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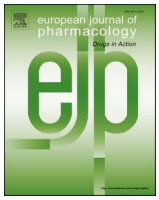

Evaluating student understanding of pharmacodynamics core concepts

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ABSTRACT

Pharmacodynamics is an essential subdiscipline of pharmacology that underpins safe and effective prescribing and therapeutic decision-making, as well as drug discovery and development. The exponential increase in the number of therapeutic drugs has prompted members of the pharmacology educator community to question existing pharmacology curricula focused on individual drugs and move toward a curriculum focused on conceptual understanding. A first step towards conceptual understanding is to establish what students currently know about pharmacodynamic core concepts. A total of 218 students from 10 universities were invited to complete a questionnaire that assessed their understanding of *drug efficacy*, *drug-target interaction*, *drug tolerance*, and *structure-activity relationship*. Pairs of pharmacology experts independently assessed each student's response and flagged any misconceptions that arose. The experts then compared their evaluations, achieved a consensus decision, and grouped the misconceptions into themes. Less than 25% of students provided core concept meanings that fully aligned with those of the expert group. By contrast, more than 75% of students could apply the core concept to a novel scenario at least in part. Overall, 480 misconceptions were identified and grouped into 55 misconception themes. The concept of drug efficacy was the core concept with which students struggled most. It is unclear why students were better able to apply their knowledge than to define the core concepts, although this might reflect a focus on active learning in pharmacology courses globally. The deficits in defining and understanding pharmacodynamic core concepts, and the misconceptions revealed in student responses, can be used by educators to guide their efforts.

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1. Introduction

Pharmacodynamics (PD) is a subdiscipline of pharmacology that focuses on the effects of drugs on the body. Its importance is highlighted by its inclusion in consensus documents on what should be included in curricula to facilitate safe and effective prescribing (Brinkman et al., 2018), as well as those that identify core knowledge within any pharmacology curriculum (Wallace et al., 2021; White et al., 2023). While health professionals and pharmacology graduates need to have a solid understanding of PD, there is insufficient time and space in curricula to teach the PD of all drugs. To allow for adequate PD knowledge, teaching core concepts related to PD will ensure graduates have the necessary background knowledge to understand the PD of any drug they encounter.

Core concepts are defined as "big, important, fundamental ideas, which experts agree are critical for all students in their discipline to learn, remember, understand, and apply" (White et al., 2023). Recently, the identification (White et al., 2023) and elaboration (Guilding et al., 2024) of 24 core concepts in pharmacology highlighted 8 core concepts specific to PD that should form part of any pharmacology curriculum. The identification of core concepts in other disciplines has had major benefits for education reform and curriculum design, resulting in better understanding among students (Hake, 2011; McFarland and Michael, 2020; Hsu and Halpin, 2022) and they have potential to aid learning in pharmacology (Guilding et al., 2023). Key to these advances in other disciplines was the development of concept inventories, which allow educators to determine student understanding of the core concepts and adapt teaching accordingly (Hestenes et al., 1992; Allen et al., 2004; Krause et al., 2004; Epstein, 2013; Stefanski et al., 2016; McFarland et al., 2017; Veilleux and Chapman, 2017; Porter et al., 2019). The first step in creating a concept inventory is the identification of student misconceptions around core concepts (Rye et al., 1997; Netere et al., 2024). Consequently, in this study, we investigated student understanding and application of four core PD concepts. This paper forms the second part of a project focused on pharmacology misconceptions (Guilding et al., 2023) and builds on the study by Babey et al. (submitted to this special issue), in which we examined student misconceptions of 4 pharmacokinetics core concepts. This paper examines student misconceptions of four PD core concepts, using a different cohort of students and analysts. More specifically, we sought to answer the following research questions:

1.1. Research questions

RQ1. What is students' understanding of the pharmacodynamic core concepts *drug efficacy, drug-target interaction, drug tolerance and structure-activity relationship*?
RQ2. To what extent do student conceptions of those core concepts align with expert understandings of those concepts?
RQ3. To what extent are students able to apply the core concepts to predict outcomes or solve novel problems
RQ4. Which of those concepts are most prone to misconceptions? Which are the most common misconceptions held by students?

