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ORIGINAL ARTICLE

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The effect of a decision support system on the incidence of prescription errors in a PICU

Fatema Hashemi BSc[1] | Thomas G. van Gelder PharmD[2] | Casper W. Bollen MD, PhD[3] | Yves T.B. Liem PharmD, PhD[2] | Toine C.G. Egberts PharmD, PhD[1,2]

[1]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

[2]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[3]Paediatric Intensive Care Unit, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

Correspondence
Thomas G. van Gelder, Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, PO Box 85500, 3508 GA Utrecht, The Netherlands.
Email: t.g.vangelder-2@umcutrecht.nl

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Abstract

What is known and objective: Paediatric intensive care patients are at high risk for prescription errors due to the more complex process of medication prescribing. Clinical decision support systems (CDSS) have shown good results in effectively reducing prescription errors. A specific dosing CDSS was developed that can check and suggest normal dose, dose limits and administration frequencies. This study aimed to assess the effect of this CDSS on protocol deviation (as measure of prescription error) types and frequency in a paediatric intensive care unit (PICU).

Methods: A retrospective observational study was conducted evaluating 9342 prescriptions in a 4-month period before and after the implementation of a CDSS in the PICU of the University Medical Center Utrecht. Medication forms were reviewed to identify protocol deviations (and therefore possible prescription errors). The incidence and nature of deviations from evidence-based protocols that were unintended and needed to be adjusted, were determined.

Results and discussion: In the period before the dosing CDSS, we identified 45 protocol deviations in 5034 prescriptions (0.89%), 28 of which could not be justified (0.56%) and 11 needed to be adjusted (0.22%). In the period after the implementation of the CDSS, there were 21 protocol deviations in 4308 prescriptions (0.49%) of which ten without a valid reason (0.23%) of which two were adjusted (0.05%).

What is new and conclusion: The specific dosing CDSS was able to significantly reduce unintentional prescription dose deviations and the number of prescriptions that needed to be adjusted, in an existing low incidence situation.

KEYWORDS
clinical pharmacy, computerised decision support, paediatrics, prescribing, prescribing practices

1 | WHAT IS KNOWN AND OBJECTIVE

In the last two decades, the prevention of medication errors has gained much attention and awareness from caregivers, as it affects thousands of patients annually.[1] Medication errors can have a considerable effect on patient morbidity and mortality and health care costs, about half of which are considered preventable.[1-7] Medication errors can occur at various stages of the medication ordering and delivery process, such as prescribing, transcribing, dispensing and administration.[8] Critically ill patients, particularly children in a paediatric intensive care unit (PICU), are vulnerable and at risk.[1-4,7,9] Prescribing errors in PICU are amongst the most frequent medication errors, mostly being dosing errors.[2] There are multiple reasons for a higher prescription error rate in a PICU setting. Firstly, drug dosing in paediatric patients is complex, due to a lack of clear dosing guidance, a lack of clinical trial evidence and doses are often extrapolated from adult doses.[10,11] Secondly, most drug doses are on individual basis, depending on multiple factors including age, weight and body surface area, making standardized prescriptions less common than in the adult population.[7,9,12] Lastly, critically ill children present an even greater challenge due to the changed pharmacokinetic and pharmacodynamic properties associated with organ failure and concomitant use of other medication.[2]

In order to prevent prescription errors, much time and effort have been put into the development of computerized physician order entry (CPOE) systems.[2] CPOE systems are computer-based systems that standardize the medication ordering process and allow physicians to enter medication orders per patient in a more structured manner to ensure a complete order with no missing data. There are several advantages of using CPOE for medication prescribing over handwritten paper orders: it enhances the legibility and completeness of prescriptions, there is no lost paperwork and it leads to a standardized format that offers a structured, clear and unambiguous list of prescribed medications per patient.[13] However, these advantages are mostly non-clinical and do not prevent the majority of prescription errors in paediatric care settings. Electronic prescribing alone does not actively prevent the prescription of an incorrect drug, dose or frequency.[2,14,15]

The addition of clinical decision support systems (CDSS) to CPOE systems has been found to reduce prescription error rates more significantly.[2] CDSS is a technological intervention that targets the ordering stage of medications, where approximately half of all medication errors occur.[3] It is used in electronic prescribing to guide clinicians to choose a correct evidence-based prescription for an individual patient, thereby supporting individualized pharmacotherapy.[10] CPOE systems can have CDSSs implemented to varying degrees. A basic CDSS provides automated support regarding drug doses, routes and frequencies.[16,17] As CPOE/CDSSs in PICUs have been mainly focused on the correct ordering of continuous infusions and not on prescriptions of drugs given intermittently, further development of more comprehensive CDSSs is warranted.[18,19]

Given these analyses and results, a new specific dosing CDSS to guide medication ordering was implemented in the PICU of the Wilhelmina Children's Hospital in the Netherlands. The new decision support system performs a full medication check and provides decision support for discontinuous medication, using dosing information from evidence-based protocols.

This study aimed to assess the effect of a new clinical decision support system on protocol deviations in medication prescriptions in an academic PICU.

2 | METHODS

2.1 | Setting

This study was conducted in a 16-bed PICU of the Wilhelmina Children's Hospital, a tertiary children's hospital, part of the UMCU in The Netherlands. In March 2020, a specific dosing CDSS was introduced in the PICU. A dosing CDSS had already been incorporated for continuous dosing for some years and has since March 2020 been extended to intermittent dosing regimens. The CDSS was incorporated in a CPOE, that is part of a Patient Data Management System (PDMS), Metavision (iMDsoft).

2.2 | The clinical decision support system description

The main purpose of the implementation of this CDSS is to increase medication safety and prevent harm to patients, by automatically checking and displaying dosing limits, calculated medication doses and frequency of administration. The new support system operates by using dosing information from Dutch paediatric and adult formularies—KinderFormularium (KF)[20] and Farmacotherapeutisch Kompas (FK)[21]—as well as local hospital protocols.

To perform the check and calculations, four components of the prescription are needed in the electronic prescribing system, three of which must be entered by the physician: 1) the generic drug, 2) the route of administration and 3) the indication for prescribing the drug. The fourth component, patient category (eg age, gestational age, weight and body surface area), is directly taken from the PDMS, so do not have to be manually entered for each prescription. After these components are known, the CDSS will immediately display the specific dosing information, including recommended dose, upper and lower limits, and a list of applicable administration frequencies.

