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Evaluation and validation of a clinical decision support system for dose optimisation in hospitalized patients with (morbid) obesity – a retrospective, observational study

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Abstract

Background Obesity changes a patient's pharmacokinetics and pharmacotherapeutic advices should be personalized to ensure proper treatment. Currently, implementations of advices regarding the obese population are lacking and weight and body mass index (BMI) are rarely monitored. The Maasstad Hospital built a clinical decision support system (CDSS) for pharmacists, based on current Dutch guidelines, to supply therapeutic advices for (morbidly) obese patients based on patient characteristics. In this study we evaluated whether patients receiving inadequate pharmacotherapy are indeed identified via this CDSS and to which extent irrelevant alerts are generated. Moreover, it is investigated to which extent pharmacists carry on the generated advices and to which extent physicians act upon these.

Methods The research concerned a retrospective observational study performed at the Maasstad Hospital in Rotterdam, the Netherlands between January 2021 and august 2021. The drugs included were dalteparin, apixaban, dabigatran, edoxaban, rivaroxaban, vancomycin and ciprofloxacin. Dispensing data, patient characteristics and CDSS processing were collected. Dispensing data was included when the patient's weight or BMI could potentially lead to dose adjustments via the CDSS. The CDSS was evaluated for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Additionally, excess alerts, defined as irrelevant alerts on the moment of assessment, of the CDSS and adherence to the CDSS were investigated.

Results 1218 alerts over 3735 drug dispenses were generated. 568 alerts (46.6%) resulted in a pharmacotherapeutic advice by the pharmacist to the physician. In most cases, the sensitivity, specificity, PPV and NPV were 100.0% with varying 95% CIs. For some drugs technical adjustments were needed, including the initially incorrect BMI setting of vancomycin within the CDSS, resulting in a high excess alerts of 56.9%. Dabigatran had a NPV of 22.2% 95% CI [6.3–54.7] and a sensitivity of 56.3% 95% CI [33.2–76.9]. Overall excess alerts varied from 22.2% to 56.9%. Depending on the drug, the advices resulted in 6.9–100.0% real pharmacotherapy adjustments in practise.

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Conclusion The (morbid) obesity CDSS functions as expected and identifies the (morbidly) obese patients with inadequate pharmacotherapy. The adherence of physicians and the follow-up in practise varies widely and requires further investigation.

Trial registration Non-WMO research W21.218.

Keywords (Morbid) obesity, Clinical decision support system, Personalized medicine, Evaluation, Antibiotics, Anticoagulants, Hospital pharmacy

Background

Worldwide the number of obese patients is estimated to be more than 1 billion [1]. Even more concerning is that from this population, more than 55 million individuals are morbidly obese [2, 3]. Obese patients have altered physiology, resulting in changes in pharmacokinetics [2–7]. These changes leaves the (morbidly) obese patient (further called obese patients) at risk for inadequate treatment which can lead to treatment failure [8]. To ensure optimal pharmacotherapy for obese patients, identifying and monitoring this population and adjusting drug regimens is crucial.

In the Netherlands, multiple means for computer-based medication surveillance, supervised by pharmacists, are available. Clinical rules and contra-indications (CIN) play a crucial role in this digital surveillance. A clinical rule contains pharmacotherapeutic advices based on a patient's characteristics and pharmacotherapy and focusses on medication safety and medication optimalisation. Clinical rules are integrated in most Dutch hospitals' EHR (electronic health record) and the advices are formulated by the Royal Dutch Pharmacists Association, the KNMP (Koninklijke Maatschappij ter bevoordering der Pharmacie), the pharmacotherapy database of the Netherlands. Examples of clinical rules are the need for laxatives with opium treatment and TDM (therapeutic drug monitoring) for aminoglycosides and vancomycin. Eleven clinical rules are now part of a standard package integrated in the EHR [9, 10]. The eleven clinical rules monitor interactions and adequate drug usage. In short the themes hold: switch of antibiotics, coumarins, hyponatremia, potassium, stomach protection by proton-pump inhibitors, methotrexate, renal clearance, indication of laxatives during opiate treatment, oral oncolytic treatment, TDM and vitamin D suppletion. More elaboration of these clinical rules can be found in Supplementary File A. A clinical rule uses a decision tree to select patients of interest for more detailed pharmacotherapeutic evaluation. After an alert is generated the pharmacist assesses the advice in HiX (Healthcare Information eXchange (electronic health record system)), whereafter the follow-up actions are documented digitally in the EHR and are caried out. Multiple clinical rules can be referred to as a clinical decision support system (CDSS) and will henceforth be referred to as a CDSS. Specific patient characteristics used by the CDSS depends on the aim of the rule. Parameters taken into account may include dispensing time, dosage, height, weight, renal function, the presence/absence of drug levels etc. A CIN is a system which works with disease or condition labels that are documented in the EHR. Such labels include "*asthma*", "*diabetes*" or "*morbid obesity*". "*Decreased renal function*" is also one of these labels, but does not take into account the exact measure of the renal function (such as the eGFR) when prescribing. The labelling can be done manually (by looking up the label and documenting this), or is automatically performed when drugs are prescribed (for example the derived contra-indication "*asthma*"). Downsides to this labelling is that the manual action of labelling is not performed or labels are not removed (automatically) when the label does not apply anymore. For example when a patient undergoes bariatric surgery or when the renal function recovers. The CIN alert is generated when drugs are prescribed and action may be needed based on the documented labels. Currently, obese patients are not effectively detected using the conventional medication surveillance systems, among which contra-indications and clinical rules. Multiple causes can be identified for the lack in current obesity pharmacotherapy surveillance. Firstly, weight and height are insufficiently monitored in community pharmacies, as these are most of the time not considered essential measurements [11]. But even with weight and height registration, there is no automatic medication surveillance by for example CINs [12]. To use the CIN "*morbid obesity*" it must be manually entered in the computer system of the healthcare facility [13, 14]. As this is a manual action, most pharmacies fail to execute this. Additionally, using this CIN would show the pharmacist all available dosing advices for all patients with a body mass index (BMI) greater than 40 kg/m^2, even when certain advices apply for a BMI greater than 30 kg/m^2. This results in patients being missed by the CIN. Also, when the pharmacotherapy is conform the guidelines, the CIN will still generate alerts, which creates an excess in alerts and an increased alert fatigue and workload. In this study, we have defined alert fatigue as mental fatigue resulting from excess alerts that were irrelevant at the moment of assessment. This convergence of factors is therefore conceived as inconvenient [15].

