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ORIGINAL ARTICLE

Defining and unpacking the core concepts of pharmacology education

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Abstract

Pharmacology education currently lacks a research-based consensus on which core concepts all graduates should know and understand, as well as a valid and reliable means to assess core conceptual learning. The Core Concepts in Pharmacology Expert Group (CC-PEG) from Australia and New Zealand recently identified a set of core concepts of pharmacology education as a first step toward developing a concept inventory—a valid and reliable tool to assess learner attainment of concepts. In the current study, CC-PEG used established methodologies to define each concept and then unpack its key components. Expert working groups of three to seven educators were formed to unpack concepts within specific conceptual groupings: *what the body does to the drug* (pharmacokinetics); *what the drug does to the body* (pharmacodynamics); and *system integration and modification of drug–response*. First, a one-sentence definition was developed for each core concept. Next, sub-concepts were established for each core concept. These twenty core concepts, along with their respective

Marina Santiago and Elizabeth A. Davis contributed equally to the study.

The authors mourn the loss of our wonderful colleague, friend, and co-author, Associate Professor Elizabeth Davis, who passed away on October 26, 2021, and pay tribute to her enormous contribution to pharmacology education.

definitions and sub-concepts, can provide pharmacology educators with a resource to guide the development of new curricula and the evaluation of existing curricula. The unpacking and articulation of these core concepts will also inform the development of a pharmacology concept inventory. We anticipate that these resources will advance further collaboration across the international pharmacology education community to improve curricula, teaching, assessment, and learning.

KEYWORDS
concept inventory, core concept, health science education, pharmacology education, postgraduate education, science education, undergraduate education, unpacking

1 | INTRODUCTION

In the early 1990s, physics educators were astonished to discover the low level of conceptual understanding of their graduates. Hestenes et al.[1] demonstrated that even the best-prepared fourth-year physics majors at elite US institutions were unable to apply key concepts. Since then, dedicated scholarly efforts to improve conceptual learning have transformed physics education internationally. Well-documented gains in students' deep understanding of core physics concepts, as well as in educators' ability to promote and assess that learning, have been among the true success stories of higher education reform. The strides made by physics educators, and more recently across a range of other disciplines, have yet to be made in the discipline of pharmacology.

A consensus list of core concepts could advance pharmacology education in a number of ways. Disciplines such as psychology[2,3]; information technology/cybersecurity[4]; dietetics[5]; biology,[6]microbiology,[7,8] and mathematics[9] have shown those core concepts can provide disciplines with evidence-based foundations for conceptual curricula. Concept inventories—valid and reliable tools to assess the attainment of core concepts—can be developed to assess and evaluate these conceptual curricula. In biological sciences, for example, core concepts provide focus on what is important and encourage depth in the face of exponential growth in content.[10,11] Pharmacology is one of several health science disciplines in which the explosion of biomedical knowledge troubles curriculum designers and educators. Moreover, health professional educators have specific needs to integrate knowledge from a range of primary disciplines, including chemistry, physiology, mathematics, and statistics.[10] Core concepts would therefore assist educators and students to focus on deep learning and the development of enduring conceptual frameworks.

1.1 | Using and unpacking core concepts

The identification of core concepts within a discipline allows educators to focus on the foundational knowledge that is most important for graduates to know and understand. However, for educators to embed core concepts attainment into their curricula some disciplines have found it useful to develop supporting resources and materials. In biology, the *Vision and Change* initiative[12] has been extensively developed by expert educators, and includes definitions of core concepts[10] and instruments to assist educators to teach and assess student learning of core concepts.[13] In some sub-disciplines of biology, such as physiology, more extensive resources have been developed to unpack each core concept in detail, identifying sub-concepts and cases that exemplify each concept.[11,14] The methods used to provide these resources usually involved multiple stages of discussions among many educators: for example, *Vision and Change* emerged from "a series of conversations at regional and national meetings… more than 500 biologists and biology educators discussed the need to reform undergraduate biology education and provided a set of unifying recommendations".[10] In physiology,Michael et al[11] developed a more rigorous and stage-wise method for unpacking core concepts, with an expert group developing a proposed unpacking, which was then refined via input from survey respondents.