2. Methodology

2.1. Human ethics approval

The project "Core Concepts of Pharmacology – testing student understanding" was approved by the Monash University Human Research Ethics Committee under Project ID 37467 which included all the universities involved in the study. The following universities required institutional approval in addition to the Monash overarching approval: University of New England (HRE23-007), University of Surrey (Project ID FHMS 23–24 038), East Tennessee State University (Project ID 0623.18e-ETSU), and Nazarbayev University (NU-IREC ID: 752/21082023). The remaining universities did not require additional ethics approval.

2.2. Participant recruitment

Students enrolled in medical, pharmacy, veterinary medicine, science, biomedical science, and pharmaceutical science programs were asked to participate in the study by authors (AMB, CR, JN, KK, MA, MH, NK, TH, WL) who taught in the relevant program. Students from different years of study were included but should have completed at least one introductory pharmacology course. Students were informed that participation was entirely voluntary and anonymous and would not count towards their mark or grade for any of their coursework. Students received an explanatory statement and completion of the survey was to be taken as an indication of their consent to participate in this research study.

2.3. Quiz design & delivery

A short quiz, approximately 15 min duration, was developed to i) explore student ability to understand and apply the core concepts of pharmacology, and ii) identify misconceptions held regarding the core concepts being tested (see Fig. 1). The same design was used for a parallel study that focused on pharmacokinetic concepts, described in Babey et al. (in press).

2.3.1. Quiz design

To ensure that the quiz could be completed within the 15-min timeframe and to minimize the potential for survey fatigue, it was decided to focus on four PD concepts. To identify these concepts, we first ran a pilot study to identify the most difficult PD core concepts. The pilot study involved 10 pharmacy students who identified clusters of related concepts on which the quiz would focus. From the list of 24 core concepts defined and unpacked previously (Guilding et al., 2024), the four PD concepts with which students struggled most were chosen as the focus for the quiz, namely: *drug efficacy, drug-target interaction, drug tolerance, and structure-activity relationship.* We are currently performing quizzes for the next batch of core concepts. The pilot study focused on the concepts that students found most difficult, with the view that the learning gains from working on these would be the greatest.

For each core concept, two types of questions were asked. The first question type required students to explain what they understood the core concept to mean. This question provided an open-ended opportunity for students to use their own words to explain their understanding of the core concept, and was intended to address Research Question 1 (*to what extent do students understand the core concept)*. The second question type involved an analysis of, or prediction from a simple scenario that required students to successfully employ the core concept in order to answer the question. Questions of this type were initially designed by members of the research team individually and then critiqued by the whole group. An example of each question-type is shown below.

Example – Core Concept: Structure-activity relationship.

1. Explain what you understand the term 'Structure-Activity Relationship' to mean
2. Drug A binds to a specific target. Chemical modification of Drug A is used to synthesise Drug B. What factors will determine whether Drug B is more effective than Drug A?

Students were also asked a series of demographic questions followed by eight randomised questions: two questions for each of the four concepts.

2.3.2. Quiz delivery

The quiz was constructed in Qualtrics and delivered via a hyperlink or QR code. In some cases, students were offered food as an incentive