CDSSs concerning obesity have been studied in various settings. Previous studies describe systems that play a role in ensuring detection of obesity at a younger age and/or the weight gain/loss process [16–18]. However, these CDSSs are limited to obesity as a disease and do not focus on comorbidities and their treatment. Several studies have been performed on validating support systems [17–19]. These validations assessed the number of actions carried out as a result of CDSS alerts. However, to the best of our knowledge, no previous study has described a CDSS concerning dosage advices in obese patients, nor did any study evaluate the correctness of alerts of a CDSS [20–25]. Hence, there is currently no gold standard for obesity surveillance regarding pharmacotherapy.

In 2020 and 2021, a custom made CDSS for obesity regarding dalteparin (divided into a clinical rule for therapeutic dosing, prophylactic dosing and monitoring anti-Xa levels), apixaban, dabigatran, edoxaban, rivaroxaban, vancomycin and ciprofloxacin (and collectively called the (morbid) obesity CDSS) was developed by the hospital pharmacy in the Maasstad Hospital and integrated in the EHR. This selection of drugs was established by the pharmacist expert group of the Maasstad Hospital as these drugs are classified as high-risk medication and pharmacotherapeutic advices of the KNMP were available [26–35]. The most recent measurements of a patient's weight and height at the moment of prescription were evaluated by a decision tree and used to generate an alert by the CDSS, as shown in Fig. 1. Conform hospital protocol, the pharmacist is obliged to process all generated alerts by evaluating the relevance of the alert and to document considerations and the actions taken. It was programmed that the CDSS evaluates all admitted patients every night. When weight, height or dosage is changed, it is detected overnight and if applicable, a new alert is generated.

To ensure that the obese population is properly treated, a validation and evaluation of the CDSS that has been implemented at the Maasstad Hospital was performed. We evaluated whether the CDSS works as intended and analysed whether it is an effective way to identify the obese patients (based on their current height and weight and/or BMI) who need an adapted dosage. Moreover, we evaluated how healthcare experts approach the generated advices.

Methods

Design

A retrospective observational study was performed to evaluate and validate the obesity CDSS. Included drugs were dalteparin, apixaban, dabigatran, edoxaban, rivaroxaban, vancomycin and ciprofloxacin. The research was conducted in the hospital pharmacy of the Maasstad Hospital in Rotterdam, the Netherlands. Dispensing data was collected of September 2021 up to and including February 2022 was included from HiX. The study was reviewed by the Medical Research Ethics Committees United (MEC-U) September 20th 2021 and was deemed not subjected to the Medical Research Involving Human Subjects Act (WMO) (trial registration W21.218). Therefore, ethics approval was waived according to national regulations. In accordance with local regulations, this study was reviewed by the local feasibility committee of the Maasstad Hospital to obtain local approval. Local approval by the board of directors of the Maasstad Hospital was obtained November 8th 2021. Informed consent was waved based on article 458 of the Dutch Medical Treatment Contracts Act (WGBO). Patients were excluded if they had a registered objection (opt-out) against participating in scientific research in their EHR at the moment data was extracted from the EHR.