In pharmacology, as in other disciplines, identifying the core concepts was a necessary first stage,[15] but there are additional tasks that must be accomplished before these core concepts can be used to improve pharmacology teaching and learning. Educators will need more than new names for core concepts in order to use them to inform curriculum design and teaching approaches.

This study represents the second stage, namely to define and unpack the core concepts of pharmacology education, describing each element and identifying the key underpinning facets (sub-concepts). We aimed to build on and adapt methods developed by colleagues in physiology.[11] Experienced Australasian pharmacology educators worked iteratively to unpack the 20 core concepts, after which a round of feedback from an independent group of Australasian pharmacology experts helped us further clarify and refine the subconcepts. By unpacking this initial set of core concepts of pharmacology education, this Australasian study sought to create a foundation upon which the international pharmacology community could build.

The third stage will progress our work from Australia and New Zealand[15] to produce a global list of core concepts in the discipline, and a concept inventory to test their attainment. This work, now underway, will involve international pharmacology educators,

researchers, and students and will be conducted under the banner of the International Union of Basic and Clinical Pharmacology (IUPHAR) Education Section.

2 | METHODS

2.1 | Ethics approval

MUHREC project ID 22727 "Core concepts" was approved as low risk by the Monash University Human Research Ethics Committee.

2.2 | Overall study design

We previously identified core concepts of pharmacology education using a systematic process, starting with an exploratory survey, then utilizing a "Core Concepts of Pharmacology Education Expert Group" (CC-PEG) to extract and identify core concepts from survey responses.[15] The same group conducted the current study, with the aim of unpacking those core concepts. The CC-PEG comprised 12 participants (4 male, 8 female) who were selected, based on expressions of interest, to form the expert group. This group was pharmacology educators who had, on average: 17 years of pharmacology teaching experience; 4 pharmacology teaching awards, and 24 publications (a mix of education and biomedical research). Eleven CC-PEG members represented four of the six states and one of the two territories in Australia, and the twelfth represented New Zealand. The independent expert review was carried out by five internationally recognized experts in pharmacology; four male and one female.

2.3 | Expert group activities—Working Group formation

The CC-PEG met in a virtual environment each fortnight for approximately 3 months during 2021. The 20 core concepts were divided into three clusters of related concepts for unpacking. Three working groups were created—one to focus on each cluster—each containing between three and six CC-PEG members, who self-nominated for the working group(s) that best reflected their expertise.

Two working groups of the CC-PEG were named using common chapter headings within introductory sections of textbooks. A third working group was formed to unpack concepts that did not fit into either of the above groups, such as *individual variation*, or had not met the 80% agreement threshold set in the first stage of this project[15]: *pharmacological homeostasis* and *drugs and complex systems*. Given that the agreement for these two core concepts was more than 70%, we wanted to determine whether unpacking these concepts would reveal latent concepts that could be more clearly labeled and articulated upon discussion. The final working group structure was therefore:

- Pharmacokinetics, which we termed "What the body does to the drug" (six concepts),
- Pharmacodynamics, which we termed "What the drug does to the body" (nine concepts), and
- System integration and modification of drug–response (four concepts).

Finally, during discussions within the groups, it became clear that we needed one additional and over-arching core concept, namely *drugs*, and this concept was unpacked by the entire CC-PEG. Therefore, the final number of core concepts unpacked was 20.

2.4 | Unpacking of core concepts within working groups

Members were asked to define each of the concepts assigned to their working group, using a single sentence, and then to unpack concepts by applying the instructions below, which ensured that all concepts were unpacked by at least one group member:

> "Unpacking" of a core concept into its constituent ideas (sub-concepts). Please unpack each concept by identifying 2-4 sub-concepts that must be attained in order to understand and apply the "parent" concept.
>
> For example, in physiology the core concept of homeostasis was unpacked into sub-concept Homeostatic processes require a sensor inside the body. We decided as a group to stay with one level of sub-concepts as standard, but if you are so inclined you may identify sub-sub-concepts! Please make sure you describe each sub-concept in a sentence.

Working groups met initially to reach consensus on both the wording of the definition and the specific constituent ideas included as sub-concepts.

2.5 | Refinement of unpacking of core concepts across working groups

CC-PEG members were then asked to review and provide input on the definitions and sub-concept descriptions for all core concepts other than the ones they had developed within their own working group. The feedback provided included: (i) suggested changes to the wording of definitions and sub-concepts; (ii) inclusion of new sub-concepts and deletion of others; and, (iii) transfer of sub-concepts to another, more appropriate, core concept. After consulting with the members, working group leaders (MS, ED, and PW) were responsible for making final decisions on changes to the unpacking of their core concepts.

