# 1

# General Introduction

> The only thing I could safely prescribe was paracetamol and I prescribe lots of different medications all the time...which I've done on the basis of common sense or asking as opposed to actually knowing how to. (*Junior doctor*)[1]

Prescribing medicines is a privilege that distinguishes a medical doctor from other healthcare providers and carries with it responsibility for patients, society, and the profession. In order to choose the most suitable drug treatment for an individual patient, doctors have to prescribe rationally. Rational prescribing as defined by the World Health Organisation (WHO) is "the situation in which patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for a sufficient length of time, with the lowest cost to them and the community".[2] In order to teach rational prescribing to medical students, the WHO published the Guide to Good Prescribing in 1994[2] and the Teachers Guide to Good Prescribing in 2001.[3] These manuals provide a 6-step method for rational prescribing (WHO 6-step) as shown in Figure 1. The WHO 6-step method has been adopted worldwide by many medical schools and has proven to be the only educational intervention with high-quality evidence of effectiveness.[4,5]

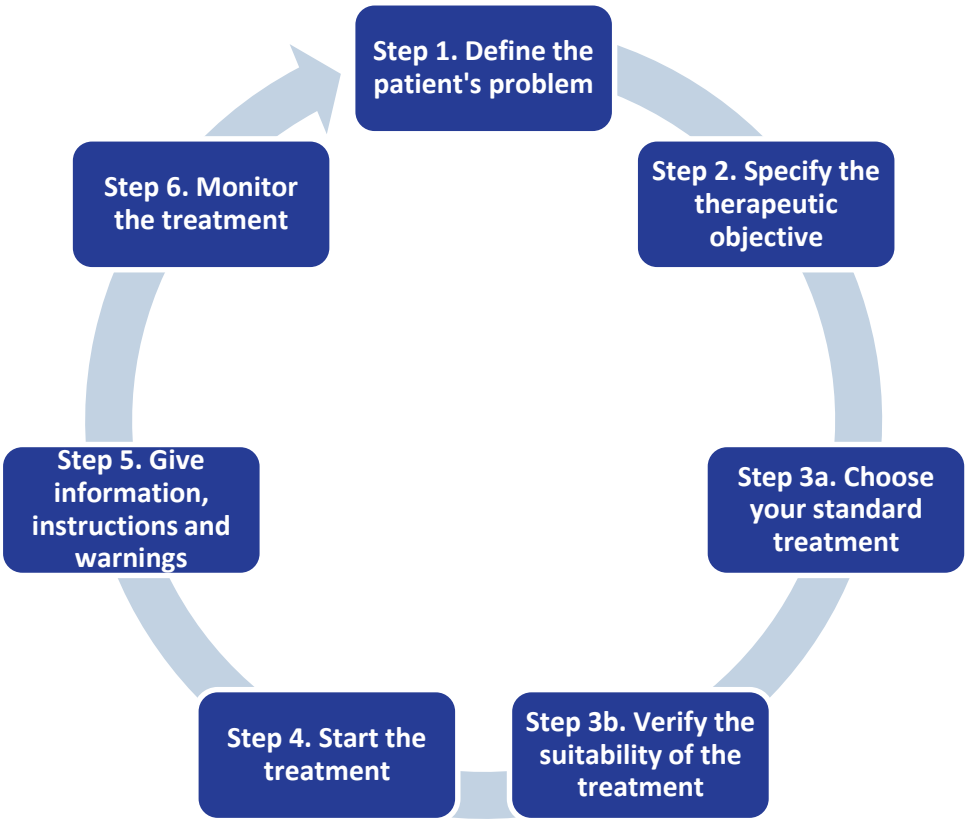


**Figure 1.** WHO 6-step method for rational prescribing.

## Prescribing competence

The workload of prescribers is increasing progressively because of several trends, such as increased numbers of patients and medicines, sicker and older patients, more complicated regimens because of polypharmacy and multimorbidity, higher patient expectations, and increasing pressure on healthcare systems.[6] Specifically, the demands being placed on junior doctors in hospitals are high because they prescribe many times a day, often high-risk therapies such as anticoagulants, insulin and opioids analgesics. Moreover, they have the least experience and usually prescribe with minimal supervision from senior clinicians and work under high pressure with many patients to care for and a high patient throughput.[1] The complexity of prescribing in daily clinical practice as junior doctor is illustrated by the case described in Box 1.