For a more comprehensive description of how the CDSS works, see Appendix 1.

2.3 | Study design and population

A retrospective before/after observational study was conducted to assess the incidence and nature of medication prescription protocol deviations before and after the implementation of the CDSS.

The study population consisted of all patients with at least one medication prescription during their PICU stay and admitted to the

PICU in either of the following 4-month periods: period 1, October 2019 through January 2020 and period 2 April 2020 through July 2020 (the CDSS was implemented in March 2020). Patients admitted more than once during the study period were considered new patients at every admission. The need for informed consent was waived because of a study population of over 500 patients.

2.4 | Definition and classification of protocol deviations

The main measure of outcome in this study was the incidence of each type (nature) of protocol deviation.

Protocol deviations were defined as deviations in the dose and/or frequency of administration in a medication prescription, according to the local and/or national drug dosing guidelines.[20,21] Two types of protocol deviations were distinguished: 1. outside recommended dose limits and 2. outside recommended frequency limits, as illustrated in Figure 1. Each type was then subdivided into whether a prescribed dose or frequency was above the recommended upper limit or below the recommended lower limit, respectively.

Both types were again subdivided into the categories: reason known and reason unknown. The reason for a deviation in frequency and/or dose was classified as 'known' when the prescribing physician intentionally chose to deviate from the protocols with the reason being documented by the clinical pharmacist. The reason was also classified as 'known' if the prescribing physician had documented this in the PDMS. The PDMS records of patients with a protocol deviation of unknown reason were reviewed to assess if there was a reason to deviate from the protocol. The reason was classified as 'unknown' when it could not be ascertained by the clinical pharmacist whether the deviation was on purpose or not.

Prescriptions with an unknown reason for deviation were further categorized based on whether or not the prescription was adjusted. There could be varying reasons for a prescription to not be adjusted: the clinical pharmacist may not suggest an adjustment because the deviation did not have a significant clinical consequence, the clinical pharmacist may have suggested an adjustment, but the physician has not adjusted the prescription, or the patient was discharged before the prescription was reviewed by the clinical pharmacist. Prescriptions were classified as 'adjusted' if the new dose/frequency was within the recommended limits.

Each patient could have multiple prescriptions with protocol deviations and every prescription could have both types of deviations, that is both outside recommended dosing limits and outside recommend frequency limits.

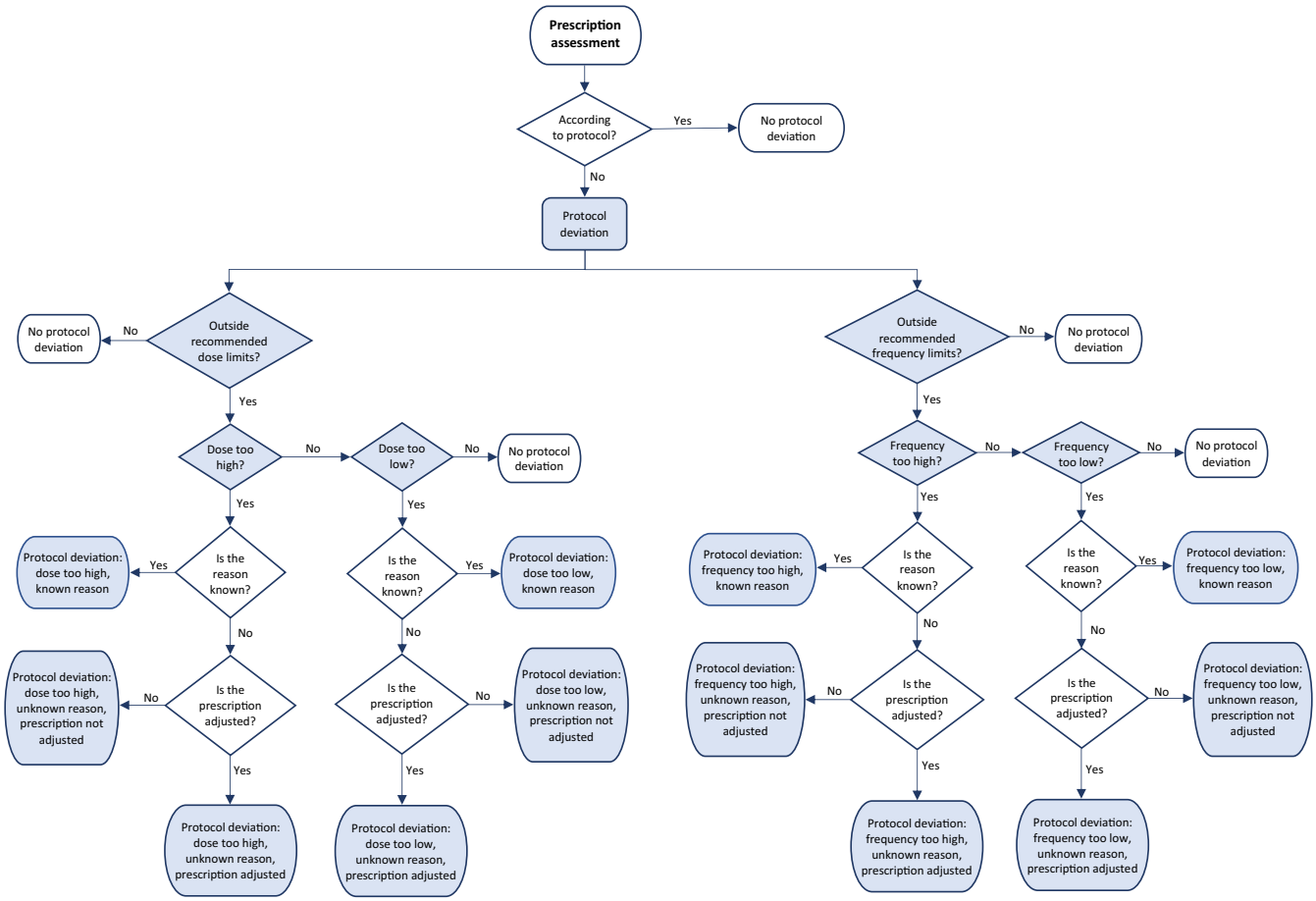

FIGURE 1 Protocol deviation classification flowchart. Protocol deviations were classified in the deviation types shown in blue

2.5 | Data collection and management

In order to identify protocol deviations in prescriptions, medication forms used by pharmacy technicians and clinical pharmacists were reviewed for each patient admitted in period 1 and period 2. These medication forms are used to document new, changed and incorrect prescriptions after reviewing the drug-order list of every patient, which is done by pharmacy technicians. After documentation, the form is forwarded to the clinical pharmacist to review the same day, on weekdays. A total of 8 months of data were collected through these forms. The documented protocol deviations were reviewed and classified according to Figure 1. For an example of what this medication form looks like, see Appendix 2.

