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# Implementation of the WHO-6-step method in the medical curriculum to improve pharmacology knowledge and pharmacotherapy skills

**Carolina J. P. W. Keijsers,[1,2] Wieke S. Segers,[2] Dick J. de Wildt,[3] Jacobus R. B. J. Brouwers,[2] Loes Keijsers[4] & Paul A. F. Jansen[2]**

*[1]Department of Geriatric Medicine, Jeroen Bosch Hospital, 's-Hertogenbosch, [2]Department of Geriatric Medicine and Expertise Centre Pharmacotherapy in Old Persons, University Medical Centre Utrecht, Utrecht, [3]Department of Translational Neuroscience, University Medical Centre Utrecht, Utrecht and [4]Faculty of Social Sciences, Utrecht University, Utrecht, The Netherlands*

**Correspondence**
Mrs Carolina J. P. W. Keijsers MD, Department of Geriatric Medicine, Jeroen Bosch Hospital, PO Box 90153, 5200 ME 's Hertogenbosch, The Netherlands.
Tel.: +31 73 553 8629
Fax: +31 73 553 8555
E-mail: k.keijsers@jbz.nl

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## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The only validated tool for pharmacotherapy education for medical students is the 6-step method of the World Health Organization.
- It has proven effective in experimental studies with short term interventions.
- The generalizability of this effect to the setting of a contextual-rich medical curriculum is unclear.

## WHAT THIS STUDY ADDS

- The WHO-6-step had positive effects on students' knowledge of basic and applied pharmacology and improved their pharmacotherapy skills, satisfaction with the education and self-reported confidence in prescribing.
- The positive effects on students' pharmacology knowledge and pharmacotherapy skills identified in short term educational intervention studies were replicated after implementation of the method in a medical curriculum.

## AIM

The only validated tool for pharmacotherapy education for medical students is the 6-step method of the World Health Organization. It has proven effective in experimental studies with short term interventions. The generalizability of this effect after implementation in a contextual-rich medical curriculum was investigated.

## METHODS

The pharmacology knowledge and pharmacotherapy skills of cohorts of students, from years before, during and after implementation of a WHO-6-step-based integrated learning programme were tested using a standardized assessment containing 50 items covering knowledge of basic ($n = 25$) and clinical ($n = 24$) pharmacology, and pharmacotherapy skills ($n = 1$ open question). All scores are expressed as a percentage of the maximum score possible per (sub)domain.

## RESULTS

In total, 1652 students were included between September 2010 and July 2014 (participation rate 89%). The WHO-6-step-based learning programme improved students' knowledge of basic pharmacology (mean score ± SD, 60.6 ± 10.5% *vs.* 63.4 ± 10.9%, $P < 0.01$) and clinical or applied pharmacology (63.7 ± 10.4% *vs.* 67.4 ± 10.3%, $P < 0.01$), and improved their pharmacotherapy skills (68.8 ± 26.1% *vs.* 74.6% ± 22.9%, $P$ 0.02). Moreover, satisfaction with education increased (5.7 ± 1.3 *vs.* 6.3 ± 1.0 on a 10-point scale, $P < 0.01$) and as did students' confidence in daily practice (from −0.81 ± 0.72 to −0.50 ± 0.79 on a −2 to +2 scale, $P < 0.01$).

## CONCLUSIONS

The WHO-6-step method was successfully implemented in a medical curriculum. In this observational study, the integrated learning programme had positive effects on students' knowledge of basic and applied pharmacology, improved their pharmacotherapy skills, and increased satisfaction with education and self-confidence in prescribing. Whether this training method leads to better patient care remains to be established.

## Introduction

Prescribing medication is an important component of patient care [1]. Although medications are beneficial to patient health and wellbeing, their incorrect prescription can have harmful effects [2, 3]. Half of all prescribing errors are potentially preventable, and recent studies indicate that these errors are often caused by prescribing physicians' limited knowledge of pharmacology and pharmacotherapy [4, 5]. This means that such errors could be avoided in the future, if the pharmacology education given to medical students is improved [6–8]. Indeed, medical students often feel unprepared for their prescribing task when they graduate and have expressed a wish to have more opportunities to acquire these skills in practice [8]. One possible reason why students feel unprepared is that they usually copy their supervisors' medication choices, without thinking autonomously about potential choices [9]. Hence, in order to improve prescribing in clinical practice, it is important that this autonomous thinking process is stimulated during medical training.

The only validated pharmacology and pharmacotherapy education tool is the 6-step method of the World Health Organization's guide to good prescribing (WHO-6-step). This method specifically aims to improve the prescriber's thinking process [10–13], (Figure 1) and seems to be a valuable prescribing tool for trainees. The guide encourages rational pharmacotherapy, by requiring users to apply relevant underlying basic pharmacology knowledge to specific patient characteristics (Step 3b in Figure 1), e.g. changed pharmacokinetics [10, 11]. Several studies have addressed the effectiveness of the WHO-6-step, and short term educational interventions have shown the method to provide robust improvements in students' pharmacotherapy skills, measured at each of the six steps [14–20]. One study reported an improved knowledge of basic pharmacology [20], and other studies reported the transfer of pharmacotherapy knowledge to unrehearsed patient cases and improved long term results [14, 16, 19]. However, as mentioned, these studies involved short term interventions, and results achieved in experimental studies may not always extrapolate to the real-life setting of the contextual rich environment of medical education [21, 22]. Two studies investigated the long term effects of implementation of the WHO-6-step in a medical curriculum and reported positive effects on WHO-6-step skills and a transfer effect. However, only a small selection of students participated in the studies and outcomes other than treatment decisions related to various steps of the WHO-6-step were not investigated [23, 24].