As illustrated by this case, rational prescribing is a challenging task for junior doctors since it involves a mixture of knowledge, skills and attitudes integrated into the complex social context of the clinical workplace.[7] Poor prescribing may lead to prescribing errors and adverse drugs events (ADEs), which may cause prolonged hospital stays, unplanned hospital readmissions, significant morbidity and mortality, and high financial costs for healthcare authorities.[8,9] In 2008, the HARM study reported that 2.4% of all hospital admissions and 5.6% of all emergency admissions in the Netherlands were related to ADEs.[9] Almost half (46%) of these admissions were potentially preventable. One or more prescribing errors were detected in most (71%) of the preventable admissions. In other European countries, 2.5% to 10.6% of all hospital admissions are related to ADEs, of which prescribing problems are also the most common underlying cause.[10] A recent

An 82-year-old woman presented to the emergency department after a fall at home. She was unable to stand or bear weight and complained of right hip pain. Her medical history reported chronic kidney failure, depression, diabetes mellitus type 2, essential hypertension, heart failure and hyperlipidaemia. Her medications on admission were citalopram, enalapril, furosemide, gliclazide, metformin, metoprolol, simvastatin and spironolactone. A hip radiograph showed a right intertrochanteric fracture for which she received a dynamic helical hip screw. The day after the operation, the patient reported increasing pain, not diminishing with paracetamol, and nausea. The new ward doctor decided to prescribe medicines to relieve her symptoms. Since he had little clinical experience in pain management, he wanted to refer to the local hospital guideline but could not find it. He was distracted by a phone call from a nurse about a new patient coming over from the acute admission unit. Since he had more patients to visit during the ward round, the doctor decided to prescribe diclofenac for the pain and ondansetron for the nausea, which he had done previously for other patients, with generally good results. The electronic prescribing system triggered several alerts, but because he was pressed for time he did not pay close attention to them. In the following days, the patient reported fatigue and lethargy. Laboratory tests showed a critically elevated serum potassium level and a seriously reduced kidney function, most likely due to a combination of diclofenac, enalapril, furosemide, and spironolactone. These drugs were immediately stopped, and the patient recovered after treatment with intravenous calcium, insulin/glucose, and sodium polystyrene sulfonate.

**Box 1.** Prescribing in daily clinical practice.

report showed that the number of medication-related hospital admissions in the Netherlands has increased from ±19,000 (2.4%) in 2008 to ±49,000 (3.0%) in 2013, although this increase is partly due to the increasing age and frailty of patients. The healthcare costs of medication-related hospital admissions are substantial. In the Netherlands, preventable medication-related admissions amount to €5.7 million per 1 million inhabitants annually.[9] In the UK and Germany, the annual costs are estimated to be €11.9 and €5.2 million per 1 million inhabitants, respectively.[10,11] As mentioned earlier, junior doctors tend to make prescribing errors. Studies in the UK found an error rate of 7-10% among prescriptions written by junior doctors while senior consultants, both in hospital and general practice, have a prescribing error rate of around 5-6%.[1,12-15] In the Netherlands, junior doctors also make more prescribing errors than their senior colleagues.[16] There are a number of possible causes for the high error rate among junior doctors. Besides environmental (e.g., high workload, distractions) and patient (e.g., polypharmacy, multimorbidity) factors, individual (e.g., lack of experience and knowledge) and organizational (e.g., lack of access to local guidelines) factors contribute to the occurrence of these errors.[12,17,18] A lack of sufficient prescribing competencies (i.e., knowledge, skills and attitudes) among junior doctors is frequently mentioned,[1,12,17-20] which might be due to inadequate undergraduate education and training in clinical pharmacology and therapeutics (CPT). Indeed, recent studies in the UK showed that medical students and recent graduates feel underprepared for, and anxious about, prescribing,[21-23] a concern echoed by their supervisors.[24] Additionally, medical students tend to copy the drug treatment of their supervisors during clinical clerkships instead of basing their choices on their own independent analysis of the problem.[25] Although it is often stated that medical students in Europe lack prescribing competencies, which can ultimately result in prescribing errors with negative patient outcomes, reliable evidence is hard to find because assessment methods vary significantly between medical schools and none have been applied or validated internationally. This was one of the motives for the studies described in this thesis.