Prescriptions assessed for protocol deviations included all forms of prescriptions except once-only medications and loading doses, since the CDSS only generates an alert for deviations in continuous and intermittent prescribed drugs. Protocol deviations based on improper dose or frequency adjustment for renal impairment were excluded, because the CDSS does not alert for this deviation. Protocol deviations of drugs with no local or national dosing guidelines for the indication that the drug was prescribed for were also excluded.

Patient demographics (gender, age at admission, length of ICU stay, reason for admission and number of prescriptions) were collected through the PDMS Metavision (iMDsoft). Data were stored in the online data management platform Castor EDC.

2.6 | Statistical methods

Data were statistically analysed using SPSS Statistics version 26. The chi-square test was used to determine the significance of the observed differences in frequency and type of protocol deviations before and after the implementation of the CDSS. For analysis of the demographic data, the independent *t* test was used for the age at time of admission, length of PICU stay and medication orders per patient and the chi-square test was used for the remainder. A *p*-value ≤0.05 indicates a statistical significance.

3 | RESULTS

Five hundred and four paediatric patients were included in this study. There were no significant differences in gender, length of PICU stay and medication orders per patient between the two study periods and study populations (Table 1). A significant difference was observed in age at time of admission and the admission diagnosis categories respiratory system, surgical, infections and multisystem.

3.1 | Frequency and nature of the protocol deviations

During the 8 months study period, a total of 9342 prescriptions were ordered, in which 66 protocol deviations were found. Of these, 45

TABLE 1 Demographic data of study patients before and after the implementation of the dosing CDSS

Characteristics	Pre-CDSS *N* = 266	Post-CDSS *N* = 238	*p* value[a]
Male—N (%)	163 (61.3)	132 (55.5)	0.19
Age at time of admission—median (range) in months	49.2 (0 – 234.6)	85.2 (0 – 245.7)	0.02
Length of PICU stay—median (range) in days	1.0 (0 – 76)	1.0 (0 – 74)	0.42
Admission diagnosis categories—N (%)[b]			
Respiratory system	47 (17.7)	15 (6.3)	<0.001
Cardiovascular system	10 (3.8)	9 (3.8)	0.99
Neurological	9 (3.4)	7 (2.9)	0.77
Haematology/oncology	14 (5.3)	21 (8.8)	0.12
Endocrine/metabolic	3 (1.1)	7 (2.9)	0.15
Gastrointestinal	3 (1.1)	1 (0.4)	0.37
Surgical	121 (45.5)	134 (56.3)	0.02
Renal	1 (0.4)	0	0.34
Infections	49 (18.4)	17 (7.1)	<0.001
Multisystem and other	18 (6.8)	31 (13.0)	0.02
Medication orders per patient—N	18.9	18.1	0.75

[a]The independent *t* test was used for age at time of admission and length of PICU stay and the chi-squared test was used for the remainder.

[b]Total percentage of admission diagnosis categories, pre- and post-CDSS, exceeds 100% because one patient could have multiple diagnoses for admission.

protocol deviations were found in the period pre-CDSS and 21 protocol deviations post-CDSS. Table 2 gives an overview of the types of protocol deviations, as identified according to Figure 1, and their frequencies. A significant reduction was observed in the total number of protocol deviation per 100 prescriptions, from 0.89% pre-CDSS to 0.49% post-CDSS ($p = 0.02$). The number of protocol deviations outside the recommended dosing limits significantly decreased from 0.74% pre-CDSS to 0.39% post-CDSS ($p = 0.03$).

The frequency and nature of protocol deviations per type before and after implementation of the dosing CDSS are shown in Table 3. The frequency of the deviation 'dose too low' decreased from 0.22% to 0.07% ($p = 0.07$), while 'dose too high' (66.7%) remained the most common type of deviation, amongst the dosing- and frequency deviations. No significant changes in frequency deviations were observed. Deviations with an unknown reason significantly reduced from 0.56% to 0.23% ($p = 0.01$) of which the prescriptions that were adjusted decreased from 0.22% to 0.07% ($p = 0.07$). Pre-CDSS the number of 'unknown reason' deviations (62.2%) were higher than with a known reason (37.8%), while post-CDSS most of the deviations were with a known reason (52.4%).

3.2 | Drug categories with protocol deviations

The protocol deviations both pre- and post-CDSS were most frequently observed in the drug category antibacterials for systemic use (Table 4). Pre-CDSS, 37.8% of all deviations occurred in this drug category, whereas post-CDSS 19.0% of the deviations occurred in prescriptions for antibacterials and 19.0% for antimycotics. The total number of drugs prescribed per drug category pre- and post-CDSS was assessed, and no significant difference in the prescription rate was found in either category. The percentage antibacterials for systemic use was 11.8% of the total number of prescriptions pre-CDSS and 10.6% post-CDSS ($p = 0.07$). The percentage antimycotics for systemic use was 3.3% of the total number of prescriptions pre-CDSS and 3.1% post-CDSS ($p = 0.61$). However, a significantly higher prescription rate of drugs for obstructive airway disease was observed pre-CDSS, 1.7% of the total number of prescriptions pre-CDSS and 0.1% post-CDSS ($p = <0.001$).