Dispensing data

Dispensing data was collected based on the inclusion criteria shown in Table 1. Patients were 18 years or older and had a clinical admission with a prescription for either apixaban, dabigatran, edoxaban, rivaroxaban, dalteparin, vancomycin or ciprofloxacin. Intensive care unit (ICU) patients were excluded, as their EHR data is not documented in HiX, but a dedicated EHR program for ICU patients (MetaVision). For all drugs, separate patient inclusion criteria were defined, as shown in Table 1.

Data extraction and selection

Power Query facilitated the data extractions from HiX (v. 6.1) to Microsoft Excel (v. 2016) [36]. Patient data collected included sex, age, weight, height, BMI (calculated), bariatric surgery (yes/no), drug dispensed, daily dose, administration route, the alert generated and the documented actions (including written text). The data after implementation of the CDSS resulted in eight months for the anticoagulants and five-and-a-half months for the antibiotics in 2021. The year 2020 was excluded, as the pandemic of the SARS-CoV-2 virus was at its prime and daily care was adjusted to the needs of the patients during the pandemic. Further required details of the patients were documented manually, as some data could not be extracted by Power Query. All patients were screened regardless of BMI or weight, to identify patients missed by the CDSS due to incorrectly documented weight or height. The data was further reviewed for completeness and correctness. If either weight or height was wrongly documented this was manually rectified. Thereafter, the data was filtered based on the inclusion criteria stated in Table 1. Included prescriptions were verified by another pharmacist to ensure the integrity of the data. All data was hereafter coded.