2.6 | Independent expert review

Once a complete draft of the definitions of each concept and related sub-concepts had been produced, we consulted experts in pharmacology from Australia and New Zealand, who had not previously been involved in the process, to provide input. Five internationally recognized experts, each having delivered numerous invited international pharmacology plenaries, provided detailed feedback on the unpacking of the core concepts, with the final decision again made by working group leaders. The CC-PEG met a further three times to incorporate the feedback received and finalize the core concept unpacking.

2.7 | Sources of information used

CC-PEG members were asked to record any textbooks, online materials, or other sources of information to which they referred when developing their definitions of concepts or identifying sub-concepts.

2.7.1 | Textbooks and publications

Rang, H.P., Flower, R., and Henderson, G. (2018). Rang & Dale's Pharmacology. 9th Ed. Elsevier. Amsterdam.

Derendorff, H. and Schmidt, S. (Eds) (2019) Rowland and Tozer's Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications. 5th Ed. Wolters Kluwer.

Neubig, R.R., Spedding, M., Kenakin, T., Christopoulos, A. and International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification. (2003) *International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification. XXXVIII. Update on terms and symbols in quantitative pharmacology*. Pharmacological Reviews 55(4): 597–606.

Brunton, L.L., Chabner, B., and Knollmann, B.C. (Eds.) (2018) Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th Ed. McGraw-Hill Education New York, NY, USA.

Birkett, D.J. (2009) Pharmacokinetics Made Easy. 2nd Ed. McGraw-Hill Education. Sydney, Australia.

Katzung, B.G., and Trevor, A.J. Basic and Clinical Pharmacology. 15th Ed. McGraw-Hill Education. Sydney, Australia.

Kelly, E. (2013). Efficacy and ligand bias at the μ-opioid receptor. British Journal of Pharmacology, 169(7), 1430–1446.

2.7.2 | Websites

https://www.msdmanuals.com
https://www.pharmacologyeducation.org
https://www.icp.org.nz

3 | RESULTS

3.1 | Unpacking of core concepts

The definitions and unpacking of each of the 20 identified core concepts of pharmacology education are provided below. During the unpacking process, questions arose as to whether some of the concepts should be renamed. In some cases, the CC-PEG agreed to make minor modifications following those discussions. For example, *drug selectivity and specificity* was renamed *drug selectivity* given that drug specificity for a single target is now recognized as a theoretical concept not supported by empirical evidence, at least for small molecule drugs and likely even for antibody and nucleic acid therapeutics. For each concept described below, the opening sentence names and defines the concept. Sub-concepts that are required to fully understand the primary concept are then provided as bullet points.

3.2 | Core concept 1: The central concept of pharmacology

1. **A drug** is a substance that, when introduced into the body, produces a biological effect.

- Drugs can be classified based on the nature of the target to which they bind, the clinical outcome they produce, or their physicochemical properties.
- Some drugs are small molecules that produce effects via interactions with proteins, whilst other drugs, such as antibodies, antisense oligonucleotides, or small interfering RNA (siRNA), exert their effects as biological agents.
- Drugs may exert their effects through multiple targets and/or target subtypes.
- Some drugs do not bind to a macromolecular target; rather, they alter internal conditions to elicit a response (e.g., antacids change stomach pH; activated charcoal binds toxins and chemicals to prevent their absorption).

3.3 | Core concepts 2–7: What the body does to the drug

2. **Drug absorption** refers to the movement of the drug from its site of administration to the systemic circulation.

- The interaction between the physical and chemical characteristics (e.g., ionization, lipophilicity, molecular size, and functional groups) of a drug and the various environments encountered during absorption determine how (and if) it enters the body.
- The transfer of a drug across a membrane may involve a number of processes including active transport (uptake/efflux); passive diffusion; carrier-mediated transport.

- The absorption rate is a measure of how quickly the drug enters the biological system.
- The release of a drug from its dosage form, and into solution, determines whether a drug is available to be absorbed, as well as the rate and extent of absorption.