Given the limited number of studies investigating the effect of implementation of the WHO-6-step in the contextual rich environment of a medical curriculum, the generalizability of previous experimental findings

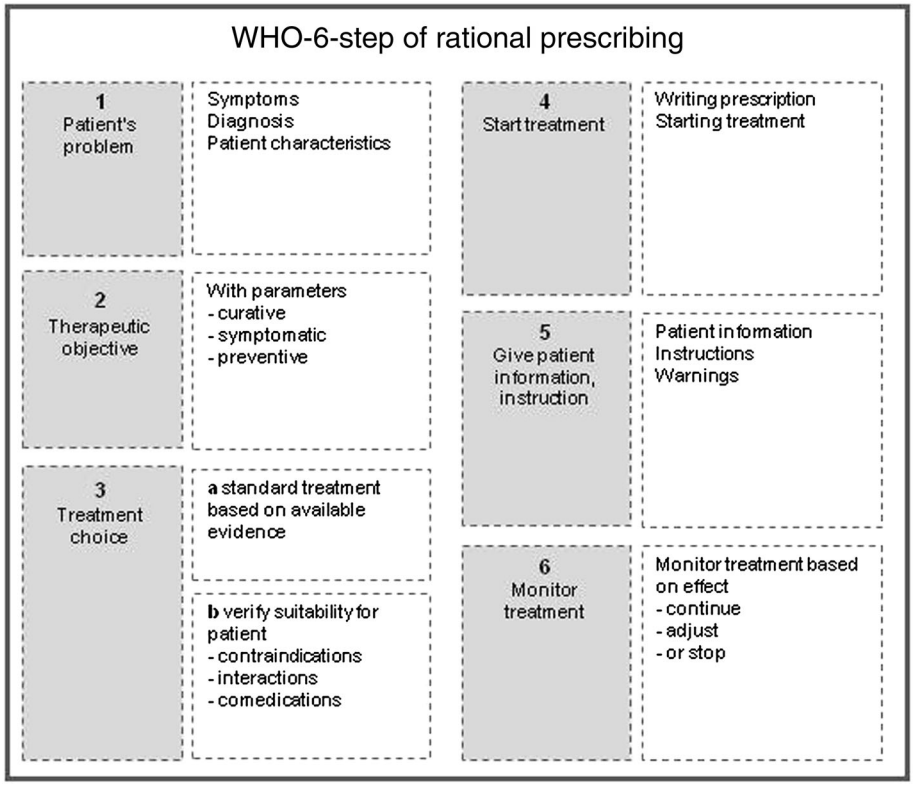


**Figure 1**

WHO-6-step of rational prescribing from the Guide to Good Prescribing

is uncertain. The aim of this study was to investigate whether an integrated learning programme incorporating the WHO-6-step and given throughout the medical curriculum would increase students' knowledge of basic and applied pharmacology and improve their prescription writing skills.

## Methods

Medical students from different entry years, representing cohorts before, during and after curriculum reorganization, were compared with each other in terms of their pharmacology knowledge and pharmacotherapy skills at fixed points in their educational careers, in our case halfway and at the end of their study. Figure 2 shows the study design graphically. Knowledge of basic pharmacology and clinical or applied pharmacology, and pharmacotherapy skills were assessed using a formative standardized assessment. The specific educational intervention, the outcome measurements, the assessment, the study samples and analyses are described in more detail below.

## Educational intervention

Dutch medical curricula offer a 6 year two phase Bachelor (3 years) and Master (3 years) programme, with secondary school diplomas as entry requirement. Curricular changes made at Utrecht Medical School included incorporation of the WHO-6-step into the curriculum as part of an integrated, longitudinal learning programme in pharmacology and pharmacotherapy. Almost all course modules covered aspects of pharmacology and pharmacotherapy education, and learning goals (in terms of relevant pharmacology and pharmacotherapy principles and drug groups) were set throughout the curriculum. The WHO-6-step method was used during large (interactive) lectures, small group tutorials and small group practical lessons (see Figure 1), in order to increase the patient context of education. For example, in the third year clerkship in internal medicine, students use the WHO-6-step to prepare a patient case with diabetes and cardiac failure. Students are required to study the pharmacodynamics of relevant drugs, prior to discussion in a tutorial. The total number of contact hours was also increased, by 58 h, mainly in the Bachelor phase (Table 1). Other curricular changes were the obligatory use of the E-learning program Pscribe, which is based on the WHO-6-step, for some tutorials [25] the introduction of interdisciplinary lectures and tutorials for certain subjects for medical and pharmacy students and the introduction of an additional elective course in the third year (it was poorly attended). No other major curricular changes were introduced during the inclusion period.