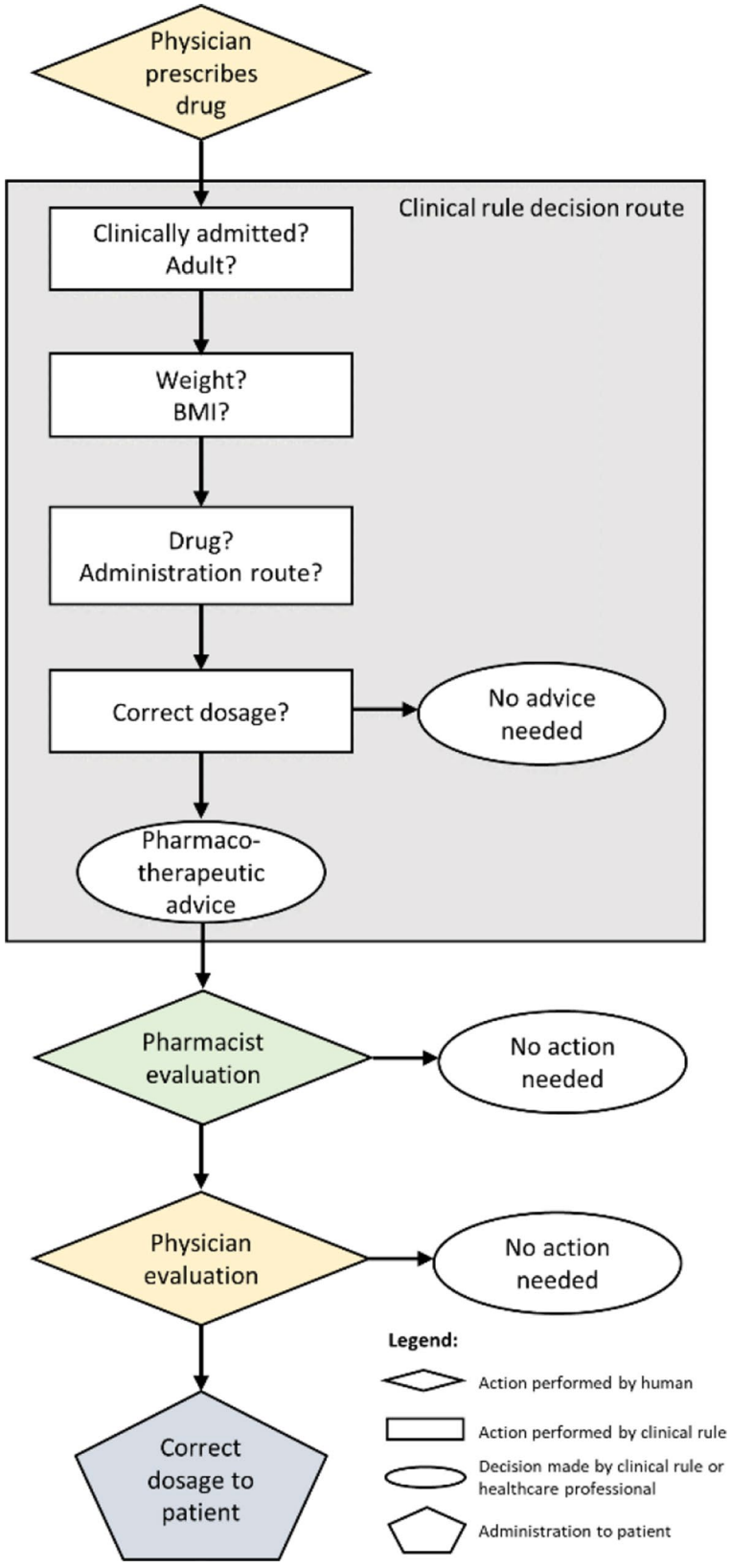

Fig. 1 Flowchart of work process of the morbid obesity CDSS. A physician prescribes medication electronically and the CDSS will evaluate the drug prescription overnight. Hereafter, when a pharmacotherapeutic advice is deemed necessary by the CDSS, a pharmacist evaluates this advice. If an advice is deemed necessary, the physician will be contacted. The physician then either accepts this advice or discards it if dose adjustment is deemed unnecessary for that patient. In yellow: physicians. In green: pharmacists. In blue: patient care. In grey: CDSS in the EHR system HiX

Table 1 Inclusion criteria for dispensing data regarding patients characteristics and the pharmacotherapeutic advice of the CDSS

General inclusion criteria								
Age		≥ 18 years						
Admission		Clinical						
Inclusion criteria by drug								
Drug	**Dalteparin – prophylactic treatment (≤ 7500 IE dalteparin daily)**	**Dalteparin– therapeutic treatment and anti-Xa**	**Apixaban**	**Dabigatran**	**Rivaroxaban**	**Edoxaban**	**Vancomycin**	**Ciprofloxacin**
BMI or weight	≥ 30 kg/m^2	≥ 100 kg	≥ 35 kg/m^2 AND > 175 kg	≥ 35 kg/m^2	≥ 35 kg/m^2 AND > 173 kg	≥ 35 kg/m^2 AND > 140 kg	≥ 35 kg/m2 AND/OR ≥ 100 kg	≥ 30 kg/m2 AND/OR ≥ 100 kg
Advice	BMI 30–40 kg/m^2: increase daily dosage to 5000 IE.	100–189 kg and dosage ≠ 170–230 IE/kg: adjust dosage to 200 IE/kg.	Weight > 175 kg: avoid use.	BMI ≥ 35 kg/m^2: avoid use.	Weight > 173 kg: avoid use.	≥ 140 kg: avoid use.	≥ 100 kg and/or BMI ≥ 35 kg/m2: Prescribe loading dosage of 1500 mg, continue 30 mg/kg via continuous infusion.	BMI ≥ 30 kg/m2 and 100–144 kg: increase dosage to 3dd400 mg iv or 2dd 750 mg orally.
	BMI ≥ 40 kg/m^2: increase daily dosage to 7500 IE.	≥ 190 kg: adjust dosage to 36.000 IE/day.						BMI ≥ 30 kg/m2 and ≥ 144 kg: increase dosage to 4dd400 mg iv.
		Monitor anti-Xa level on day 3.						

Abbreviations: BMI, body mass index

Outcome measures

The primary outcomes of this research were the sensitivity, specificity, PPV and NPV [20–25, 37–39]. The reference (gold) standard was defined as all patients with a BMI above the threshold value and having a prescription for the included medications, that should be identified by the rule. The full calculations are shown in supplementary file B. Consequently, excess alerts were quantified as the percentage of unnecessary alerts out of all generated alerts. Unnecessary rules were defined as rules that were not applicable in any way when assessed by the pharmacist. This was investigated by extracting all actions performed by the pharmacist after the alert was generated. A general overview was made of follow-up of the rule by healthcare professionals. All alerts were analysed for correctness of alert (technically and human input), relevance of alert, acceptance by pharmacist, type of registration in HiX, type of intervention, acceptance by physician and administration to patient.

Statistical analysis

The sensitivity, specificity, PPV, NPV and the excess alerts were calculated with 95%-confidence interval (Wilson Score interval). Where applicable, the standard deviation (SD) was reported as σ. All calculations were performed in Microsoft Excel (v. 2016) or Stata (v14.2).

Results

Patients and alert count

Baseline demographics are summarized in Table 2. It should be noted that due to the small number of patients, the baseline data of apixaban, edoxaban and rivaroxaban is excluded in this table. A total of 1218 alerts were generated over 1934 patients. Vancomycin and ciprofloxacin generated 58 and 65 alerts respectively in five-and-a-half months. However, the clinical rules for apixaban, dabigatran, edoxaban and rivaroxaban only generated zero, nine, one and zero alerts respectively, during the eight-month period. Most alerts were generated for dalteparin collectively, as there were 1086 alerts generated in eight months (Table 3).