3. **Drug distribution** refers to reversible transfer of a drug between locations in the body after absorption.

- The physical and chemical properties (e.g., ionization, lipophilicity, molecular size, and functional groups) of a drug influence its movement into and between different biological compartments.
- The compartment characteristics (e.g., pH, blood flow, lipid:water ratio, and uptake/efflux transporters) influence the differential distribution of drug throughout the body.
- Drug binding to plasma proteins and tissue constituents can influence the movement of a drug within the body.
- The apparent volume of distribution is a theoretical concept reflecting the extent to which the drug has moved from the plasma into the tissues.

4. **Drug metabolism**, or biotransformation, refers to the chemical modification of the drug within the body.

- Biotransformation may occur through functionalization (e.g., reduction, oxidation, or hydrolysis), or by conjugation with other biomolecules.
- The efficiency of drug-metabolizing enzymes is influenced by multiple factors, including genetic variation, disease state, and the co-administration of drugs that increase (induce) or decrease (inhibit) enzyme activity.
- Biotransformation usually facilitates the removal of the drug from the body.
- The product of biotransformation (metabolite) has its own absorption, distribution, metabolism, excretion, and potential drug activity.

5. **Drug excretion** refers to the physical processes leading to the irreversible removal of drug and its metabolites from the body.

- The removal of a drug from the body may occur via the kidneys into the urine, through the hepatobiliary system, or through other body systems (e.g., breast milk, lungs, skin, and saliva).
- Drug excretion by an organ is dependent on the physicochemical properties of the drug, as well as the anatomy and physiology of the organ (including the occurrence of transporters).

6. **Drug elimination** refers to the loss of drug through metabolic or excretion processes, so that it is no longer able to be measured in its original form. (Elimination differs from excretion in that it includes both the chemical modification and the physical removal of the drug, whereas excretion involves only the physical removal processes.)

- Drug elimination is usually influenced by the concentration of the drug and its clearance, which is a measure of the efficiency of the removal mechanism.
- Drug clearance is the volume of plasma that is cleared of the drug per unit time (e.g., liters/hour).
- Overall drug clearance is the sum of hepatic clearance, renal clearance, and clearance by other routes.
- If the rate of elimination equals the rate of administration, a steady-state concentration of the drug is achieved.
- Elimination half-life is the time taken to reduce the drug concentration in the plasma by half.

7. **Bioavailability** refers to the fraction of the administered dose that reaches the systemic circulation as an unmodified drug.

- Bioavailability is quantified by comparing the area under the curve of the plasma concentrations achieved with a formulation compared with that seen after intravenous administration.
- The concentration of available drug in the plasma is influenced by its release from the administered preparation, as well as its absorption, excretion, and metabolism.
- Only a fraction of the drug may enter the systemic circulation if it undergoes pre-systemic biotransformation, which is referred to as first-pass metabolism.

3.4 | Concepts 8–16: What the drug does to the body

8. **Drug target** refers to the site to which the drug binds to produce an effect.

- A drug target is usually a macromolecule.
- Molecular drug targets are usually proteins, or less commonly, nucleic acids.
- Most drugs exert their effect through interaction with "classic" protein targets such as receptors, enzymes, ion channels, and transporters.
- Interaction of a drug with a target is described in different ways depending on the target (e.g., agonist, antagonist, substrate, and inhibitor).

9. **Mechanism of drug action** refers to the way in which a drug interacts with its target to modify biological function.

- Drugs usually alter the rate or magnitude of an intrinsic response.
- Drugs can either activate, inhibit, enhance, or attenuate intrinsic responses.
- Many drugs bind to the same site (orthosteric site) within a protein as an endogenous activator, mimicking or inhibiting the action of the endogenous activator.
- Some drugs exert their effects by binding to an allosteric site that is spatially distinct from the active, orthosteric, binding site.

10. **Drug affinity** refers to the ability of a drug to bind to its target.

- Affinity is dependent on the chemical interactions between the drug and the target (bonding), as well as the steric match of the drug to its target (conformation and size).
- Affinity is commonly quantified through the determination of the concentration of drug required to occupy 50% of the drug target at equilibrium (K_D, equilibrium dissociation constant).

11. **Drug efficacy** refers to the ability of a drug to produce a given response from the target.