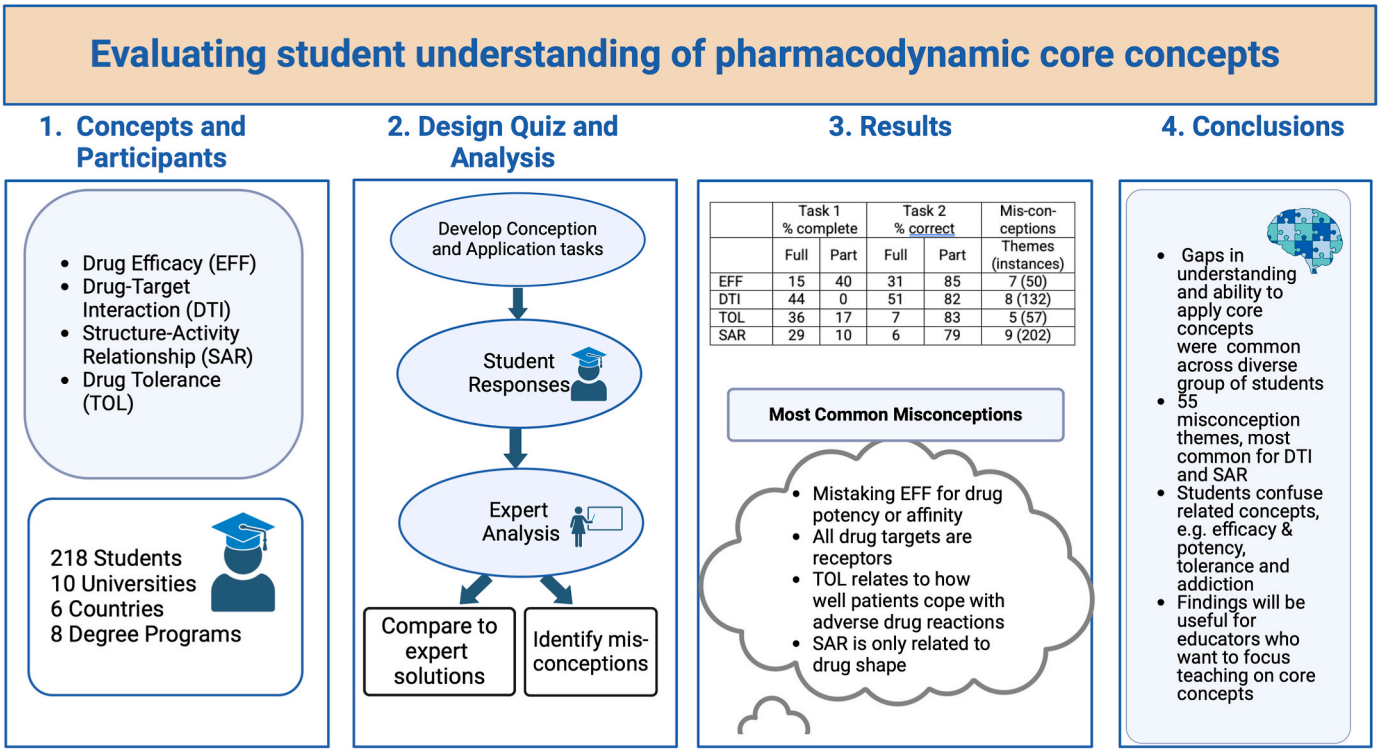

Fig. 1. Overview of the study design, methods and results.

while they completed their survey.

2.4. Data analysis

2.4.1. Identifying 'essential elements' of each core concept

To determine the extent of student understanding of the core concept, student responses to the task *"Explain what you understand the term [insert core concept] to mean"* were compared to expert definitions of the core concept in the form of "essential elements (EE)". The research team examined the definitions of the core concepts (Guilding et al., 2024), and identified EEs of the core concept, defined as *"discrete ideas present in the IUPHAR-Ed definition of the core concept"*. PW and KV performed the initial identification of the EEs of the core concept, which were later refined following feedback from the Research Team.

2.4.2. Analysis of the responses to prompts asking students to "explain what you understand the term [insert core concept] to mean"

A team of expert analysts (RKL, MC, FM, TH) evaluated the responses to the questions. In pairs, analysts made any refinements necessary to the EEs for the core concept in order to analyse responses using their shared understanding. Next, analysts individually read each of the student responses, and determined whether each contained the EE in full, partially, or not at all. Subsequently, the two analysts came together to reach consensus on any discrepancies. For each student response, analysts highlighted any underlying misconceptions, using the definition "*an illogical or unclear presupposition incongruent with the current state of scientific knowledge/professional standard"* (Olde Bekkink et al., 2016).

2.4.3. Analysis of responses to questions asking students to apply each core concept in a novel scenario or context

In pairs, analysts produced an indicative answer - accurate, logical, and acceptable - to the question posed for a single core concept. Analysts then chose one of the following options from a drop-down list regarding each student response: *No response*; *Off track or incorrect response; Correct but surface level; Partly correct but some errors or misconceptions; Accurate and logical response with reasoning provided.*

For each student response, analysts highlighted any text they believed to be incorrect, and identified any underlying misconceptions. Two experts independently assessed each of the student responses, and coded misconceptions in Excel. Individual misconceptions were then grouped together into broader emergent categories (Rye et al., 1997).