Technical aspects and excess alerts

Direct oral anticoagulants

For the direct oral anticoagulants (DOACs) apixaban, edoxaban and rivaroxaban, there was not enough data to calculate the sensitivity, specificity, PPV, NPV and excess alerts. For dabigatran, the specificity and PPV were both 100.0% 95% CI [34.2, 100.0] and [70.1, 100.0] respectively. However, the sensitivity and NPV were 56.3% 95% CI [33.2, 76.9] and 22.2% 95% CI [6.3, 54.7]. Additionally, it was observed that seven patients who used dabigatran did not show up in the clinical rule, as their prescription was documented as stopped until further notice. Furthermore, for one patient an incorrect height was documented. The excess alerts were 22.2% 95% CI [6.3, 54.7], which was the lowest observed excess alerts of the study (Table 3).

Antibiotics

Ciprofloxacin had a sensitivity of 100.0%, 95% CI [95.4, 100.0], a specificity of 100.0%, 95% CI [96.9, 100.0], a PPV of 100.0%, 95% CI [95.4, 100.0] and a NPV of 100.0%, 95% CI [96.6, 100.0]. The excess alerts were 24.6% 95% CI [15.8, 36.3]. However, one case occurred in which the patient's weight was documented incorrectly. For vancomycin, the sensitivity and NPV were both 100.0%, 95% CI [91.0, 100.0] and [93.2, 100.0] respectively. However, the specificity was only 73.6%, 95% CI [62.4, 82.4], the PPV was 67.2%, 95% CI [54.4, 77.9]. Most noticeable was the percentage of excess alerts of 56.9%, 95% CI [44.1, 68.8]. In addition, it was ascertained that the BMI was set to 30 kg/m^2, instead of 35 kg/m^2.

Dalteparin

Lastly, for dalteparin collectively, the sensitivity and PPV both resulted in 100.0%, 95% CI [99.6, 100.0] and specificity and NPV for both was 100.0%, 95% CI [99.8, 100.0]. However, the excess alerts were the second highest, namely 39.8%, 95% CI [36.9, 42.7]. The dalteparin outcomes were split into the three different clinical individual rules (therapeutic dosage, anti-Xa level monitoring and prophylactic dosage). Dividing these rules failed to highlight any noticeable differences between them (Table 3). In the dalteparin data, 28 patients were

Table 2 Prescription information, included prescriptions and patient demographics

	Dalteparin collectively	Dabigatran	Edoxaban	Vancomycin	Ciprofloxacin
Prescriptions/unique patients, n/n	3448/1812	17/13	2/2	90/29	178/78
Male, n(%)	700 (38.6)	7 (53.9)	N/A	17 (58.6)	52 (66.7)
Age (years), mean (SD)	56.7 (17.0)	64.6 (17.4)	N/A	60.4 (11.7)	62.6 (13.9)
Weight (kg), mean (SD)	102.7 (19.2)	115.6 (15.3)	N/A	109.5 (21.6)	115.3 (19.5)
Height (cm), mean (SD)	169.9 (10.4)	173.4 (7.1)	N/A	175.1 (13.0)	167.7 (7.6)
BMI (kg/m^2), mean (SD)	35.6 (5.8)	38.4 (4.45)	N/A	35.8 (6.8)	37.1 (7.4)
Prophylactic/therapeutic, n (%)/n (%)	1700 (93.8), 112 (6.2)	N/A	N/A	N/A	N/A

Abbreviations: BMI, body mass index; SD, standard deviation; N/A, not applicable

Table 3 Generated alerts and the sensitivity, specificity, PPV, NPV and excess alerts

Drug	Alerts	Sensitivity (n1/n2; % + 95% CI)	Specificity (n3/n4; % + 95% CI)	Positive predictive value (n1/n5; % + 95% CI)	Negative predictive value (n4/n6; % + 95% CI)	Excess alerts (n7/n8; % + 95% CI)
Dabigatran	9	9/16; 56.3 [33.2, 76.9]	2/2; 100.0 [34.2, 100.0]	9/9; 100.0 [70.1, 100.0]	2/9; 22.2 [6.3, 54.7]	2/9; 22.2 [6.3, 54.7]
Ciprofloxacin	65	65/65; 100.0 [95.4, 100.0]	118/118; 100.0 [96.9, 100.0]	65/65; 100.0 [95.4, 100.0]	118/118; 100.0 [96.6, 100.0]	16/65; 24.6 [15.8, 36.3]
Vancomycin	58	39/39; 100.0 [91.0, 100.0]	53/72; 73.6 [62.4, 82.4]	39/58; 67.2 [54.4, 77.9]	53/53; 100.0 [93.2, 100.0]	33/58; 56.9 [44.1, 68.8]
Dalteparin - collectively	1086	1086/1086; 100.0 [99.6, 100.0]	2408/2408; 100.0 [99.8, 100.0]	1086/1086; 100.0 [99.6, 100.0]	2408/2408; 100.0 [99.8, 100.0]	432/1086; 39.8 [36.9, 42.7]
Dalteparin - anti-Xa level	116	116/116; 100.0 [96.8, 100.0]	173/173; 100.0 [97.8, 100.0]	116/116; 100.0 [96.8, 100.0]	173/173; 100.0 [97.8, 100.0]	38/116; 32.8 [24.9, 41.7]
Dalteparin - therapeutic	154	154/154; 100.0 [97.6, 100.0]	173/173; 100.0 [97.8, 100.0]	154/154; 100.0 [97.6, 100.0]	173/173; 100.0 [97.8, 100.0]	62/154; 41.0 [40.3, 48.2]
Dalteparin - prophylactic	816	816/816; 100.0 [99.5, 100.0]	2235/2235; 100.0 [99.8, 100.0]	816/816; 100.0 [99.5, 100.0]	2235/2235; 100.0 [99.8, 100.0]	332/816; 40.5 [37.2, 43.9]