From an educational point of view, prescribing competencies can be described as a combination of knowledge, skills and attitudes.[26] Knowledge encompasses pharmacological facts and basic principles that are necessary to make rational and optimal therapeutic plans; it includes the principles needed to organize these facts into useful information and to recognize when essential facts are missing.[26] Skills include cognitive (e.g., verifying the suitability of the drug), motor (e.g., administering a drug) and communication (e.g., providing information and instructions to the patient) skills that are important for therapeutic reasoning and rational prescribing, as defined by the WHO 6-step method.[2] Attitudes are the perception of what constitutes valid information, what kind of information is likely to be in error, and what new information must be continuously acquired from reliable sources.[26] Different evaluation methods can be used to assess these competencies in medical students. According to the assessment framework of Miller (Figure 2),[27] medical students must demonstrate that they have *factual knowledge* to prescribe rationally, for example in a multiple-choice examination. Subsequently, they must demonstrate that they *know how* to use this factual knowledge that they have acquired, for example by formulating a therapeutic plan for a written patient case (application of knowledge). Also, students must not only be able to demonstrate that they *know* and *know how*, but also need to *show how* they prescribe when

confronted with a simulated patient (demonstration of prescribing). Lastly, it is important what a medical student actually *does* when prescribing in clinical practice for real patients under the supervision of a senior clinician (prescribing integrated into practice). Since few studies have evaluated students' prescribing competencies according to these four competence levels, this was another reason to perform the studies described in this thesis.

## Medical education in Europe

> ...if a nurse says, "Oh prescribe some sedation for this patient," well, you know, you've got to know which one to give, how much to give, whether it interacts with anything else she's on? Can she have it? You know, all these factors that we just never really covered [during medical school]...it's very much you pick it up as you go along.[1] (*Junior doctor*)

As mentioned earlier, a potential reason for the lack of prescribing competencies among junior doctors could be shortcomings in CPT education in the undergraduate medical curriculum, both in quality and quantity. In the 1960s, CPT emerged as a new discipline, and many medical schools incorporated CPT into their curricula as a distinct course.[6] Since the introduction of problem-based learning between the 1970s and the 1980s, medical curricula have changed from more basic scientific disciplines, such as pharmacology, physiology and anatomy, to integrated organ- and disease-based programmes (see example in Figure 3). This transformation has come in response to concerns that students were being overburdened with scientific facts and that there was too little training in problem-solving and communication skills. As a result, the clinical knowledge and performance of medical students have improved both before and after graduation.[28,29]