2.4.4. Text-mining analysis of student responses

The responses for each quiz question were combined to produce a corpus. An online N-gram analyser, http://guidetodatamining.com/ngramAnalyzer/, which mines the text to determine the frequency of each term/phrase, was used to identify and quantify the most common word strings within the corpus. The top 10 monograms (nouns or verbs) were identified, excluding words contained in the question or the core concept itself. These were then organised thematically, and bi-grams (2 collocated words), tri-grams and 4-g were explored to reveal context.

3. Results

3.1. Demographics and prior experience of students

A total of 218 students from 10 universities responded to the quiz (Table 1). Approx half the institutions were research intensive institutions. The majority of responses were from Australia (n = 155), with substantially fewer responses from the United Kingdom (n = 25), Brazil (n = 17), Kazakhstsan (n = 11), the United States (n = 5), and China (n = 2). As expected, based on the geographic location of respondents, English was the most common first-language. Importantly, the questionnaire was translated into Portuguese, which permitted students from Brazil to respond to questions in their first language.

Respondents were enrolled in 8 different training programs, including patient-care professions (e.g., pharmacy, medicine, and nursing) and veterinary medicine, as well as undergraduate science programs. The majority of learners (75%) had taken less than 3 pharmacology courses before responding to the questionnaire. Just over half of the students were in their second year of study.

Not all students responded to all questions. More students completed

Table 1
Demographics and response rates of participants.

Element	Details	N	%
Program	Pharmacy	100	46
	Pharmaceutical Science	53	24
	Medicine	26	12
	Veterinary Medicine	18	8
	Pharmacology/Toxicology	8	3
	Science	7	3
	Biomedical Science	3	1
	Advanced Clinical Practice	1	<1
	Medicinal Chemistry	1	<1
	Nursing	1	<1
Year of study	1	15	7
	2	122	56
	3	64	29
	4	10	4
	5	4	2
	6	3	1
University	Monash	83	38
	N. England	59	27
	Surrey	22	10
	UFSC	15	7
	Sydney	13	6
	Nazarbayev	11	5
	ETSU	5	2
	Newcastle	3	1
	Hong Kong	2	1
	UFAM	2	1
1st Language	English	120	55
	Not English*	97	45
	Not provided	1	<1
Prior pharmacology courses	1	89	40
	2	77	35
	3	33	15
	4	5	2
	5 or more	10	5
Number of responses to questions	Drug Efficacy – conception	176	81
	Drug Efficacy – application	181	83
	Drug-Target Interaction – conception	182	83
	Drug-Target Interaction – application	177	81
	Drug Tolerance– conception	183	84
	Drug Tolerance – application	192	89
	Structure-Activity Relationship–conception	142	65
	Structure-Activity Relationship – application	163	75

the application questions on the topics of *drug efficacy*, *drug tolerance*, and *structure-activity relationship* than those who supplied meanings for these terms. Conversely, more respondents provided a meaning for *drug-target interaction* (n = 182) than completed the application question on that core concept (n = 177).

3.2. Student conceptions and misconceptions regarding drug efficacy

A total of 176 students provided a response to explain the concept of *drug efficacy*. The text-mining indicated that the most common ideas related to *drug efficacy* being an ability or property of the drug, that it related to the drug producing a maximal effect, and that the effect

Table 3
Thematic analysis of student questions regarding *drug efficacy*.