Abbreviation: CI, confidence interval. *Values*: n1 = true positive alert; n2 = true positive alert + false positive alert; n3 = false positive alert; n4 = true negative alert; n5 = true positive alert + false positive alert; n6 = false negative alert + true negative alert; n7 = alerts deemed as unnecessary; n8 = total alerts generated

observed with an incorrect height, weight, or patients whose body temperature was erroneously noted as weight or height. Moreover, there were multiple occasions in which dalteparin was prescribed multiple times, where it should have been a single prescription, resulting in excess alerts. Furthermore, 67 cases were found where no rule was generated for the overdosing of 7500 IE dalteparin for patients with a BMI 30–40 kg/m^2 within the prophylactic clinical rule.

Acceptance rate and adherence

The acceptance rate by the pharmacist was analysed as well as whether the advices were carried out by the physician. In Table 4 the process of pharmacotherapeutic advice acceptance is summarized. Firstly, an advice was generated (alerts) and evaluated by a pharmacist (actions by pharmacist), who if deemed relevant, carries on the advice to the physician. The physician evaluates this advice and decides if it should be honoured (actions by physician) and carried out (administration to the patient). The vancomycin clinical rule resulted in nine advices from the pharmacist to the physician, of which only four drug advices were followed by the physician (6.9%). For the dalteparin anti-Xa level clinical rule this discrepancy was ascertained as well, in which 33 (28.5%) times the physician accepted the advice and only 19 (16.4%) times it was carried out. This was also observed for the prophylactic dalteparin dosing clinical rule, where there were 324 accepted advices (39.6%) and it was carried out 267 (32.5%) times (Table 4). Moreover, the choices and advices given by the pharmacist were also logged. The logged categories consisted of no action, switch of medication, dosage increase, dosage decrease, continuous administration, TDM or an additional measurement/laboratorial measurement. For vancomycin, the two main choices made were to not take any action (nine times) or to advice TDM (nine times). For several rules, an additional laboratorial measurement was advised, which consisted of mostly new measurements of weight (Table 5).

Discussion

In this research we evaluated the CDSSs regarding sensitivity, specificity, NVP and PPV, the excess alerts and follow-up. The CDSS built by the Maasstad Hospital can successfully and adequately identify obese patients. This research also identified all actions taken by the pharmacist and whether physicians followed this advice. Firstly, the sensitivity, specificity, NPV and PPV are discussed.

Strengths and limitations

The strengths of our investigation lies in the evaluation of both the system itself, as well as the adherence to the system. We show that it is very important to analyse custom-made systems even after implementation. This

Table 4 Acceptance rate of healthcare professionals in absolute numbers and %

	Alerts	Actions (alerts accepted) by pharmacist, *n* (%)	Actions (alerts accepted) by physician, *n* (%)	Administration to the patient (alerts fully accepted), *n* (%)
Dabigatran	9	7 (77.8)	4 (44.4)	4 (44.4)
Edoxaban	1	1 (100.0)	1 (100.0)	1 (100.0)
Ciprofloxacin	65	43 (66.2)	29 (44.6)	24 (36.9)
Vancomycin	58	16 (27.6)	9 (15.5)	4 (6.9)
Dalteparin – collectively	1086	502 (46.2)	386 (35.5)	309 (28.5)
Dalteparin – anti-Xa level	116	51 (44.0)	33 (28.5)	19 (16.4)
Dalteparin – therapeutic	154	56 (35.9)	29 (18.6)	23 (15.6)
Dalteparin – prophylactic	816	395 (48.4)	324 (39.7)	267 (32.7)

Table 5 Advices given by the pharmacist

	No action	Drug switch	Dosage increase	Dosage decrease	Continuous administration	TDM	Laboratorial measurement
Dabigatran	1	6	N/A	N/A	N/A	N/A	N/A
Edoxaban	N/A	1	N/A	N/A	N/A	N/A	N/A
Ciprofloxacin	11	N/A	31	N/A	N/A	N/A	1
Vancomycin	9	N/A	2	N/A	1	9	N/A
Dalteparin - collectively	74	N/A	390	3	N/A	43	1
Dalteparin - anti-Xa level	16	N/A	N/A	1	N/A	33	1
Dalteparin - therapeutic	22	N/A	32	1	N/A	9	N/A
Dalteparin - prophylactic	36	N/A	358	1	N/A	1	N/A

Abbreviation: TDM, therapeutic drug monitoring; N/A, not applicable

way the pharmaceutical care for patients is protected. Another strength is that all prescriptions and all patients were checked individually, to ensure the integrity of all documented rules, measurements and actions.