The deviations in antibacterials for systemic use pre-CDSS were mostly due to a too high dose (53%; Appendix 4), and 35% of the deviations in this drug category were adjusted. Post-CDSS, 50% of

TABLE 2 Comparison of the types of protocol deviations before and after the implementation of the dosing CDSS

Protocol deviation type	Total number of prescriptions Pre-CDSS $N = 5034$ (%)	Total number of prescriptions Post-CDSS $N = 4308$ (%)	*p* value
Total number of protocol deviations	45 (0.89)	21 (0.49)	0.02
Outside recommended dosing limits[a]	37 (0.74)	17 (0.39)	0.03
Dose too high	26 (0.52)	14 (0.32)	0.16
Known reason	11(0.22)	9 (0.21)	0.92
Unknown reason	15 (0.29)	5 (0.12)	0.06
Prescription adjusted	9 (0.18)	2 (0.05)	0.06
Prescription not adjusted	6 (0.12)	3 (0.07)	0.44
Dose too low	11 (0.22)	3 (0.07)	0.07
Known reason	5 (0.10)	0	0.04
Unknown reason	6 (0.12)	3 (0.07)	0.44
Prescription adjusted	0	0	
Prescription not adjusted	6 (0.12)	3 (0.07)	0.44
Outside recommended frequency limits[a]	8 (0.16)	4 (0.09)	0.37
Frequency too high	5 (0.10)	2 (0.05)	0.35
Known reason	1 (0.02)	2 (0.05)	0.48
Unknown reason	4 (0.08)	0	0.06
Prescription adjusted	1 (0.02)	0	0.36
Prescription not adjusted	3 (0.06)	0	0.11
Frequency too low	3 (0.06)	2 (0.05)	0.78
Known reason	0	0	
Unknown reason	3 (0.06)	2 (0.05)	0.78
Prescription adjusted	1 (0.02)	1(0.02)	0.91
Prescription not adjusted	2 (0.04)	1 (0.02)	0.66

[a]Dutch paediatric and adult formularies (Kinderformularium, Farmacotherapeutisch Kompas) and local hospital PICU protocols For examples of the protocol deviation types, see Appendix 3.

TABLE 3 Frequency and nature of the types of protocol deviations before and after the implementation of the dosing CDSS

Type of protocol deviation	Total number of prescriptions			Total number of protocol deviations	
	Pre-CDSS *N* = 5034 (%)	Post-CDSS *N* = 4308 (%)	*p* value	Pre-CDSS *N* = 45 (%)	Post-CDSS *N* = 21 (%)
Dose too high	26 (0.52)	14 (0.32)	0.16	26 (57.8)	14 (66.7)
Dose too low	11 (0.22)	3 (0.07)	0.06	11 (24.4)	3 (14.3)
Frequency too high	5 (0.10)	2 (0.05)	0.35	5 (11.1)	2 (9.5)
Frequency too low	3 (0.06)	2 (0.05)	0.78	3 (6.7)	2 (9.5)
Known reason	17 (0.33)	11 (0.26)	0.47	17 (37.8)	11 (52.4)
Unknown reason	28 (0.56)	10 (0.23)	0.01	28 (62.2)	10 (47.6)
Adjusted	11 (0.22)	3 (0.07)	0.06	11 (24.4)	3 (14.3)
Not adjusted	17 (0.38)	7 (0.16)	0.10	17 (37.8)	7 (33.3)

TABLE 4 Drug categories with protocol deviations before and after the implementation of the dosing CDSS

Drug category (ATC-code)	Total number of protocol deviations		Number of protocol deviations that were adjusted	
	Pre-CDSS *N* = 45 (%)	Post-CDSS *N* = 21 (%)	Pre-CDSS *N* = 11 (%)	Post-CDSS *N* = 3 (%)
Drugs for acid-related disorders (A02)	0	1 (4.8)		
Antiemetics and anti-nauseants (A04)	3 (6.7)	0		
Drugs for constipation (A06)	0	1 (4.8)		
Vitamins (A11)	1 (2.2)	1 (4.8)	0	1 (33.3)
Mineral supplements (A12)	0	1 (4.8)	0	1 (33.3)
Antithrombotic agents (B01)	0	1 (4.8)		
Antihaemorrhagics (B02)	1 (2.2)	1 (4.8)		
Antihypertensives (C02)	0	1 (4.8)		
Diuretics (C03)	2 (4.4)	1 (4.8)		
Urologicals (G04)	2 (4.4)	0	1 (9.1)	0
Pituitary and hypothalamic hormones and analogues (H01)	1 (2.2)	0		
Corticosteroids for systemic use (H02)	2 (4.4)	0		
Antibacterials for systemic use (J01)	17 (37.8)	4 (19.0)	6 (54.5)	1 (33.3)
Antimycotics for systemic use (J02)	3 (6.7)	4 (19.0)	1 (9.1)	0
Antivirals for systemic use (J05)	1 (2.2)	0		
Immunosuppressants (L04)	0	2 (9.5)		
Anaesthetics (N01)	1 (2.2)	0		
Analgesics (N02)	4 (8.9)	0	3 (27.3)	0
Antiepileptics (N03)	1 (2.2)	0		
Psycholeptics (N05)	2 (4.4)	1 (4.8)		
Nasal preparations (R01)	1 (2.2)	0		
Drugs for obstructive airway diseases (R03)	1 (2.2)	0		
All other therapeutic products (V03)	2 (4.4)	2 (9.5)		

Note: For a more detailed overview of the frequency of each type of protocol deviation in the different drug categories, see Appendix 4.

the deviations in antibacterials were due to a too high dose and 50% due to a too low dose, of which 25% (one prescription) was adjusted (Appendix 4).

The protocol deviations that were adjusted pre-CDSS were found most often in prescriptions for antibacterials for systemic use (54.5%), followed by prescriptions for analgesics (27.3%). There were three protocol deviations adjusted post-CDSS, all of which were found in different drug categories. The three prescriptions were for the drugs riboflavin, magnesium gluconate and meropenem (Table 5). All three were dosed intermittently. However,

TABLE 5 Effect of the dosing CDSS on the drugs with a protocol deviation that needed to be adjusted post-CDSS implementation

Drug (ATC-code)	Continuous or intermittent dosing?	Type of protocol deviation	Does the CDSS generate an alert?
Riboflavin (A11HA04)	Intermittent	Frequency too low for unknown reason, prescription adjusted	No
Magnesium gluconate (A12CC03)	Intermittent	Dose too high for unknown reason, prescription adjusted	Yes
Meropenem (J01DH02)	Intermittent	Dose too high for unknown reason, prescription adjusted	Yes

dosing protocols for riboflavin were not incorporated in the CDSS; therefore, the system could not have prevented this deviation. The total number of protocol deviations that were adjusted for which the CDSS generated an alert (and could thus be prevented) thereby reduces from 3 to 2 deviations (0.05%). Compared to the adjusted deviations pre-CDSS, this was a significant reduction from 0.22% to 0.05% ($p = 0.03$).