Misconception (n)	Source Question*	Exemplar
Mixing up drug efficacy (which refers to magnitude of drug response) with drug potency (which refers to amount or concentration of a drug required to produce a particular response) (11)	conception	*"The concentration of a certain drug needed to reach an effect'*
Misconception that efficacy relates to the duration of effect (1)	conception	*"How long the drug activate in the body"*
Mixing up drug efficacy with drug affinity (1)	conception	*"How well it binds to the right target"*
Drug efficacy is dependent on the amount of receptor occupancy/binding (13)	Application	*"No, as a partial agonist is more easily displaced and does not reach the same maximum effect"*
A drug with higher affinity will have higher intrinsic efficacy (12)	Application	*"A full agonist have higher affinity in comparison to a half agonist. Thus, drug b would not have the same maximal effect "*
A drug with higher potency will have higher intrinsic efficacy (6)	Application	*"No, partial agonist less likely to bind and lower potency only partially agonises so effect won't be maximal"*
All drugs exert their maximal effect at the same concentration (6)	Application	*"Partial agonists have a lower maximal effect at the same concentrations."*

Table 2
N-grams analysis of student questions regarding *drug efficacy and drug target interaction*.

PD Concept	Common Themes	Common Terms (n) – Concept	Common Terms (n) – Application
Drug efficacy	Ability or property of a drug	*ability (52) ability of a drug to (19), how well the drug (10), how effective the drug is (5), extent (9)*	
	(Ability to) Produce a response/ desired therapeutic/maximal effect	*Effect (78), desired effect (18), produce an effect (6), the desired therapeutic effect (4), maximal (7), maximal response/effect (7), drug to exert its effect (3), response (60), produce a response (5)*	
	Effect occurs after binding to a target	*Target (29), bound (16), binding to (8), once bound to its target (3)*	
	(Drug B) would have lower efficacy/cause less activation of the receptor		*Activate (20), activate the receptor (10), efficacy (20), lower maximal effect (22) lower/ less efficacy (7)*
	Conformational change		*Conformational change (5), fully activate the receptor (3)*
Drug-target interaction	Nature/Properties of drug target	*receptor (68), enzyme(s) (12), ion channel (3), protein (17)*	*target (68), receptor (65), binding site (7), bind to the target (3)*
	Specificity of interaction	*specific (17), specific interaction (3)*	
	Nature of interaction	*binding/binds (61), conformational change (5), hydrophobic (5), chemical interaction (5)*	*interaction (12), competitive (12)*
	Effect on target function	*agonist (11), activate/activation (7), antagonist (8), response (17), inhibition (2)*	
	Nature/Properties of the drug		*affinity (41), agonist (32), antagonist (24), efficacy (14)*
	Concentration/amount		*concentration (19), concentration of drug (4), amount (17)*
	Metabolism		*metabolism (9)*

followed binding (Table 2). Analysis of student responses (Table 3) indicated that almost all (97%) fully or partly included EE2, the idea that *efficacy* is a response to the drug, once bound (Fig. 2a). In contrast, EE1, which states that *efficacy* is a consequence of drug binding to a target was present in only 28% of responses (Fig. 2a). The top 3 misconceptions identified in student explanations (Table 3) included confusion between *drug efficacy* and drug potency or drug affinity, and the idea that *drug efficacy* relates to duration rather than magnitude of the effect.

To further evaluate student understanding of *drug efficacy* in context, the following conceptual application question was asked:

> *"Drug A is a full agonist at a certain receptor type and Drug B is a partial agonist at that receptor. Would you predict that Drug B would have the same maximal effect as Drug A? Explain your thinking."*

Of the 181 responses to this question, 31% provided accurate and logical responses, and only 14% were off track or incorrect (Fig. 3). Thematic analysis of the responses highlighted themes of lower efficacy by a partial agonist, less activation of a receptor, and also conformational change. These themes align with EE3, with very few students identifying this EE fully in their responses. The most common misconceptions identified in student answers for the application task, similarly to the conception task, indicated confusion between affinity, potency and *efficacy*, and interestingly, the idea that all drugs exert their maximal effect at the same concentration.

3.3. Analysis of drug-target interaction

The first question on this concept sought to determine student understandings of *drug-target interaction*. 167 students provided their explanation of this concept. The text-mining (Table 4) revealed that student answers focused on the nature of drug target (e.g. receptor), the nature of interaction and the consequent effect of target interaction (e.g. response).