Limitations of this research were that not all data, such as dosage, were correctly logged in the EHR. For example: the prescription stated in the medication history was conflicting due to multiple orders or the regimens were stated to be not administered. Due to this research being retrospective, this information could therefore not be retrieved anymore. Secondly, the majority of the data concerns patients who received dalteparin. Lastly, the timespan of data of the CDSS was limited. This was due to the large workload of the department responsible for data extraction.

Sensitivity, specificity, NPV, PPV and excess alerts

The data showed that the CDSS performance is accurate in identifying the obese population in HiX, in contrast to for example the CIN "*morbid obesity*", which has multiple issues, such as the overgeneration of alerts. The CDSS performed as accordingly, as the sensitivity, specificity, PPV and NPV reached up to 100.0% most times. This underlines the added value of a CDSS for alerting pharmacists to adjust pharmacotherapy. However, for some drugs errors were found in the programming of the CDSS. Therefore, it is vital to check the decision tree itself. Now, multiple alerts were generated to evaluate pharmacotherapy for patients, when it was unnecessary. This contributed to low values found for the PPV and specificity for vancomycin. The evaluation of the CDSS also revealed new insights for the route of patient care for dabigatran. Our data analysis showed that eight patients were not shown in the CDSS. Investigating these patients revealed that the dabigatran prescriptions were temporarily stopped while being admitted to the hospital, which was part of normal routine care. However, upon being discharged from the hospital, patients resume taking the drug. However, these patients should have been evaluated by a pharmacist and been included in the clinical rule of dabigatran. These patients were at risk of being discharged with an incorrect treatment due to not being evaluated by the CDSS. Another observation made was the usage of 7500 IE dalteparin for patients in the BMI range of 30–40 kg/m^2 (n = 66). These patients should not have been prescribed 7500 IE of dalteparin, but 5000 IE, as this dosage was incorrectly prescribed (too high). The clinical rule initially only focussed on patients being undertreated. The possibility of patients being treated with a higher dosage was not taken into account and has since been adjusted.

Earlier research concerning CDSS and their sensitivity, specificity, PPV and/or NPV showed varying results, ranging from 8.0% up to 100.0% [23, 38, 39]. Important to note is that outcomes were not uniformly defined across studies. For example, the study of Rommers et al.,

investigated the effectiveness of the rule, based on the predictive capacity of adverse drug events. This approach to the CDSS is different from our research, as we evaluated the functioning of the CDSS regarding the correctness of the alerts generated instead of the effectiveness of the rule [39].

Excess alerts, as described in literature, ranges from approximately 20% up to 80% [22, 24, 40]. While analysing the excess alerts in this study, incorrectly entered values of patient characteristics contributed to the problem of lower achieved values. Incorrectly entered values by healthcare professionals are a problem of human hand and tackling this problem was not in the scope of this research, but could be a potential target for later research. The excess alerts of vancomycin were the highest observed within this research. Several reasons for the higher excess alerts could be identified. The most important factor is the co-existence of another clinical rule regarding the same drug. Vancomycin has an already developed TDM clinical rule as earlier mentioned and the newly developed (morbid) obesity clinical rule. Due to the fact that TDM is also carried out, sometimes even before the (morbid) obesity clinical rule alert is generated, rules are generated in duplicate. This causes pharmacists to wait for the results of the performed TDM, which results in the pharmacist deeming the morbid obesity clinical rule irrelevant. This phenomenon shows that improvements should be made to the clinical rule of vancomycin to decrease the excess alerts. After this was discussed with the pharmacists of the Maasstad Hospital, it became clear that improving this aspect might be possible by combining clinical rules. This should be the next step in optimizing CDSS appliance. Another factor contributing to higher excess alerts for all drugs, is the fact that sometimes a prescription is put in the EHR in duplicate or more, when it only should be prescribed once. This was for example seen in dalteparin. A prescription was entered in the EHR multiple times, where it should have been only once. Sometimes healthcare professionals do not see the previous prescription, or forget to take out the older one. Due to multiple prescription inputs, cumulative dosages change and alerts are correctly representing the patient's situation. Another noteworthy observation was that in some clinical situations, the dosage does not require adjustment. Most common are patients undergoing bariatric surgery, who have a BMI above 40 kg/m^2, receiving dalteparin. Due to the increased bleeding risk of bariatric surgery, dalteparin is not dosed higher than 5000 IE, following local guidelines of the hospital. However, these patients are still identified by their weight or BMI in the decision tree, resulting in unnecessary triggering of the CDSS, contributing to excess alerts. This observation lends itself for an opportunity to explore new choices within the decision tree to optimize the system. Ancker et al. described the problem of repeated alerts and alert fatigue within one patient. This research addressed the fact that if CDSS alerts are generated within the same patient multiple times, healthcare professionals are less likely to accept them [40]. Our research did not focus on this subject, however, future research could potentially investigate more in-depth on this matter. Additionally, Ancker et al. suggested a potential target to reduce alert fatigue, namely to reduce within-patient repeats, which is also supported by our observed alert fatigue especially for vancomycin and the anti-Xa level clinical rule of dalteparin, and should therefore be considered in future optimization [40].