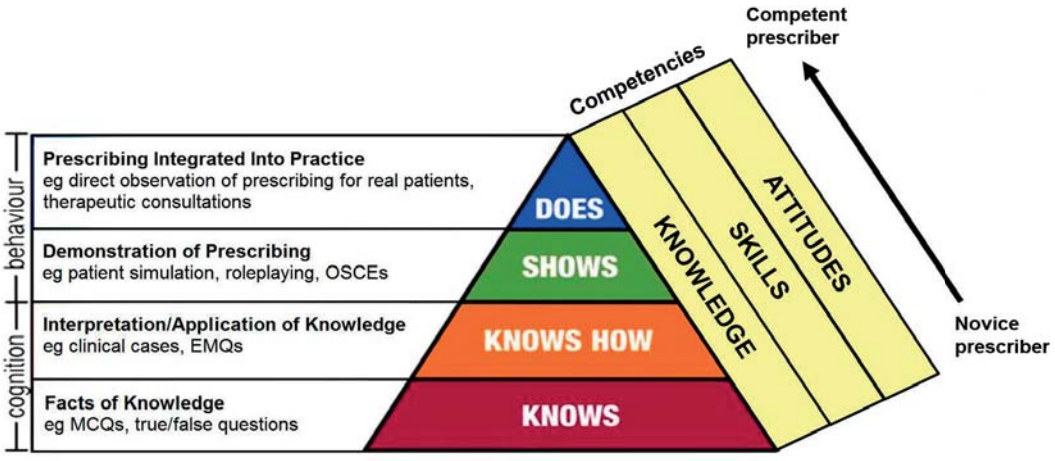


**Figure 2.** Miller's pyramid adapted to evaluate prescribing competencies. Based on the work of Miller;[27] adapted from Burn & Mehay (Jan 2009). EMQs, extended matching questions. MCQs, multiple-choice questions. OSCE, objective structured clinical examination.

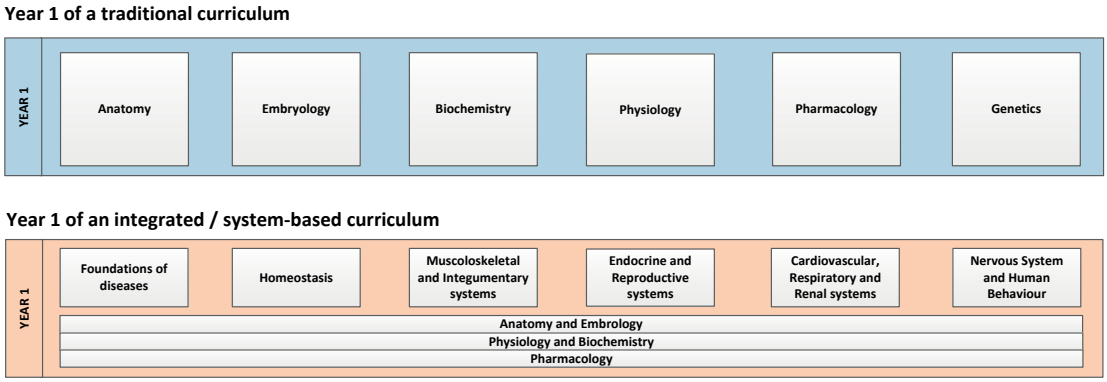


**Figure 3.** Example of the first year of a traditional and integrated medical curriculum.

However, CPT – a discipline that is factually rich and not organ-based – was often integrated into problem-orientated courses and became less visible in medical curricula, even totally disappearing in some.[30] Indeed, a survey conducted under the auspices of the WHO in 1988 showed that a large proportion of European medical schools devoted no or very little teaching time to clinical pharmacology and that there was a lack of trained individuals and posts in this field.[31] So, has CPT education in European medical schools improved in the meantime? The results of several local studies are worrying. In Italy, a survey among physicians in 1998 showed that undergraduate pharmacology teaching was mainly theoretical and that more attention should be given to clinical pharmacology.[32] In Germany, 8 of 35 medical schools in 2004 had no clinical pharmacology department responsible for teaching.[33] In France, a survey among medical schools in 2006 showed that too little time was devoted to teaching basic and clinical pharmacology.[34] In the UK, a survey among CPT teachers in 2009 showed large differences in the quality and quantity of CPT education between medical schools.[35] This marked variation in CPT education was also found in a survey of Dutch medical schools in 2012. Additionally, half of the Dutch medical schools hardly assessed the prescribing competencies of their students before graduation.[36] Despite these concerns, the current structure of CPT education in Europe is not known and this should be clarified in order to identify whether poor undergraduate CPT education is the reason for the lack of prescribing competencies among junior doctors. This was another motive for our studies.