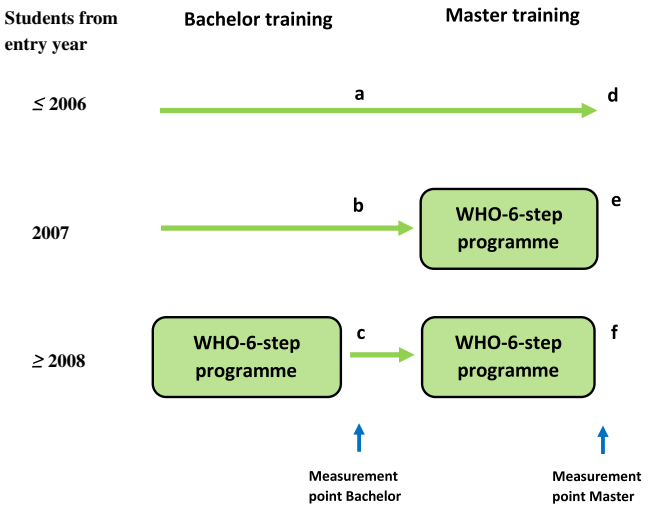


**Figure 2**

Study design with or without WHO-6-step programme at different measurement points a to f

Comparisons in this study:

1) Effect after *full intervention* in Master students: d (baseline) *vs.* f (full intervention).

2) Effect of *Bachelor* intervention before *vs.* after in Bachelor students: a + b (baseline) *vs.* c (Bachelor intervention).

3) Effect of *Master* intervention before *vs.* after in Master students: d (baseline) *vs.* e (Master intervention only).

4) Additional effect of *Bachelor intervention* in Master students with intervention: e (Master intervention only) *vs.* f (full intervention)

## Outcome measurements

Knowledge of basic pharmacology and clinical or applied pharmacology, and pharmacotherapy skills were assessed using a formative standardized assessment which covered three domains: basic pharmacology knowledge ($n = 25$ multiple choice questions), clinical or applied pharmacology knowledge ($n = 24$ multiple choice questions) and pharmacotherapy skills ($n = 1$ open question on writing a prescription). The domain basic pharmacology knowledge had subdomains: pharmacokinetics ($n = 7$), pharmacodynamics ($n = 7$), interactions and side effects ($n = 4$) and ATC groups (anatomic therapeutic chemical classification; $n = 7$)). The domain applied pharmacology knowledge had subdomains: prescribing ($n = 7$), prescribing in special groups ($n = 7$), interactions and side effects ($n = 3$) and drug information, regulations and law ($n = 7$). Further details on the assessment are given below. One researcher (CK) marked the assessments on pharmacology knowledge and pharmacotherapy skills. Multiple choice questions were scored as right or wrong (0–1), the maximum score 25 points for basic knowledge and 24 points for applied knowledge. The open question on prescriptions written by the students was evaluated for completeness and readability, and each correct item was awarded a score of 1 point: 1) name patient and date of birth, 2) name physician

**Table 1**

Quantity of education: scheduled contact hours of pharmacology and pharmacotherapy education before and after implementation of the WHO-6-step programme

| | | Before implementation of WHO-6-step | | | | After implementation of WHO-6-step | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study phase | Study year | Lectures | Tutorials | Practical lessons | Total/year | Lectures | Tutorial | Practical lessons | Total/year | Change |
| **Bachelor** | **Year 1** | 8 | 6 | 4 | 18 | 39 | 16 | 2 | 57 | +39 |
| | **Year 2** | 0 | 0 | 0 | 0 | 7 | 5 | 0 | 12 | +12 |
| | **Year 3** | 0 | 0 | 0 | 0 | 4 | 2 | 0 | 6 | +6 |
| | **Total 1–3** | 8 | 6 | 4 | 18 | 50 | 23 | 2 | 75 | **+57** |
| **Master** | **Year 4** | 5 | 8 | 4 | 17 | 6 | 2 | 0 | 8 | −9 |
| | **Year 5** | 0 | 0 | 0 | 0 | 0 | 8 | 0 | 8 | +8 |
| | **Year 6** | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 2 | +2 |
| | **Total 4–6** | 5 | 8 | 4 | 17 | 8 | 10 | 0 | 18 | **+1** |
| **Both phases** | **Total 1–6** | 13 | 14 | 8 | 35 | 58 | 33 | 2 | 93 | **+58** |

and signature, 3) drug and dose, 4) number, 5) label instruction. All scores are expressed as percentages of the maximum score possible per domain and subdomain.

Additionally, in order to establish population characteristics, all participating students filled out a short questionnaire prior to the written formative assessment regarding their age, gender, entry year of the study and previous relevant studies. Five additional questions concerned pharmacology education, namely, average hours of self-study, interest in the subject, importance of pharmacology knowledge, and confidence in own pharmacology and pharmacotherapy knowledge and skills in clinical practice. Lastly, students were asked to score the pharmacology and pharmacotherapy education on a 10 point scale (1–10).