- Efficacy represents the degree to which different drugs, acting at the same target, produce variable magnitudes of response when occupying the same proportion of target molecules.
- Efficacy is graded (not all-or-nothing) and is dependent on the drug, the target, and tissue components.
- Full agonists produce the maximal response of the system.
- Partial agonists do not produce the maximal system response even at saturating concentrations.
- Antagonists have zero efficacy and produce no response when tested in isolation.
- Inverse agonists reduce basal system responses by suppressing spontaneous receptor activity.
- Clinical efficacy describes how well a drug treatment achieves its therapeutic aim and is distinct from drug efficacy.

12. **Drug selectivity** refers to the concentration-dependent preference of a drug for one target over others.

- Most drugs show selectivity, based on the relative affinity of the drug for each target.
- Selectivity depends on chemical structure, molecular size, and electrical charge.
- Selectivity decreases with increasing drug concentration.

13. **Drug potency** refers to the amount of a drug, expressed as the concentration or dose, required for a given level of effect.

- Potency depends on both target (affinity and efficacy) and tissue (receptor number and drug availability) parameters.
- The higher the potency, the lower the dose required for a given level of effect.
- Highly potent drugs are often considered desirable because lower doses can be used and therefore, less drug is available to cause off-target adverse effects.
- Agonist potency is most commonly measured as the effective concentration required to produce 50% of the maximal response (EC_{50}).
- Antagonist potency can be measured as the concentration that reduces the response to an agonist.

14. **Concentration–response relationship** refers to the relationship between increasing drug concentration and magnitude of response.

- As the concentration or dose of a drug increases, the magnitude of the response increases from a threshold until a maximum response is obtained.
- Concentration–response relationships are used to determine and compare agonist potency (EC_{50}) and maximal effect (E_{max}).
- Concentration–response relationships are used to determine whether a drug is an antagonist, a partial agonist, or a full agonist.
- Concentration–response relationships are used to determine and compare antagonist potency, as well as the type of antagonism.
- Surmountable antagonists reduce agonist potency but not agonist maximum effect.
- Insurmountable antagonists will reduce the maximum effect of an agonist, with or without effects on agonist potency.

15. **Drug safety** refers to the balance of therapeutic benefits over harms.

- All drugs are potential poisons; it is the dose that is critical.
- The higher the drug dose, the lower the selectivity, and the greater the chance of harm.
- Adverse drug reactions are unwanted effects at therapeutic doses.
- Drugs can interact with other drugs, food, complementary medicines, and disease to cause harm at therapeutic doses.

16. **Drug tolerance** refers to the reduced response to a drug following repeated or prolonged exposure.

- Drug dose must be increased to maintain clinical efficacy when tolerance develops.
- Drug tolerance involves multiple mechanisms, such as up- or down-regulation of target number as a result of repeated drug administration.

3.5 | Concepts 17–20: System integration and modification of drug response

17. **Therapeutic window** refers to a concentration range bounded at the lower end by the minimum concentration that produces the desired clinical effect and at the upper end, the concentration that produces unacceptable effects or where no further benefit is observed.

- Target plasma concentrations are described by exposure metrics (e.g., AUC and $C_{ss,avg}$) and correlate with the extent and duration of optimal clinical response.
- Therapeutic window informs the target plasma concentration range when determining individualized dosages through therapeutic drug monitoring.

18. **Pharmacological homeostasis** refers to the interplay between drug response and physiological homeostatic mechanisms.

    - Drug action occurs in the context of homeostasis.
    - Drug action can alter the activity of homeostatic sensors (e.g., TRP channels), homeostatic control centers (e.g., altered set points for temperature with NSAIDS), or homeostatic effectors (e.g., adrenoceptor up-regulation with beta-blockers).
    - Drug action is in turn modified by homeostatic processes (e.g., tolerance due to receptor down-regulation, baroreflex blunting the effect of anti-hypertensive medications).

19. **Drugs and complex systems** refers to the interplay between drugs and patients, the latter being an integrated network of cells, tissues, and organs.

    - Drug action results from the complex interactions between cells, organs, and body systems.
    - Drug action in one cell type, organ, or system can affect other cell types, organs, or systems that interact with the first cell type, organ, or system.
    - Prediction of drug response in patients can be confounded by behavioral factors, such as poor adherence to treatment, and biological factors, such as the interplay between cells, organs, and body systems in disease contexts.