Acceptance rate and adherence

In addition, adherence to the rule was analysed by investigating the acceptance rate by pharmacist and physician, and whether the advice reached the patient. A great decrease is observed in terms of adherence to the pharmacotherapeutic advice supplied by the rule. The fraction of alerts accepted by the pharmacist is partially influenced by the relevance of a rule. This could potentially highlight an underlying problem. For now, it can only be speculated what the problem could be for the low adherence seen at times of administration. Potential causes could be miscommunication, which ranges from physician to nurse or physicians agreeing on the phone but not having time or forgetting to process the advices in the EHR. Most remarkable are the low percentages observed for vancomycin and the therapeutic dalteparin and anti-Xa level clinical rule. Only 6.9%, 14.7% and 16.4% respectively of the advices of a therapeutic intervention was carried out for patients who triggered an alert. A notable observation is that vancomycin has a co-existing clinical rule, which is also the case for dalteparin as dalteparin has both an anti-Xa level and therapeutic clinical rule. As this research did not analyse the underlying causes of the low adherence in-depth, this could be a potential follow-up study to increase the added value of the CDSS and calling the physicians with advices.

The outcomes of this research show that CDSS of (morbid) obesity are capable of effectively selecting this population and generating pharmacotherapeutic alerts for the pharmacist. Yet unpublished data of the Maasstad Hospital showed that by conventional medication surveillance such as CINs and others, only 0.9% of the signals result in a consultation by a pharmacist to a physician. The data of this research show that this percentage is much higher, varying from 27.8 to 100.0%. Although not yet optimal, it is a great improvement and therefore results in more effective pharmacotherapeutic monitoring.

Conclusion

This study successfully displayed that clinically admitted obese patients can be identified with our CDSS and that the CDSS is an effective way to alert pharmacists when pharmacotherapeutic adjustments are needed based on a patient's treatment. This way the pharmacist can aim to give the correct pharmacotherapy to this population. It has also been shown that computer based systems can still have setting errors and that patients can potentially be missed. Validating such systems is of great value and importance to ensure that all patients are correctly screened by the system.

As the (morbid) obesity CDSS is not standard practice throughout every hospital, it should be the aim that CDSSs like these should be implemented the near future in all hospitals and variations of EHR. This study also shows that there are multiple options to make CDSSs even more effective. CDSSs are crucial for proper pharmacotherapeutic management in clinically admitted obese patients as they can help us identify obese patients at risk and help health professionals improve the personalized pharmaceutical treatment.

Abbreviations

BMI	Body mass index
CDSS	Clinical decision support system
CI	Confidence interval
CIN	Contraindication
DOAC	Direct oral anticoagulant
EHR	Electronic health record
HiX	Healthcare information eXchange
ICU	Intensive care unit
KNMP	Koninklijke Nederlandse maatschappij ter bevordering der Pharmacie
MEC-U	In Dutch: medisch-ethische toetsingscommissie. Translated to: Medical Research Ethics Committees United
NPV	Negative predictive value
PPV	Positive predictive value
SD	σ: Standard deviation
TDM	Therapeutic drug monitoring
WMO	In Dutch: Wet medisch-wetenschappelijk onderzoek met mensen. Translated to: medical research involving human subjects act

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

LB has contributed with the conceptualization and design of the research, the analysis, interpretation of data and has drafted the work. LB has approved the submitted version and has agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. LMW and LLK have contributed with the conceptualization and design of the research, the analysis, interpretation of data and have substantively revised it. LMW and LLK have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. TMK has contributed with the design of the research, the analysis, interpretation of data and has substantively revised it. TMK has approved the submitted version and has agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. TMB has contributed with the interpretation of data and has substantively revised it. TMB has approved the submitted version and has agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was reviewed by the Medical Research Ethics Committees United (MEC-U) September 20th 2021 and was deemed as not subject to the WMO (Medical Research Involving Human Subjects Act). The research was thereafter accepted by the local ethics committee of the Maasstad Hospital. Informed consent was waved based on article 458 of the Dutch Medical Treatment Contracts Act (WGBO). Patients were excluded if they had a registered objection against participating in scientific research in the EHR.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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