## Assessment

Students' knowledge of and skills in pharmacology and pharmacotherapy were measured with a formative written assessment based on the available literature on core curricula [1, 26, 27]. A formative assessment was chosen to eliminate the confounding variable of students' learning prior to the assessment [28]. The assessment was designed with a test matrix and covered three domains: basic pharmacology knowledge ($n = 25$ multiple choice questions), clinical or applied pharmacology knowledge ($n = 24$ multiple choice questions) and pharmacotherapy skills ($n = 1$ open question). The basic pharmacology knowledge questions tested factual knowledge obtained from study books (canonical knowledge) with short questions, e.g. 'what is a first pass effect?' The clinical pharmacology knowledge questions involved short case vignettes that required students to apply their knowledge to a specific patient, e.g. 'an 80-year-old woman with renal failure comes to the general practitioner with a complicated urinary tract infection (UTI). What is the best treatment for the UTI in this woman?' To assess pharmacotherapy skills, students had to write a prescription based on a case description. Students were told which drug was to be prescribed.

Six parallel assessments were formed using a database of 270 questions and a test matrix. An expert panel of 10 pharmacists and clinical pharmacologists was also consulted. Three versions of the assessment were used for the Bachelor medical students, with easier questions, on which the expert panel had a mean (± SD) score of 91.2 ± 6.1%. This assessment was also used in a previous study [29]. To prevent a ceiling effect, Master students were given the more difficult assessment, on which the expert panel had a mean (± SD) score of 80.8 ± 6.1%. This means that the performance of Bachelor and Master students could not be compared because different assessments were used. All assessments were used alternately during data collection to discourage the distribution of the assessment among medical students during the 4 year study period. The psychometric properties of the six assessments were adequate: this was measured by construct and content validity, and reliability in term of internal consistency, item-rest correlation ($r_{ir}$) scores and probability value for the individual questions,

## Study samples and data collection procedure

Students from Utrecht Medical School, Utrecht, the Netherlands, were included. Bachelor students were assessed after completion of the first 3 years of medical training, at the start of their 4$^{th}$ study year. Master students were assessed after completion of all compulsory courses, at the start of the 6$^{th}$ study year (subsequent education entails elective courses only). Table 2 displays

## Table 2

Baseline characteristics of the cohorts before and after implementation of the WHO-6-step programme

| | Bachelor students (*n* = 942) | | Master students (*n* = 710) | | |
|---|---|---|---|---|---|
| **Characteristic** | **Before** | **After change in Bachelor training** | **Before** | **After change in Master training only** | **After full intervention** |
| **Entry year (*n*)*** | | | | | |
| **< 2006** | 22 | – | 90 | – | – |
| **2006** | 81 | – | 233 | | – |
| **2007** | 226 | – | | 235 | – |
| **2008** | – | 217 | – | – | 148 |
| **2009** | – | 229 | – | – | 1 |
| **2010** | – | 160 | – | – | – |
| **Total n** | 329 | 606 | 323 | 235 | 149 |
| **Age (years) (mean ± SD)** | 22.7 (±2.2) | 22.1 (±1.4) | 24.9 (±2.5) | 24.0 (±1.2) | 23.7 (±1.7) |
| **Gender (Female,%)** | 66% | 76% | 68% | 72% | 85% |
| **Previous study†** | | | | | |
| **None (*n*)** | 266 | 481 | 256 | 192 | 132 |
| **Yes, not relevant (n)** | 29 | 71 | 41 | 24 | 10 |
| **Yes, relevant (*n*)** | 34 | 53 | 26 | 16 | 7 |
| **Missing data (*n*)** | – | 1 | – | 3 | – |
| **No study delay (%)** | 47% | 76% | 40% | 66% | 100% |

Groups of Bachelor students significantly differed in variables: age, gender, study delay; groups of Master students significantly differed in age, gender and study delay. These were added as covariates to the other analyses. *Missing variables on entry year and therefore some students could not be categorized into cohorts for further analyses: Bachelor students $n = 7$, Master students $n = 3$; One Master student had exemptions due to previous studies, resulting in very fast study progress. †All biomedical studies, e.g. biomedical sciences were considered as relevant previous studies, other studies, e.g. law school were considered non-relevant previous studies.

the background characteristics. A subset of the Bachelor students, comparable with the control group in this study, was also included in a study with a head to head comparison with pharmacy students [29].