4 | DISCUSSION

This study showed that a specific dosing CDSS was able to significantly reduce unintentional prescription dose deviations and the number of prescriptions that needed to be adjusted, in an existing low incidence situation.

4.1 | Study population

The comparison of the study population before and after the implementation of the dosing CDSS showed that the patients pre-CDSS were significantly younger than the patients post-CDSS. However, the specific age of a paediatric patient was considered to be not relevant for the occurrence of a deviation. Dosing, pre- and post-CDSS, is based on either age, weight or body surface area, resulting in an individualized dose. These doses are prone to prescription errors due to a high demand on physicians to adjust doses as children grow.[22] This can occur in both young and older children, if a wrong age or body size is taken. Therefore, it is unlikely that the significant difference in age between the study populations had an effect on the incidence and nature of the observed protocol deviations, pre- and post-CDSS, as long as the age, weight and/or body surface area are up to date in the PDMS. Kadmon et al studied the risk factors for electronic prescription errors in PICU patients and found that the use of CDSS can lead to more errors in older children due to overdosing. Default prescriptions in milligrams per kilograms are not appropriate for older children, as it could result in a dose that is higher than recommended for adults. Overdosing could be prevented by customized dose limits in milligrams per kilograms for younger children and in milligrams for older children. The CDSS in this study provides both types of limits; therefore, this risk factor is not relevant.

The difference in the admission diagnosis categories was due to the study periods in which the pre-CDSS period had a higher incidence of respiratory tract infections. However, this did not result in a significantly higher use of antibiotics-, antimycotics- or antivirals for systemic use and the number of medications per patient were comparable. There was a significantly higher prescription rate of drugs for obstructive airway disease due to the respiratory tract infections. These infections, mostly respiratory syncytial virus (RSV) infections, are not treated with antibiotics or antivirals, thus the lack of significant difference in prescription rate of these drugs.

4.2 | Frequency and nature of the deviations

Computerized physician order entry with clinical decision support was associated with a significant reduction of 45% (from 0.89% to 0.49%) in the total number of protocol deviations. The protocol deviation incidence rate before the implementation of the CDSS was already very low compared to medication prescription error rates found in other studies (differing from 3.4% to 8%).[2,23-25] The low incidence situation could be attributed to physicians' awareness, double-checking drug doses prescribed by unauthorized prescribers (eg physician assistants and residents) and the pre-CDSS CPOE design that already provided a direct link to the Dutch paediatric formulary, where the drug doses could be checked and calculated manually. Also, the CDSS was already implemented for continuous infusions for some years, resulting in less deviation in these prescriptions. The exclusion criteria in this study (ie once-only medication, loading doses and dose deviations due to renal impairment) may have reduced the number of protocol deviations found in this study compared to other studies where a higher error rate is observed.

Most of the protocol deviations in this study, pre- and post-CDSS, concerned deviations outside the recommended dosing limits, rather than outside the recommended frequency limits. A significant decrease can be seen in the number of deviations 'outside recommended dosing limits', but not in the deviations 'outside recommended frequency limits' as a result of an existing low incidence. Maat et al [6] studied the incidence of prescription errors in paediatric electronic prescriptions and identified 1.2% of all medication orders with a frequency *below* and 1.0% *above* the recommended limits. This was less than the identified dose deviations, 10.9% and 7.8%, respectively. This study identified 0.06% of all orders with a frequency *below* and 0.10% *above* the limits, with no significant decrease after CDSS implementation. The findings in this study confirm that most deviations and interventions are made due to a wrong dose.

Amongst these deviations, 'dose too high' remained the most observed deviation. In contrast, Maat et al [6] observed that orders with a dose *below* recommended limits were higher than the orders with a dose *above* the limits. This was a reason to include lower recommended limits in the CDSS and generate alerts for underdosing. After implementation of the CDSS, we observed a 41% reduction in the of the 'dose too low' deviations, whereas the 'dose too high' deviations increased. There were no 'dose too low' deviations adjusted pre- and post-CDSS, the adjustments in dose were all because of 'dose too high' deviations.

The number of 'adjusted' deviations decreased from 0.22% pre-CDSS to 0.07% post-CDSS. The frequency of the 'adjusted' deviations pre-CDSS was already lower than reported in other studies.[6,26] Maat et al [6] studied the incidence of clinical pharmacy interventions in electronic medication orders with minimal clinical decision support and found that 1.1% of all medication orders needed an intervention, of which 36% were because of a possibly wrong dose. This is in line with what Ghaleb et al [26] found in handwritten orders in the PICU. This suggested that CPOE with minimal clinical decision support does not reduce the dosing problems and associated interventions in the PICU. In a study by Potts et al,[27] the frequency of medication errors after CPOE implementation was reduced by 95.9%. However, these errors were mostly due to illegibility and incorrect or missing information that required interpretation and clarification. Potential adverse drug events were reduced by 40.9%, with no significant reduction in errors involving dose and interval. This was explained by a lack of decision support. The more specific dosing CDSS in this study has proven to be more effective in reducing interventions involving dose and frequency, by integrating drug formularies and (off-label) hospital protocols and calculating the doses. There are still drugs that have not yet been integrated into the CDSS, but the only protocol deviation found for these drugs was for riboflavin. To analyse the effect of the CDSS, this deviation could ultimately be disregarded, as the CDSS has no effect on the drug dose and observed deviation. This leaves 2 adjusted protocol deviations post-CDSS as opposed to 11 adjusted deviations pre-CDSS, resulting in a significant decrease of 77% in 'adjusted' deviations after implementation of the specific dosing CDSS ($p = 0.03$).

The CDSS in this study provided (yellow and red) signals as alerts to protocol deviations for almost all drug orders. There was no differentiation between signals for low-risk drugs and high-risk drugs. This could potentially lead to alert fatigue and less prescriber compliance.[28] Several studies have shown that the implementation of hard alerts and tiering of alerts resulted in a change in provider prescribing behaviour.[29-31] Tran et al [31] found that upper hard limits had the highest number of alerts for patient-controlled analgesia, preventing errors that had the highest risk for harm to patients. In this study, the 'dose too high' deviations were the major class of deviations, which is in line with what Tran et al found. By tiering the alerts and setting nonoverridable hard alerts for high-risk drugs, the severity of the deviations could become clear and structured during the drug ordering process. However, caution must be paid to prevent these alerts from impeding timely delivery of drugs to patients. Balasuriya et al [29] incorporated 24 h of available pharmacy input to avoid barriers in drug delivery.

