentary tract and metabolism (A) drugs, slightly differing from the most UL prescribed drug classes, which included nervous system (N) and cardiovascular system (C) drugs. Accordingly, the most frequently prescribed drugs as OL were ampicillin, gentamicin, and fentanyl; as for UL drugs, caffeine was the most prescribed one. In fact, antibiotics remain the most prescribed drug class across neonatal intensive care settings, with obvious differences between NICUs justified by the different units' experience, local microorganism susceptibility patterns and antibiotics availability [6, 31, 45]. Ampicillin, OL for age in newborns (only approved above 12 months of age in some countries), and gentamicin, often used OL for frequency, remain the standard of care for empirical treatment of early-onset neonatal sepsis, which persists worldwide as one of the most common and life-threatening conditions for neonates, particularly preterm [28, 30, 45, 46]. As for fentanyl, due to the unpredictable conversion of morphine to more active metabolites, especially in premature neonates, medicines with more predictable metabolism, such as fentanyl, are preferred for intermittent or acute pain management, apart from being OL for age [28, 30, 47]. Besides being a common treatment for the management of apnea of prematurity complications, caffeine continues to be used as an extemporaneous preparation, possibly because of its assured efficiency and the lower cost associated with the galenic form, compared to the licensed alternative [28, 30, 48]. Therefore, therapeutic areas requiring more targeted research should include antibiotics such as ampicillin and gentamicin, and drugs such as fentanyl and caffeine.

In this review, as predicted, over two-thirds of NICU patients were premature who (in particular, very premature and with lower birth weights) are even more likely to receive a larger amount of medication and, therefore, OLUL drugs [27, 49]. Additionally, longer length of stay in the NICU and worse disease severity were reported as risk factors for OLUL prescribing. On that account, within the pediatric population, neonates, especially in the intensive care setting, are a prevailing susceptible group that should be addressed in future research.

Besides the increased probability of ADR in NICUs and related to OLUL prescribing, none of the studies included in this systematic review addressed specific ADR. In this matter, and highlighting the importance of ADR investigation, one recent Italian study in premature neonates focused on OLUL and nephrotoxicity found that extremely low birth weight newborns were more likely to receive associations of drugs with potential renal toxicity [50]. It is of utmost importance to carry out more studies with active ADR monitoring as the EREMI study, a large multicenter French study evaluating the relationship between ADR and OLUL prescribing [51]. This type of studies should increase awareness of OLUL drug use and identify risk factors of related ADR to establish preventive measures in these vulnerable populations.

Internationally, different measures have been developed to encourage more research and clinical trials in the pediatric population, both by EMA and FDA. Though, in agreement with the last European Commission's 10-year report after the European pediatric regulation of 2007, studies included in this review do not show significant improvements in OLUL prescription in NICUs populations; on the contrary, and besides new updates on product specifications, there was a minor impact in overall prescription. [25, 30, 41]. Three studies made comparisons with previous works in the same NICUs, about a decade earlier, 2 of them European [25, 41] and 1 Asian [37]. The European ones compared results before and after the European implementation of the pediatric regulation in 2007, and both reported no significant changes neither in terms of prescription pattern nor in the impact on the authorization status of commonly prescribed drugs. Both reported that new evidence was introduced to neonatal pharmacotherapy, and new data was included in SmPC, but with a minor impact on OLUL prescription in NICUs [25, 41]. An Asian study also reported that 15 years later, current drug prescribing patterns in the same NICU were similar and the prevalence of OLUL medications was even higher [37].

Strengths and limitations

Besides some existing reviews in the literature addressing OLUL prescriptions in the pediatric age, to the authors' knowledge this was the first systematic review focusing on newborns admitted to NICUs and with recent data from the last 10 years. A strength in this study was the significant and global representation of newborns and NICUs, including mostly prospective observational cohort studies. An important limitation of this review was the lack of standardization in the definition of OL and UL

drugs, making the comparison between studies more difficult and less accurate. Other limitations include the shortage of data from low and extremely low birth weight populations, which could be particularly prone to OLUL drugs: it may have underestimated the impact of these prescriptions in this population. Additionally, studies with neonatal populations that did not specifically evaluate the pattern of OLUL prescriptions in NICUs (including simultaneously data from intermediate care or other neonatal wards) were not included, therefore potentially excluding a significant number of newborns.

Conclusion

OLUL use of medications in newborn patients admitted in NICUs remains a widespread practice worldwide, with a significantly high number of newborns receiving at least 1 OLUL drug. Despite international efforts to develop more clinical trials in the pediatric population, and mitigate the pattern of OLUL prescribing, few changes have been noticed, especially in this age group. More efforts must be made by these regulatory entities to ensure the development of safer drugs for the neonatal period. Antibiotics such as ampicillin and gentamicin, and drugs as fentanyl and caffeine, being the most frequently prescribed in an OLUL manner, should be the main focus of future clinical trials.

Declaration of interest

The Authors report no conflicts of interest. The Authors did not receive any funding for the present study.

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Annex 1. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

Study reference	Questions														Quality rating
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
20	Y	Y	Y	Y	N	NA	Y	NA	Y	NA	Y	NA	NA	N	Good
21	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	Y	Good
22	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	N	Good
23	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	Y	Good
24	Y	Y	Y	Y	N	NA	Y	NA	Y	NA	Y	NA	NA	Y	Good
25	Y	Y	Y	Y	N	NA	Y	NA	Y	NA	Y	NA	NA	N	Good
26	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	Y	Good
27	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	Y	Good
28	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	Y	Good
29	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	Y	Good
30	Y	Y	Y	Y	N	NA	Y	NA	Y	NA	Y	NA	NA	N	Good
31	Y	Y	Y	Y	N	NA	Y	NA	Y	NA	N	NA	NA	Y	Good
32	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	Y	Good
33	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	Y	Good
34	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	N	Good
35	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	Y	Good
36	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	N	NA	NA	Y	Good
37	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	Y	Good
38	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	Y	Good
39	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	Y	Good
40	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	N	NA	NA	N	Good
41	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	Y	Good
42	Y	Y	Y	Y	Y	NA	Y	NA	Y	NA	Y	NA	NA	Y	Good

Y: yes; N: no; NA: not applicable.
Questions:
1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?