Students were asked to participate during voluntary, scheduled study activities in four academic years between 2010–2011 and 2013–2014. The assessment was formative and did not count towards the students' study results. Figure 2 shows the study design and the measurement points in the Bachelor and Master phases, before and after the educational intervention. Students from different entry years were assessed. To test the effect of WHO-6-step implementation, the mean scores for knowledge of basic and applied or clinical pharmacology, pharmacotherapy skills, and satisfaction and motivational factors of students from different cohorts were compared. The effect of the full intervention, which means WHO-6-step training was given in both the Bachelor and Master phases, was investigated in Master students by comparing measurement points d (baseline measurement) and f (intervention). The effect of the intervention given in the Bachelor phase only was studied by comparing Bachelor students' performance at points a + b (baseline measurement) *vs.* c (intervention). The effect of the intervention given in the Master phase only was studied by comparing Master students' performance at points d (baseline measurement) and e (intervention). Lastly, the effect of the intervention given in the Master phase only *vs*. in both study phases on Masters students' performance was studied by comparing e *vs*. f. It should be mentioned that the assessment points were for students who did not have a study delay. If students had a study delay, they were included in later assessments.

## Data analysis

Response rates were calculated by comparing the number of participants to the number of medical students recorded in the University digital registration system. For the other analyses ANOVAs and ANCOVAs to correct for the possible confounding effect of age, gender and study duration were used. Covariates were chosen based on baseline differences. In all models, effect sizes (Cohen's d) were calculated for all significant differences. Effect sizes $<0.5$ were considered small, 0.5–0.8 medium and $>0.8$ large [30]. A $P$ value of $<0.05$ was considered significant. Data were collected and analyzed using Excel and IBM SPSS version 22.0 (IBM).

## Ethical considerations

This study involving medical students falls outside the scope of the Dutch Law on Medical Research (WMO).

The Dutch Ethics Review Board for medical educational research (NVMO-ERB) was not operational at the start of the study. The students, all 18 years or older, were informed about the study in advance in the written study materials. They gave active verbal consent and participated on a voluntary basis. All data were collected anonymously.

## Results

In total, 1652 medical students were enrolled in this study, 942 Bachelor students (response rate 87%) and 710 Master students (response rate 92%), from September 2010 to July 2014 (Table 2). One student withdrew consent after inclusion without giving a reason and data for this participant were deleted. The cohorts of Bachelor and Master students differed in terms of age, gender and proportion of students without a study delay.

## Main results

The main results are given in Table 3. Master students who received the full WHO-6-step intervention (in the Bachelor and Master phases) significantly outscored the control Master students who did not receive the WHO-6-step intervention in the following domains: basic pharmacology knowledge, applied pharmacology knowledge, and pharmacotherapy skills. After correction for possible confounding variables, most effects remained significant, except for the domain pharmacotherapy skills.

Bachelor students who received the WHO-6-step intervention in the Bachelor phase had a significantly better knowledge of basic pharmacology than did control Bachelor students who did not receive the WHO-6-step intervention. This difference remained significant after correcting for potential confounders. Similarly, Master students who received the WHO-6-step intervention in the Master phase only had a better knowledge of basic and applied knowledge pharmacology than did the control Master students who did not receive the WHO-6-step intervention. The difference in applied pharmacology knowledge was no longer significant after correction for confounders.

In summary, the WHO-6-step intervention was effective when used in either the Bachelor or the Master phase and improved students' knowledge of basic pharmacology, and in the Master phase it led to a better knowledge of applied pharmacology. When used in both phases, students had a better knowledge of basic and applied pharmacology. The significant results had small effect sizes ranging from 0.23 to 0.35 (Cohens d).

### Table 3

Main results: percentage of maximal assessment scores before and after implementation of the WHO-6-step programme for Bachelor and Master students

| | Bachelor students | | Statistics | Master students | | | Statistics | |
|---|---|---|---|---|---|---|---|---|
| Domain (no of questions) | Before<br>Mean ± SD | After change in Bachelor training<br>Mean ± SD | Before *vs.* after Bachelor training<br>*P* values/adj† | Before<br>Mean ± SD | After change in Master training only<br>Mean ± SD | After full intervention<br>Mean ± SD | Before *vs.* after Master training only<br>*P* values/adj† | Before *vs.* after full intervention<br>*P* values/adj† |
| **Basic pharmacology knowledge (*n* = 25)** | 67.8 (9.9) | 70.1 (10.0) | **<0.01/< 0.01** | 60.6 (10.5) | 63.1 (9.8) | 63.4 (10.9) | **<0.01/ <0.01** | **<0.01/<0.01** |
| **Pharmacodynamics (*n* = 7)** | 68.8 (14.9) | 71.3 (14.9) | | 57.3 (16.4) | 60.0 (16.2) | 60.6 (17.5) | | |
| **Pharmacokinetics (*n* = 7)** | 67.9 (16.6) | 69.3 (16.2) | | 66.0 (20.4) | 66.1 (20.2) | 67.1 (18.8) | | |
| **Interactions and side effects (*n* = 4)** | 65.9 (15.6) | 67.7 (17.0) | | 66.9 (19.9) | 67.8 (20.4) | 69.8 (18.6) | | |
| **ATC groups (*n* = 7)** | 65.3 (18.5) | 68.1 (18.3) | | 54.6 (21.3) | 57.9 (19.6) | 56.4 (18.6) | | |
| **Applied pharmacology knowledge (*n* = 24)** | 71.5 (10.6) | 72.2 (11.4) | 0.38/0.85 | 63.8 (10.5) | 65.6 (10.5) | 67.4 (10.3) | **0.04**/0.10 | **<0.01/<0.01** |
| **Prescribing (*n* = 7)** | 63.8 (16.1) | 64.4 (16.2) | | 57.1 (17.8) | 59.0 (17.2) | 62.9 (16.4) | | |
| **Prescribing in special groups (*n* = 7)** | 72.7 (19.2) | 74.2 (19.8) | | 66.6 (18.7) | 68.3 (18.1) | 69.9 (17.3) | | |
| **Drug information, regulations and law (*n* = 7)** | 78.8 (17.9) | 78.0 (19.8) | | 64.4 (21.1) | 66.3 (21.7) | 65.6 (22.6) | | |
| **Interactions and side effects (*n* = 3)** | 65.9 (15.6) | 67.7 (17.0) | | 66.7 (19.9) | 67.7 (20.3) | 69.8 (18.6) | | |
| **Prescription writing skills (*n* = 1)** | 67.3 (26.1) | 69.6 (28.7) | 0.23/0.41 | 68.8 (26.1) | 72.7 (24.3) | 74.6 (23.0) | 0.07/0.35 | **0.02**/0.11 |