The EEs of the core concept as identified by experts are shown in Fig. 2b. Analysis of student responses indicated that most included EE1 "drug interacts with a target" (79 %) and EE3 "specific nature of the interaction, such as binding or conformational change" (53 %) as part of their explanation, however EE2 "biological effect as a result of drug interaction with target" and EE4 "defines the word target" appeared in only approximately 20% of explanations (Fig. 2). Within the analysis of student conceptions, some key misconceptions were evident (Table 4). The most frequent of these was that all drug targets are receptors, with nearly 32% of students focusing their response on receptors rather than any other drug target.

To further evaluate student understanding of *drug-target interaction* in context, the following conceptual application question was asked:

> *"In the process of a drug binding to its target, what factors will affect the biological outcome? Briefly explain your thinking."*

160 students answered this question and a majority (51%) provided responses that were accurate and logical with reasoning provided (Fig. 3). The top 3 misconceptions identified in student answers for this question were the idea that pharmacokinetic factors rather than PD were the ones most likely to affect the biological outcome (even though the drug was already binding the target), and that a drug requires efficacy to be effective.

3.4. Student conceptions and misconceptions regarding drug tolerance

A total of 183 students provided a response for their understanding of the core concept *drug tolerance*. The most common themes that emerged in the text-mining were "higher dose required", "produce the same effect" and "reduced response to repeated administration", "different medicine is needed", "the body gets used to the drug" and "side effects" (Table 5).

In the analysis of students' responses (Table 6), the research team identified 2 EEs for *drug tolerance*: EE1: *Drug tolerance* involves diminished response to the same drug concentration/dose, or the need for increased drug concentration/dose to produce the same response, and EE2: *Tolerance* occurs following repeated or prolonged exposure to a drug. Analysis of student responses indicated that EE1 was either fully included (32%) or partially included (32%) in responses; EE2 was fully or partly present in only (42%) of student responses (Fig. 2c). The 3 most common misconceptions were that *drug tolerance* related to the ability to tolerate adverse drug reactions, confusion with drug dependence/addiction, and a misconception that patients developed drug resistance analogous to antimicrobial resistance.

To further evaluate student understanding of *drug tolerance* in context, the following conceptual application question was asked:

> *"Describe some mechanisms by which drug tolerance can develop."*

172 students answered this question of whom 7% provided responses that were accurate and logical with the biggest proportion (42%) being partly correct (Fig. 3). The top misconceptions identified in student answers for this question included believing *drug tolerance* is related to a patient's ability to withstand adverse effects or that it is a form of resistance similar to antibiotic resistance (Table 6). Students also tended to use language that humanised the mechanisms.

3.5. Analysis of structure-activity relationship

The first question on this concept sought to determine student understanding of *structure-activity relationship*. Whilst 218 students participated in this study, only 142 students provided conceptions for this concept and only 163 responded to the application question. The text-mining revealed ideas related to the "site of interaction", "binding", "biological activity" and "no idea/not sure", which provided valuable insight into the number of students who did not understand this concept (Table 7).

Analysis of student responses (Table 8) indicated that most included EE1, SAR is determined in part by structural characteristics (functional groups, bonds, charge and shape) of the drug (64% fully or partially present) and EE3 (30%) as part of their explanation, however EE2 (9%) was generally lacking from their conceptions (Fig. 2d). In the case of EE2, it was clear from the analysis that students only considered structural considerations of the drug but did not really appreciate the importance of the structural characteristics of the binding site in the target when considering the concept of *structure-activity relationship*. In cases where students submitted partial responses, reference to the target binding site was the common part of EE2 that was omitted. The top 3 misconceptions identified in student explanations (Table 8) included: assumptions that suggested that SAR is only related to drug structure, SAR only being linked to receptor targets, and SAR being compared to the lock and key mechanism.

To further evaluate student understanding of *structure-activity relationship* in context, the following conceptual application question was asked:

> *"Drug A binds to a specific target. Chemical modification of drug A is used to synthesise drug B. What factors will determine whether drug B is more effective than drug A? "*

Overall, 170 students answered this question and most students provided responses that were surface level. As shown in Table 8, the top 3 misconceptions identified in student answers for this question included: proposal that efficacy is the only way to be an effective drug, or responses that suggested that a more effective drug would have to consider pharmacodynamics (PD) or pharmacokinetics (PK), but rarely considered how both factors could contribute towards drug effectiveness.