## European core curriculum

A key objective of every medical school should be to produce graduates who are competent to prescribe rationally. In order to do so, medical schools should teach and assess CPT in an effective manner in the undergraduate medical curriculum. Discussion about which CPT topics should be covered in the medical curriculum and how and when these should be taught and assessed has been ongoing for more than a century. As early as 1903, Dr Reynold W. Wilcox, president of the American Therapeutic Society, stated:

> ...the day had come when something more is demanded of the practitioner or physician-consultant than a diagnosis...our obligation will not be satisfied until general principles have been fitted to the particular patient. The question is: How shall we teach the medical student so that he shall be best fitted to become a useful practitioner?[37]

During the last 40 years, numerous clinical and basic pharmacologists and other educators have attempted to define a 'core' curriculum in CPT education. In 1983, Spector & Roberts were the first to specify which CPT topics should be covered in the medical curriculum in the USA, based on their own educational experience.[38] Three years later, Nierenberg defined which topics should be covered and how these should be taught and assessed, based on a survey among clinical pharmacologists and deans in the USA.[39] In 1990, the Council for Medical Student Education in Clinical Pharmacology and Therapeutics reached consensus on what medical students need to learn, understand and be able to apply in order to become competent prescribers.[26] In 2008, a similar consensus report was published by the Association of American Medical Colleges (AAMC).[40] Also educators in Europe have tried to define the content of a core curriculum in CPT. In the UK, Walley & Webb described which knowledge, skills and attitudes medical students should learn in order to become competent prescribers, based on a Delphi study among clinical pharmacologists in the UK and Ireland.[41] This Delphi study served as a basis for the 2003 British Pharmacological Society (BPS) core curriculum described by Maxwell & Walley,[6] which was further refined by Ross & Maxwell in 2012.[42] In the Netherlands, de Vries *et al*. described which skills are necessary for rational prescribing.[43] In Sweden, Midlöv *et al*. defined essential prescribing competencies for newly qualified doctors, based on a Delphi study among physicians.[44] However, all these studies were mainly focused on the local setting in a specific European country. To date, there has been no consensus about what European medical students should know about CPT by the time they graduate, and how CPT should be taught and assessed in the undergraduate medical curricula of European medical schools. This is getting more important due to increased cross-border mobility of medical students and junior doctors[45] and was the motivation for the studies described in the last part of this thesis.

## AIMS AND OUTLINE OF THE THESIS

The goal of the studies described in this thesis is to improve CPT education in the undergraduate medical curricula of European medical schools and ultimately contribute to improvements in the quality and safety of patient care. From the above, we know that the current level of prescribing competencies of European medical students is not entirely clear, that little is known about the current structure of CPT education in European medical schools, and that there is no consensus about what European medical students should know about CPT by the time they graduate, and how CPT should be taught and assessed during undergraduate medical education in European medical schools. To this end, three aims were formulated.

### Aim 1. To gain insight into the current level of prescribing knowledge skills, and attitudes of European medical students, assessed in different context settings

**Chapter 2.1** provides an overview of the literature evaluating the prescribing competencies of final-year medical students. **Chapter 2.2** investigates the prescribing knowledge, skills and attitudes of 895 final-year medical students from 17 European medical schools, using a standardized *computer-based* assessment. In **Chapter 2.3**, we re-analysed data from the study described in the previous chapter and investigated the correlation between factual drug knowledge and drug treatment appropriateness among final-year medical students from European medical schools. In the study described in **Chapter 2.4**, we studied the association between self-reported confidence in prescribing and prescribing skills in fourth-year medical students from one medical school, assessed in a *simulated patient* setting. **Chapter 2.5** evaluates the level of prescribing skills and attitudes of final-year medical students, assessed in a *real patient* setting at the end of a context-learning pharmacotherapy programme.

### Aim 2. To investigate the current quantity and quality of clinical pharmacology and therapeutics education in the undergraduate medical curriculum of European medical schools

In the multicentre study described in **Chapter 3.1**, we studied the current structure, delivery and assessment of CPT education in 185 medical schools in 27 European Union (EU) countries. We asked teachers with overall responsibility in these medical schools about the quality and quality of the teaching and assessment methods in their CPT programme. In **Chapter 3.2**, we investigated the quality of outcomes measures used in studies of CPT education.

### Aim 3. To investigate which learning outcomes medical students should have acquired in order to prescribe rationally by the time they graduate and how these should be taught and assessed during undergraduate medical education in European medical schools

**Chapter 4.1** describes a Delphi study investigating what recently graduated doctors should know about commonly prescribed drugs in order to prescribe rationally in daily practice. In another

Delphi study (**Chapter 4.2**), we aimed to reach consensus on key learning outcomes for teaching and assessing CPT in the undergraduate medical curricula of European medical schools. Moreover, we aimed to develop a blueprint for a European core curriculum describing when and how these learning outcomes could be taught and assessed.