†*P* values adjusted by ANCOVA with covariates: age, gender, study delay.

Compared with students who received the WHO-6-step intervention in the Master phase only, students who received the WHO-6-step intervention during both the Bachelor and Master phases had a better knowledge of applied pharmacology (mean ± SD 65.6 ± 10.5% *vs.* 67.4 ± 10.3%; $P < 0.04$) and better prescription writing skills (mean ± SD 62.9 ± 16.4% *vs.* 59.0 ± 17.2%; $P < 0.03$). The latter was no longer significant after correcting for confounders in the ANCOVA ($P < 0.07$). Thus introduction of the WHO-6-step intervention in the Bachelor phase improved students' pharmacology knowledge and pharmacotherapy skills slightly more than when the intervention was introduced in the Master phase.

## Students' satisfaction, study behaviour and motivation

Master students who had received the WHO-6-step intervention in both the Bachelor and Master phases had a greater appreciation of their education and were more confident in clinical practice (although on average still unconfident) than the control group of Master students who did not receive WHO-6-step intervention (Table 4). These results were still significant after correction for possible confounding variables.

Students who had received the intervention in the Master phase only expressed a greater appreciation of the education received than did students who did not receive the intervention in the Master phase. Students who received the intervention in the Bachelor phase only were more interested in the topic, were more confident (although on average still unconfident), had a greater appreciation of the education provided, and made more self-study hours per week than the control students who had not received the intervention in the Bachelor phase.

Students who received the WHO-6-step intervention in both phases were more satisfied with their education than students who received the intervention in the Master phase only (mean ± SD 6.3 ± 1.0 compared with 6.0 ± 1.2 on a 10-point scale; ANOVA $P < 0.01$, and after correction for confounders $P = 0.01$). Introduction of the WHO-6-step intervention increased students' confidence scores from very unconfident (mean ± SD – 0.69 ± 0.81) to mildly unconfident (mean ± SD – 0.50 ± 0.80) on −2 to +2 scale (ANOVA $P = 0.03$, after correction for confounders $P < 0.01$). Other factors did not differ between these two cohorts. The effect sizes of the differences in confidence and self-study hours were small (Cohens d range 0.18–0.41), whereas the differences in appreciation showed medium-sized effect sizes (Cohens d up to 0.65)

The WHO-6-step intervention hardly affected intrinsic motivational study factors such as students' interest in pharmacology and pharmacotherapy and the recognized importance of the topic (Table 4). In all groups of students, the recognized importance was higher than interest in the topic (all $P < 0.01$ on paired *t*-test), although the recognized importance did not increase in any of the groups.

## Discussion

This study shows that the WHO-6-step-based learning programme is effective in increasing students' pharmacology knowledge and pharmacotherapy skills and is appreciated by both Bachelor and Master medical students. In cohorts of students who received the full intervention (in both the Bachelor and Master phases), pharmacology knowledge and pharmacotherapy skills were improved in all domains relative to the pharmacology knowledge and pharmacotherapy skills of earlier cohorts who had not received the WHO-6-step intervention. Training in

### Table 4

Secondary results after implementation of the WHO-6-step for Bachelor and Master students