20. **Individual variation** refers to the fact that individuals respond differently to a given drug, due to exogenous and endogenous (including genetic) factors that influence drug availability and/or action.

    - Pharmacodynamic variability describes differences in the amount and/or function of drug target molecules, and/or the associated signaling cascade components that influence the degree to which a drug can exert its effect.
    - Pharmacokinetic variability describes differences in the ability of a drug to access or move around the body, as well as altered metabolism of the drug and ability of the body to excrete the drug.
    - Disease-induced variability describes differences imposed by a disease state that change the ability of a drug to access the target or act upon it.
    - Sex- and/or age-induced variability describes differences that relate to more general innate influences, rather than differences related solely to the individual.
    - Environment-induced variability describes differences that occur due to such factors as dietary influences, toxin exposure, supplements, and complementary or alternative preparations.
    - As a drug needs to be taken by the patient as prescribed in order to elicit the desired response, the level of drug adherence during treatment can have a significant influence on individual variability.

4 | DISCUSSION

In the first stage of this project, the Core Concepts in Pharmacology Expert Group (CC-PEG), identified 20 core concepts that pharmacology students should be expected to know, understand, remember, and apply correctly and effectively, years after graduation.[15] In the second stage, to define and unpack those 20 core concepts of pharmacology identified previously, CC-PEG developed an innovative, rigorous, iterative method informed by prior core concepts research in STEM disciplines.

4.1 | Research-informed methodology

The methods CC-PEG used to define and unpack the 20 core concepts of pharmacology education were informed primarily by relevant prior research in biology[10] and physiology.[11,16] To develop definitions for each core concept and to identify the relevant sub-concepts—and to ensure maximum rigor and relevance—CC-PEG adapted and extended the expert-group approach used in physiology,[16] adding additional steps. Firstly, CC-PEG extended and strengthened the iterative expert-group process used in physiology research by requiring each working group to come to *within* group agreement on definitions and sub-concepts, and then to refine and finalize that work *across* groups—through virtual discussion until consensus was achieved. Second, to further cross-check their judgments and enhance rigor, CC-PEG employed an additional group of experts in the field to conduct an independent review. Third, the comments and questions raised by the independent expert reviewers informed a final round of discussion and revision of the definitions and unpacking. By extending and enhancing the methods used in prior core concepts research, CC-PEG minimized individual biases, strengthened concept validity, and increased the likelihood these definitions and sub-concepts will be accepted and used by the broader pharmacology education community.

4.2 | Core concepts, sub-concepts, and conceptual frameworks

When unpacking physiology core concepts, Michael et al.,[16] note that "*Core concepts, or big ideas, are complex assemblages of interconnected smaller ideas*" and that unpacking of core concepts can be helpful for students who are developing a conceptual framework within the discipline. For each of the 20 core concepts, we developed a first layer of sub-concepts. For many of the concepts, CC-PEG working groups identified "layers beneath" that could have been included, for example, *drug interactions*, *adverse drug reactions*, and *hypersensitivity* under *drug safety* would benefit from further unpacking. Future studies could be conducted to unpack the full conceptual framework for some or all of these concepts. Michael et al.[17] developed a hierarchy of conceptual frameworks, in which each core concept is unpacked into critical components (equivalent to our definitions),

constituent ideas (equivalent to our sub-concepts), and further to elaborations and amplifications. A critical step in the development of conceptual frameworks is the articulation of relationships between concepts and sub-concepts. We addressed this aspect in a novel manner via a simple concept map for the core concepts of pharmacology produced as part of our previous study[15]; a future study to diagrammatically link the sub-concepts to each other would provide an invaluable tool for educators and students.

4.3 | What the body does to the drug (pharmacokinetic) concepts

Finding the appropriate wording was challenging for the working group, as it was important to ensure that concepts were clear and relevant to the novice learner while covering all possibilities for accuracy. Appropriate wording seemed of particular relevance when considering the various contexts in which those concepts will be used, which could include classrooms, laboratories, and clinical settings.

Given the interrelated nature of the core concepts we unpacked, there was extensive discussion as to the core concept with which some sub-concepts best aligned. For example, *first-pass metabolism* was initially presented as a sub-concept of *bioavailability*, but it was decided that it was a better fit under *drug elimination*. Similarly, *steady state plasma concentration*, although initially considered a sub-concept of *therapeutic window*, became a sub-concept of drug *elimination*.