4.3 | Drug categories with deviations

Pre-CDSS, antibacterials for systemic use were the most frequent drugs associated with protocol deviations, followed by analgesics, antimycotics for systemic use and antiemetics. Protocol deviations post-CDSS were still most often observed in the drug categories antibacterials and antimycotics for systemic use. The number of drugs prescribed per drug category pre- and post-CDSS was assessed. No statistically significant difference was observed between the pre- and post-CDSS prescription rate in the category antibacterials for systemic use. The higher frequency of protocol deviations in this category pre-CDSS was therefore not influenced by the number of prescriptions of these drugs.

4.4 | Limitations of the study

This study has several limitations. It was a retrospective observational study. The prescribers of the prescriptions were not studied. These could have been physicians, physician assistants or residents, all of whom have different prescribing skills and experience. Previous studies[32,33] have shown differences in prescribing skills and associated prescribing errors. However, no changes in the class of prescribers in the PICU had been made after the implementation of the CDSS. The class of pharmacy technicians who reviewed the drug-order lists, and their experience in paediatric clinical pharmacy, were also not studied. But again, no changes were made before and after the CDSS.

Other limitations are the lack of a second rater and blinding in the study. The documented protocol deviations in the medication forms were reviewed, assessed and classified by one researcher. Inter-rater variability could have influenced the identification of protocol deviations depending on the researcher that identifies them. However, the protocol deviations were classified according to a strict and clear flowchart (Figure 1), the effect of inter-rater variability is therefore considered to be minimal. Prescriptions with uncertainties about containing protocol deviations were discussed with the other researchers and clinical pharmacists involved, until an agreement was established.

The researchers were not blinded to the study period of the assessed prescriptions and protocol deviations and to the main hypothesis of the study. This could lead to information bias and has not been taken into account due to time constraints.

4.5 | Future perspectives

This study confirmed that the specific dosing CDSS that was implemented had a significant impact on the protocol deviations that

occur in the PICU. However, the severity of these deviations remains to be explored. Also, prescriptions with drug doses that needed to be altered to the renal function were excluded. Children in the PICU often have organ failures, including cardiac and renal impairment, which makes drug dosing prone to alterations based on these impairments. Future research should concentrate on the frequency and nature of protocol deviations due to renal impairment. Based on those results, the CDSS could extend to guide drug dosing in accordance with the renal function of the patients.

5 | WHAT IS NEW AND CONCLUSION

In summary, a specific dosing CDSS reduced the protocol deviation incidence rate significantly in an existing low incidence situation. As few as 0.49% of the prescriptions had a protocol deviation during the 4-month period after the implementation of the dosing CDSS in the PICU. Nevertheless, further studies are needed to investigate the impact of renal dysfunction on protocol deviations and possible improvement strategies for the CDSS pursued.

CONFLICT OF INTEREST

All authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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APPENDIX 1

A MORE COMPREHENSIVE DESCRIPTION OF THE CDSS

The CDSS performs a full medication check for discontinuous medication, using dosing information from the Dutch paediatric formulary (KinderFormularium), the pharmacotherapeutic compass (Farmacotherapeutisch Kompas) and local hospital protocols. The medication check concerns an immediate automated display of dosage when entering medication, based on the entered drug, indication, route of administration and patients age and/or weight category.

In the configuration of the CDSS, for each drug the following constraints can be defined: 1) a list of possible frequencies, 2) a normal (recommended) dose, 3) a minimum dose, 4) a maximum dose, 5) an absolute maximum dose and an absolute maximum dose per administration. With this data, the CDSS can find and calculate the correct dose and frequency of administration. The physician can modify the displayed dose or frequency if clinically required.

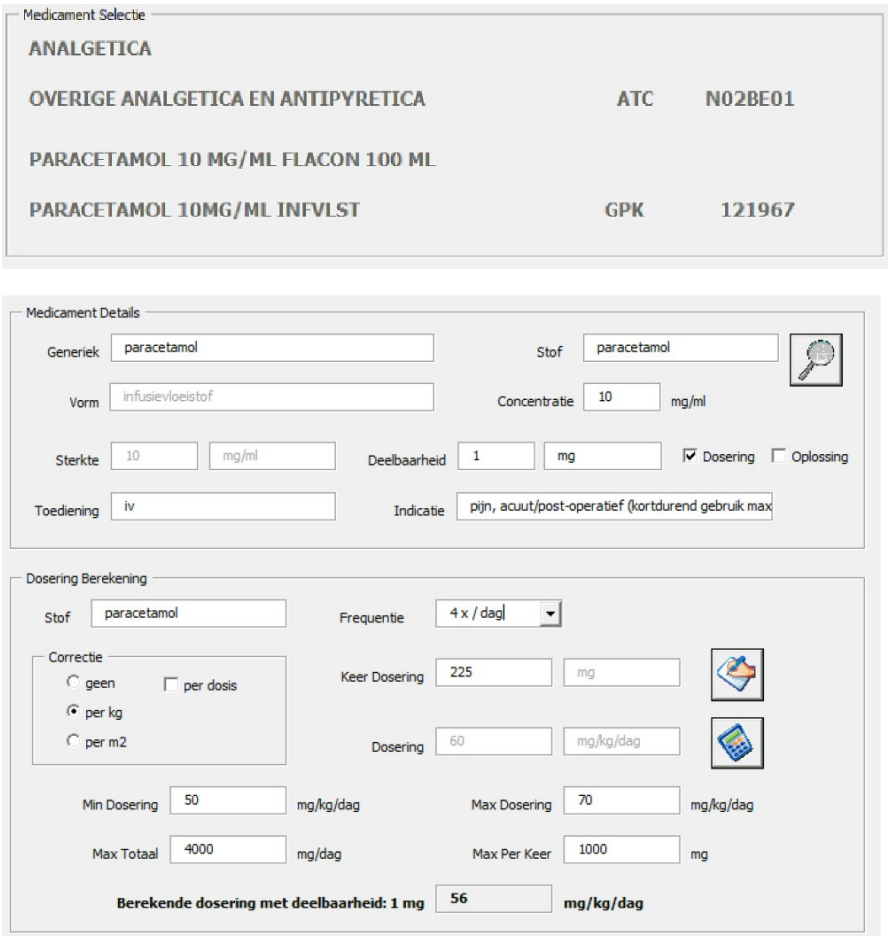
If a prescribed drug dose exceeds lower or upper limits, the CDSS generates a red signal. This indicates an incorrect dose, according to the CDSS configuration. Some drugs do not have absolute limits but have recommended doses (normal dose). The CDSS will then take a 10% deviation from the recommended dose into account and generate a yellow signal if the prescribed dose is above or below the 10% deviation. This is to notify the prescriber of a possible incorrect prescribed dose.