| | Bachelor students | | Statistics | Master students | | | Statistics | |
|---|---|---|---|---|---|---|---|---|
| Domain | Before Mean ± SD | After change in Bachelor training Mean ± SD | Before *vs.* after *P* values/adj† | Before Mean ± SD | After change in Master training only Mean ± SD | After full intervention Mean ± SD | Before *vs.* after Master training only *P* values/adj† | Before *vs.* after full intervention *P* values/adj† |
| **Interest in topic*** | 0.24 (0.92) | 0.13 (0.89) | 0.09/**0.03** | 0.29 (0.85) | 0.31 (0.82) | 0.44 (1.84) | 0.84/0.81 | 0.25/0.40 |
| **Recognized importance*** | 1.16 (0.86) | 1.07 (1.55) | 0.32/0.27 | 1.25 (0.98)) | 1.21 (0.87) | 1.22 (0.87) | 0.68/0.81 | 0.79/0.72 |
| **Confidence in clinical practice*** | −0.89 (0.74) | −0.60 (0.78) | <**0.01**/<**0.01** | −0.81 (0.72) | −0.69 (0.81) | −0.50 (0.79) | 0.07/0.13 | <**0.01**/<**0.01** |
| **Self-study hours (h week$^{-1}$)** | 0.89 (1.60) | 1.24 (2.23) | **0.01**/<**0.01** | 0.54 (0.82) | 0.49 (0.91) | 0.48 (0.83) | 0.44/0.58 | 0.40/0.97 |
| **Appreciation education (1–10 scale)** | 5.7 (1.5) | 6.5 (0.90) | <**0.01**/<**0.01** | 5.7 (1.3) | 6.0 (1.2) | 6.3 (1.0) | **0.01/0.04** | <**0.01**/<**0.01** |

*Measured on a Likert scale: −2: very disagree, −1 disagree, 0 neutral, 1 agree, 2 very agree. †*P* values adjusted by ANCOVA with covariates: age, gender, study delay

the WHO-6-step method improved knowledge of basic pharmacology in students who received the intervention in the Bachelor phase only and improved knowledge of basic and applied pharmacology in students who received it in the Master phase only. Additionally, with more training students reported greater appreciation of their education and more confidence in prescribing, although the latter was still rather low. Bachelor students who received the intervention in the Bachelor phase only reported more self-study hours. Unfortunately, other factors, such as recognized importance of and interest in pharmacology and pharmacotherapy, hardly differed between the groups who had or had not received WHO-6-step intervention. Overall, the intervention had most effect on students' appreciation of education (medium size effect), and the least effect on pharmacology knowledge and pharmacotherapy skills, and self-confidence (small effect sizes).

Earlier studies have already shown positive effects of the WHO-6-step on the performance of medical students [14–20, 23, 24]. These studies were randomized controlled trials [14–17, 19, 20, 24]. Although this study design certainly gives the highest available evidence, sometimes the study population is not representative, e.g. only the most motivated students participate and/or the context of the education is simplified. Thus results obtained in randomized controlled trials are not always generalizable to other settings, such as the contextual rich environment of a medical curriculum. As in earlier studies, this study shows that the WHO-6-step method is suitable for medical students in both the Bachelor and Master phases of their study. This study used a different outcome measure than most other studies, namely, pharmacology knowledge and pharmacotherapy skills rather than students' decisions on the different steps of the WHO-6-step. Only one other study showed the WHO-6-step to improve basic pharmacology knowledge, as measured directly after the intervention [20]. While this might seem a strange end point, studies of medication-related errors have mentioned pharmacology knowledge deficits, not a lack of skills in the WHO-6-step, as being a major concern [4, 5]. Moreover, if the skills learned with the WHO-6-step method can be transferred to other non-rehearsed patient cases [16, 24], then the WHO-6-step method might contribute to a broader knowledge of pharmacology and better pharmacotherapy skills. The WHO-6-step method might stimulate a deeper understanding of, and more active engagement in, pharmacology and pharmacotherapy, by showing students the clinical relevance of these subjects.

Although the WHO-6-step method improved pharmacology knowledge and pharmacotherapy skills, effect sizes were small, possibly due to an indirect learning effect. The clinical relevance of these small differences can be debated, but it should be borne in mind that small or even non-significant results are very common in educational implementation studies [21]. The WHO-6-step intervention had a medium-sized effect on appreciation of education. Interestingly, although writing a prescription is an explicit part of the WHO-6-step method, there was hardly any improvement in this skill. Why this was the case is unclear, but possibly the increased use of electronic prescribing diminishes the prescription writing skills of later cohorts of students, although no evidence could be found in the literature for this.

Surprisingly, findings also suggest that the improved performance of the Master students was mainly due to training in the Master phase. Students who received the WHO-6-step intervention in the Master phase only had scores nearly comparable with those of students who had received the intervention in both the Bachelor and Master phases of their study plus an additional 57 h of education during the Bachelor phase. Only applied knowledge was significantly better with longer training with the WHO-6-step method. Knowledge retention might be a problem, as suggested in earlier studies [31]. This raises questions about the described positive effects of repeated and integrated education over the years [32]. However, it should also be noted that although hardly any significant difference was found in head-to-head comparisons, the group of students who had received WHO-6-step intervention in both study phases had the highest scores on all domains. Moreover, the additional hours of formal education also increased student satisfaction, which is an important outcome measure in medical educational research [33]. Unfortunately, other outcomes, such as interest in pharmacology and pharmacotherapy and recognition of the importance of these subjects, were hardly affected. As it is stated, 'education is not filling the bucket, but lighting a fire' [34] it would appear that we failed to light a fire for the students and did not succeed in increasing their intrinsic motivation to study pharmacology and pharmacotherapy. Students recognize the importance of these subjects, but are not interested in them, and the educational intervention did not make any difference to this. It might be worthwhile to study intrinsic motivation in future research on pharmacology and pharmacotherapy education.