## DEFINITIONS USED IN THIS THESIS

Prescribing education can be divided into basic pharmacology, clinical pharmacology and pharmacotherapy. Basic pharmacology is defined as education about the basic principles of how drugs act in biological systems, including pharmacodynamics (e.g., receptor and other drug targets), pharmacokinetics (e.g., absorption, distribution, metabolism, excretion) and pharmacogenetics; clinical pharmacology refers to the application of pharmacological principles and methods in clinical practice (e.g., rational drug selection, adverse drug reactions, drug interactions, errors, adherence); and pharmacotherapy refers to the process of rational prescribing for specific clinical conditions (i.e., how to choose a specific drug for an individual patient).

## LIST OF ABBREVIATIONS

| | |
|---|---|
| **ACE** | Angiotensin-converting enzyme |
| **ADR** | Adverse drug reaction |
| **AT** | Austria |
| **BE** | Belgium |
| **BEME** | Best Evidence Medical Education |
| **BG** | Bulgaria |
| **BPS** | British Pharmacological Society |
| **BSAC** | British Society Antimicrobial Chemotherapy |
| **CAP** | Community acquired pneumonia |
| **CMSECPT** | Council for Medical Students Education in Clinical Pharmacology and Therapeutics |
| **COPD** | Chronic Pulmonary Obstructive Disease |
| **CPT** | Clinical pharmacology and therapeutics |
| **CY** | Cyprus |
| **CZ** | Czech Republic |
| **DE** | Germany |
| **DOTS** | Directly Observed Treatment Short course |
| **EACPT** | European Association for Clinical Pharmacology and Therapeutics |
| **EDK** | Essential Drug Knowledge |
| **EE** | Estonia |
| **EL** | Greece |
| **EMA** | European Medicines Agency |
| **EMQ** | Extended matching questions |
| **ES** | Spain |

| | |
|---|---|
| **EU** | European Union |
| **FI** | Finland |
| **FR** | France |
| **FY** | Foundation year |
| **GERD** | Gastroesophageal reflux disease |
| **GOLD** | Global Initiative for Chronic Obstructive Lung Disease |
| **GP** | General practitioner |
| **HR** | Croatia |
| **HU** | Hungary |
| **IE** | Ireland |
| **IPS** | Indian Pharmacological Society |
| **IT** | Italy |
| **IUPHAR** | International Union of Basic and Clinical Pharmacology |
| **IV** | Intravenous |
| **LT** | Lithuania |
| **LU** | Luxembourg |
| **LV** | Latvia |
| **MCQ** | Multiple-choice question |
| **MERSQI** | Medical Education Research Quality Instrument |
| **ML** | Mixed learning |
| **MRSA** | Methicillin-resistant *Staphylococcus aureus* |
| **MT** | Malta |
| **NL** | Netherlands |
| **NO** | Norway |
| **NOTIP** | Network Of Teachers In Pharmacotherapy |
| **NSAID** | Non-steroidal anti-inflammatory drug |
| **OSCE** | Objective Structured Clinical Examination |
| **P-drug** | Personal drug |
| **PBL** | Problem-based learning |
| **PL** | Poland |
| **PRISMA** | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| **PT** | Portugal |
| **RO** | Romania |
| **RS** | Serbia |
| **SD** | Standard deviation |
| **SE** | Sweden |
| **SI** | Slovenia |
| **SK** | Slovakia |
| **SMPC** | Summary of Product Characteristics |
| **TC** | Therapeutic consultation |
| **TDM** | Therapeutic drug monitoring |

| | |
|---|---|
| **TL** | Traditional learning |
| **UK** | United Kingdom |
| **USA** | United States of America |
| **USPI** | United States Prescribing Information |
| **VUmc** | VU University Medical Center |
| **WHO** | World Health Organisation |
| **WHO GGP** | World Health Organisation Guide to Good Prescribing |

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