When the prescribed administration frequency is not in the list of possible frequencies, a yellow alert is generated indicating a possible incorrect frequency.

Some drugs could not be incorporated in the CDSS. For these situations, the CDSS generates a yellow signal indicating that the validity of the prescription could not be checked.

No signal from the CDSS means the prescribed dose and frequency of administration could be checked and are according to the configuration (ie comply to existing dosing protocols).

The CDSS does not take renal and/or hepatic impairment into account; therefore, the calculated doses and frequencies are not automatically adjusted according to the kidney and liver function. However, in case of renal dysfunction, a prominent warning sign is shown.



AFDELING APOTHEEK UMC Utrecht
Divisie Laboratoria, Apotheek en Biomedische genetica
Registratie Klinische Farmacie
Overdrachtsformulier PICU (Pelikaan)

DEFINITIEF
versie 3
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/015/Dec2019

Unit-Bed *	Patiëntgegevens:	eGFR/CVVH/ Dialyse	Apothekersassistent**:	Apotheker:
I-3	**Patient name / patient unique number** **Patient weigh in kg** Aug 6th – Dose check done by [Name of pharmacy assistant]	6-8 eGFR 55	**Request for further check by pharmacist:** - No request for further check	**Extra check by pharmacist:** -
I-4	**Patient name / patient unique number** **Patient weigh in kg** Aug 7th – Dose check done [Name of pharmacy assistant]	7-8 eGFR>90	**Request for further check by pharmacist:** 7-8 please check the dose of voriconazol iv 2dd240 mg, amfotericine B 1dd150mg iv, ciprofloxacine iv 2dd400mg	**Extra check by pharmacist:** 7/8: Dosages ar OK
I-5	**Patient name / patient unique number** **Patient weigh in kg** Aug 8th – Dose check done [Name of pharmacy assistant]	8-8 eGFR 60	**Request for further check by pharmacist:** - No request for futher check	**Extra check by pharmacist:** -
II-1	**Patient name / patient unique number** **Patient weigh in kg** Aug 4th – Dose check done [Name of pharmacy assistant]	4/8 kreatinine not measured	**Request for further check by pharmacist:** 5-8 Please check dosage and possible drug-drug interactions with fenobarbital 4,9mg/kg/dag gestart WB	**Extra check by pharmacist:** 5-8 Dosage fenobarbital Ok, no relevanat drug-drug interactions

APPENDIX 2

EXAMPLE OF A MEDICATION FORM

	Date	[Date]
	Pharmacy technician	[Name]
	Pharmacist	[Name]

UNIT 1				
Unit-Bed	Patient characteristics:	eGFR/CVVH/ Dialysis	Pharmacy technician	Clinical pharmacist
I–3	Patient name/patient unique number Patient weigh in kg August 6th—Dose check done by [Name of pharmacy assistant]	6–8 eGFR 55	Request for further check by pharmacist: - No request for further check	Extra check by pharmacist:
I–4	Patient name/patient unique number Patient weigh in kg August 7th—Dose check done [Name of pharmacy assistant]	7–8 eGFR>90	Request for further check by pharmacist: 7–8 please check the dose of voriconazol iv 2dd240 mg, amfotericine B 1dd150 mg iv, ciprofloxacine iv 2dd400 mg	Extra check by pharmacist: 7/8: Dosages are OK
I–5	Patient name/patient unique number Patient weigh in kg August 8th—Dose check done [Name of pharmacy assistant]	8–8 eGFR 60	Request for further check by pharmacist: - No request for further check	Extra check by pharmacist:
II–1	Patient name/patient unique number Patient weigh in kg August 4th—Dose check done [Name of pharmacy assistant]	4/8 creatinine not measured	Request for further check by pharmacist: 5–8 Please check dosage and possible drug-drug interactions with phenobarbital 4.9 mg/kg/dag gestart WB	Extra check by pharmacist: 5–8 Dosage phenobarbital Ok, no relevant drug-drug interactions

APPENDIX 3

EXAMPLES OF THE PROTOCOL DEVIATION TYPES AS FOUND IN THE PHARMACY MEDICATION FORMS, CLASSIFIED ACCORDING TO FIGURE 1

Protocol deviation type	Example
Dose too high, known reason	Granisetron 110 mcg/kg/day was prescribed. According to the Dutch paediatric formulary KF the dose should have been 40 mcg/kg/day. The higher dose was according to the protocols of the children's hospital Princess Maxima Center (specialized in paediatric oncology) where the patient had been transferred from.
Dose too high, unknown reason, prescription adjusted	Benzylpenicillin 350,000 IE/kg/day was prescribed. The dose should have been 100,000 IE/kg/day according to KF. The physician was informed, and the dose was adjusted.
Dose too high, unknown reason, prescription not adjusted	Benzylpenicillin 180,000 IE/day was prescribed. The dose should have been 157,500 IE/day according to KF. Because the 14% higher dose was not considered toxic, the clinical pharmacist had approved the dose.
Dose too low, known reason	Salbutamol 0.25 mg was prescribed. The dose should have been 2.5 mg. The physician was informed, but it was stated that the lower dose was adequate according to the clinical condition of the patient
Dose too low, unknown reason, prescription adjusted	No protocol deviation of this type was found

(Continues)

APPENDIX 3 (Continued)