The differentiation of *excretion* and *elimination* was, and continues to be, a point of debate. Extensive discussion addressed whether these terms should be included as individual concepts, or whether *elimination* should be a sub-concept of *excretion* and *metabolism*. A search of the literature revealed that the terms are often used interchangeably. However, when the concept of *drug elimination* is used, it usually indicates both *drug metabolism* and *excretion* processes are active (chemical and physical processes), while *excretion* is restricted to physical removal processes alone. As the elimination rate is an important pharmacokinetic parameter in explaining drug behavior and can be used to explain the removal of drug more thoroughly than by excretion alone, we have included both as individual core concepts. We welcome the engagement of the international pharmacology community in this debate, in the expectation of achieving a consensus.

4.4 | What the drug does to the body (pharmacodynamics) concepts

The pharmacodynamics working group contended with a number of key issues. *Drug potency* was originally subsumed under *concentration–response relationship* and was thought to be implicit in concepts of affinity and efficacy. After much discussion, we agreed that drug potency constitutes a stand-alone concept. The concept of *drug specificity* and *drug selectivity* also generated extensive debate. We readily acknowledged that *drug selectivity* depends greatly on drug concentration; however, there was confusion with regard to grouping *specificity* and *selectivity* together. Recognizing that *drug specificity* encompasses both ligand specificity and binding site specificity, we agreed that drug specificity, as a chemical concept, is better understood through the lens of affinity for a target and should be included under that concept. Whilst *concentration–response relationship* was initially identified as a core concept, during the subsequent unpacking we questioned whether or not it should stand-alone or be integrated into other core concepts to provide a context for their measurement. Consensus was reached that the *concentration–response relationship* is fundamental to many key pharmacological principles and, as such, is a core concept in its own right.

Most importantly, across all discussions, we addressed the question of who the stakeholders might be. In our earlier study identifying core concepts, we defined the scope as concepts that are "*foundational for pharmacology students*".[15] Consequently, we unpacked these foundational core concepts with *all* students who study pharmacology in mind. We, therefore, decided not to further unpack more advanced, context-specific sub-concepts such as *allostery*, and to exclude as sub-concepts *conformational change*, *constitutive activity*, *biased agonism*, *spare receptors*, *and intrinsic efficacy*.

4.5 | System integration and modification of drug–response concepts

Drugs and complex systems were by far the most difficult of the three concepts to unpack. Indeed, as *drugs and complex systems* and *pharmacological homeostasis* narrowly failed to reach the pre-determined endorsement in the initial study,[15] we unpacked these concepts in an attempt to reveal latent or hidden ideas. Whilst the working group developed core and sub-concepts relating to complex, often multicellular, and multiorgan level effects of drug action, which were endorsed by the CC-PEG wider group, we believe that this group of concepts requires further discussion.

Individual variation was seen as one of the most critical of all core concepts for students to attain, and the unpacking of this concept led to the largest number of sub-concepts. By contrast, *pharmacological homeostasis* (re-named from the original concept) was fairly straightforward to unpack, based on the effect of the drug on the sensors, control centers, and effectors of homeostatic processes, as well as the modulation of the effect of the drug by those processes. Pharmacological homeostasis is arguably a sub-concept of the physiology core concept of *homeostasis* that had previously been unpacked[16] and assessed by a validated concept inventory.[18]

5 | CONCLUSION

Twenty previously identified core concepts of pharmacology education were defined, grouped under four conceptual areas, and for each, key sub-concepts were identified and explained. We believe that this work can provide educators with a resource to guide the development of new curricula and the evaluation of existing

curricula. The development of a reliable and valid instrument to assess student understanding of those core concepts (concept inventory) will also be assisted by the unpacking of each core concept. Perhaps most importantly, educators can use the unpacked core concepts of pharmacology education within their teaching contexts to help students gain mastery of the foundations of the discipline. We anticipate that this framework will provide the basis for collaboration and curriculum refresh throughout the global pharmacology community, and we invite others to join in this important work.

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CONFLICT OF INTEREST

The authors have no conflicts of interest with respect to this study.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and been involved in drafting the manuscript or revising it critically for important intellectual content; and given final approval of the version to be published. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

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

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