How robust are the positive effects of the WHO-6-step method on students' pharmacology knowledge and pharmacotherapy skills? And does the WHO-6-step itself actually influence pharmacology knowledge and pharmacotherapy skills? Given the study design with two assessment points for both the Bachelor and Master students, it is highly likely that the results are robust because they were replicated within the study. The crucial question remains, to what extent can these results be attributed to the WHO-6-step method (educational content), rather than the additional hours of education provided (quantity of education) or the introduction of a longitudinal learning programme (teaching strategy). Our results showed that it was the WHO-6-step method

in the learning programme that was responsible for the improvement in pharmacology knowledge and pharmacotherapy skills, because students who received the intervention in the Master phase only performed better than the students who did not receive the intervention, even though the number of contact hours and self-reported self-study hours was similar (17 *vs.* 18 h of formal education). In the Bachelor phase, the improvement in students' pharmacology knowledge may have been due to the four-fold increase in contact hours. It is difficult to determine whether the teaching content (the WHO-6-step method) or the teaching strategy (integrated, longitudinal programme) had the greatest influence on the improvement in pharmacology knowledge and pharmacotherapy skills in this study. This would need to be investigated in a study in which different teaching strategies, with the same educational content, are compared.

## Strengths and limitations

This study is the first to show that a WHO-6-step based learning programme incorporated into the medical curriculum improves students' pharmacology knowledge, pharmacotherapy skills and satisfaction. Selection bias is unlikely, given the large number of students who participated and the high response rate. Moreover, the programme was effective in both the Bachelor and Master phases of the curriculum. However, the study had some limitations. It was carried out in a single centre, and therefore the generalizability of the results to medical students of universities in other countries is uncertain. Given that Dutch medical curricula are very similar (e.g. same entry requirements), it is very likely that the same results would be obtained for students at other Dutch medical schools. Still, the WHO-6-step based learning programme cannot necessarily be directly duplicated in other curricula, because of differences in teacher skills, curricular content, etc. These factors are multifactorial and not static and may even change depending on student group dynamics during medical education. That said, there is no reason to believe that the WHO-6-step programme cannot be implemented in other medical schools. Another potential limitation is that the study had an observational and practice based design and was not a randomized controlled trial [35]. However, randomized controlled trials are very difficult to perform with a real curriculum, and, given its effectiveness, it would be unethical to withhold the WHO-6-step method from half of the students. As a result of our design, a long inclusion period was necessary, which has its disadvantages. As shown in the population characteristics in Table 2, changes in study regulations can affect baseline characteristics. In the Netherlands, the costs of studying are increasing rapidly and this might have resulted in differences in population characteristics. The intervention group was relatively younger, with less study delay. Moreover, the number of female students has increased steadily over the years. These differences were used as covariates in the analyses. Lastly, some comments can be made about the assessment. Most psychometric characteristics were good, although the assessments had a rather low internal consistency. The internal consistency by Guttman Lambda 2 ranged from 0.56 to 0.68 for the easier assessments and from 0.50 to 0.63 for the more difficult assessments. While it is normal to assess scores for an individual, we assessed group means, for which an internal consistency higher than 0.5 is acceptable [36, 37]. A low internal consistency is mainly a problem if there are non-significant results, because it is difficult to detect group differences if the variation in scores is large. The assessment required students to write a prescription, but it can be queried whether this task is useful, given the increase in electronic prescribing. In addition, while it is recognized that there are more pharmacotherapy skills than writing a complete and readable prescription, these other skills, such as communication skills needed for, for example, drug history taking, are hard to assess with a written assessment [38].

## Conclusions

In conclusion, the WHO-6-step method was successfully implemented in a medical curriculum as part of an integrated learning programme and had positive effects on students' knowledge of basic and applied pharmacology, pharmacotherapy skills, and satisfaction and confidence in prescribing. Both Bachelor and Master students can benefit from the method. As prescribing is a high risk task, the availability of evidence-based training is important. Further studies are needed to establish whether patients benefit from being treated by doctors trained with this method.

## Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare Professor Dr. Brouwers reports personal fees from Consultancy Europe-Expro Muenchen [Germany], personal fees from Consultancy Eijkman & Kuipers [Netherlands], personal fees from Consultancy W-Pharma Wavre [Belgium], personal fees from President Ethical Review Board, personal fees from Pharmaceutisch Weekblad, personal fees from Tijdschrift voor Praktijkgerichte Farmacotherapie MFM, grants from St. Ondersteuningsfonds EPHOR, all outside the submitted work; All other authors declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years

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## Contributors

Wrote manuscript: C. Keijsers, W. Segers, L. Keijsers, P. Jansen, D. de Wildt, J. Brouwers

Designed research: C. Keijsers, P. Jansen, D. de Wildt, J. Brouwers

Performed research: C. Keijsers, P. Jansen, W. Segers

Analysed data: C. Keijsers, L. Keijsers

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