Protocol deviation type	Example
Dose too low, unknown reason, prescription not adjusted	Low dose risperidone was prescribed. The physician was informed and would contact the psychiatrist to ascertain the reason of the lower dose. The reason remained unknown for the clinical pharmacist and dose was not adjusted in the PDMS.
Frequency too high, known reason	Rasburicase 0.4 mg/kg/day was prescribed in two doses. This should have been 0.2 mg/kg/day in one dose according to KF. The physician was informed but it was stated that the frequency and dose were consciously chosen in consultation with a paediatric oncologist.
Frequency too high, unknown reason, prescription adjusted	Azithromycin 500 mg/day was prescribed. The frequency should have been 3 times a week instead of daily according to KF. The physician was informed, and the frequency was adjusted to 500 mg three times a week.
Frequency too high, unknown reason, prescription not adjusted	Paracetamol rectal 20 mg/kg/dose four doses per day was prescribed. The frequency should have been three doses per day according to KF. As the dose did not exceed the absolute maximal dose, the clinical pharmacist did not find it necessary to adjust the prescription.
Frequency too low, known reason	No protocol deviation of this type was found
Frequency too low, unknown reason, prescription adjusted	Oxybutynin 2.5 mg two doses/day was prescribed. This should have been 2.5mg three doses/day according to KF. The physician was informed, and the frequency was adjusted to 2.5 mg three doses/day.
Frequency too low, unknown reason, prescription not adjusted	Cefazolin 100 mg/kg/day in two doses was prescribed. This should have been in 3–4 doses per day according to KF. The physician was informed, but the frequency was not adjusted in the PDMS.

APPENDIX 4

DETAILED OVERVIEW OF THE FREQUENCY OF EACH TYPE OF PROTOCOL DEVIATION IN THE DRUG CATEGORIES

Drug category (ATC-code)	Number of protocol deviations: dose too high (%)		Number of protocol deviations: dose too low (%)		Number of protocol deviations: frequency too high (%)		Number of protocol deviations: frequency too low (%)		Number of protocol deviations: known reason (%)		Number of protocol deviations: unknown reason (%)		Number of protocol deviations: prescription adjusted (%)		Number of protocol deviations: prescription not adjusted (%)	
	Pre-CDSS (*N* = 26)	Post-CDSS (*N* = 14)	Pre-CDSS (*N* = 11)	Post-CDSS (*N* = 3)	Pre-CDSS (*N* = 5)	Post-CDSS (*N* = 2)	Pre-CDSS (*N* = 3)	Post CDSS (*N* = 2)	Pre CDSS (*N* = 17)	Post CDSS (*N* = 11)	Pre CDSS (*N* = 28)	Post CDSS (*N* = 10)	Pre CDSS (*N* = 11)	Post CDSS (*N* = 3)	Pre CDSS (*N* = 17)	Post CDSS (*N* = 7)
Drugs for acid-related disorders (A02)		1 (7.1)								1 (9.1)						
Antiemetics and antinauseants (A04)	2 (7.7)		1 (9.1)						2 (11.8)		1 (3.6)				1 (5.9)	
Drugs for constipation (A06)		1 (7.1)								1 (9.1)						
Vitamins (A11)	1 (3.8)							1 (50.0)			1 (3.6)	1 (10.0)		1 (33.0)	1 (5.9)	
Mineral supplements (A12)		1 (7.1)										1 (10.0)		1 (33.0)		
Antithrombotic agents (B01)		1 (7.1)								1 (9.1)						
Antihemorrhagics (B02)	1 (3.8)	1 (7.1)							1 (5.9)			1 (10.0)				1 (14.3)
Antihypertensives (C02)		1 (7.1)								1 (9.1)						
Diuretics (C03)	2 (7.7)	1 (7.1)							2 (11.8)	1 (9.1)						
Urologicals (G04)			1 (9.1)				1 (33.3)				2 (7.1)		1 (9.1)		1 (5.9)	
Pituitary and hypothalamic hormones and analogues (H01)			1 (9.1)						1(5.9)							
Corticosteroids for systemic use (H02)	1 (3.8)						1 (33.3)		1 (5.9)		1 (3.6)				1 (5.9)	
Antibacterials for systemic use (J01)	9 (34.6)	2 (14.3)	4 (36.4)	2 (66.7)	3 (60.0)		1 (33.3)		5 (29.4)		12 (42.9)	4 (40.0)	6 (54.5)	1 (33.0)	6 (35.3)	3 (42.9)
Antimycotics for systemic use (J02)	3 (11.5)	2 (14.3)		1 (33.3)				1 (50.0)		1 (9.1)	3 (10.7)	3 (30.0)	1 (9.1)		2 (11.8)	3 (42.9)

(Continues)

APPENDIX 4 (Continued)

Drug category (ATC-code)	Number of protocol deviations: dose too high (%)		Number of protocol deviations: dose too low (%)		Number of protocol deviations: frequency too high (%)		Number of protocol deviations: frequency too low (%)		Number of protocol deviations: known reason (%)		Number of protocol deviations: unknown reason (%)		Number of protocol deviations: prescription adjusted (%)		Number of protocol deviations: prescription not adjusted (%)	
	Pre-CDSS (*N* = 26)	Post-CDSS (*N* = 14)	Pre-CDSS (*N* = 11)	Post-CDSS (*N* = 3)	Pre-CDSS (*N* = 5)	Post-CDSS (*N* = 2)	Pre-CDSS (*N* = 3)	Post CDSS (*N* = 2)	Pre CDSS (*N* = 17)	Post CDSS (*N* = 11)	Pre CDSS (*N* = 28)	Post CDSS (*N* = 10)	Pre CDSS (*N* = 11)	Post CDSS (*N* = 3)	Pre CDSS (*N* = 17)	Post CDSS (*N* = 7)
Antivirals for systemic use (J05)	1 (3.8)								1 (5.9)							
Immunosuppressants (L04)		1 (7.1)				1 (50.0)				2 (18.2)						
Anaesthetics (N01)	1 (3.8)										1 (3.6)				1 (5.9)	
Analgesics (N02)	3 (11.5)				1 (20.0)						4 (14.3)		3 (27.3)		1 (5.9)	
Antiepileptics (N03)	1 (3.8)										1 (3.6)				1 (5.9)	
Psycholeptics (N05)		1 (7.1)	2 (18.2)						1 (5.9)	1 (9.1)	1 (3.6)				1 (5.9)	
Nasal preparations (R01)			1 (9.1)								1 (3.6)				1 (5.9)	
Drugs for obstructive airway diseases (R03)			1 (9.1)						1 (5.9)							
All other therapeutic products (V03)	1 (3.8)	1 (7.1)			1 (20.0)	1 (50.0)			2 (11.8)	2 (18.2)						