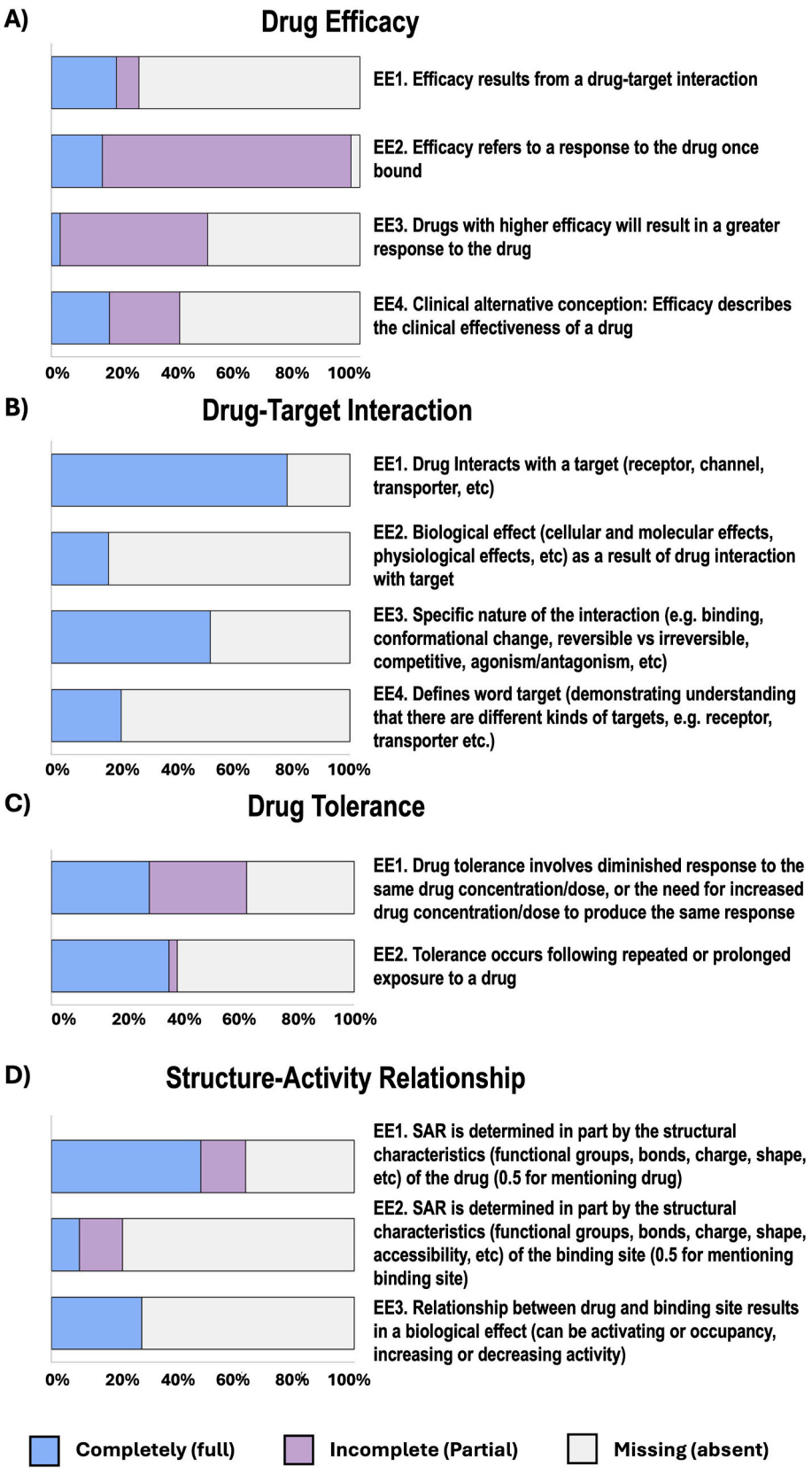

Fig. 2. Ratings of students' responses to the definitional task. Answers were coded as a complete (blue bars), incomplete (purple bars), or missing (grey bars) for each essential element.

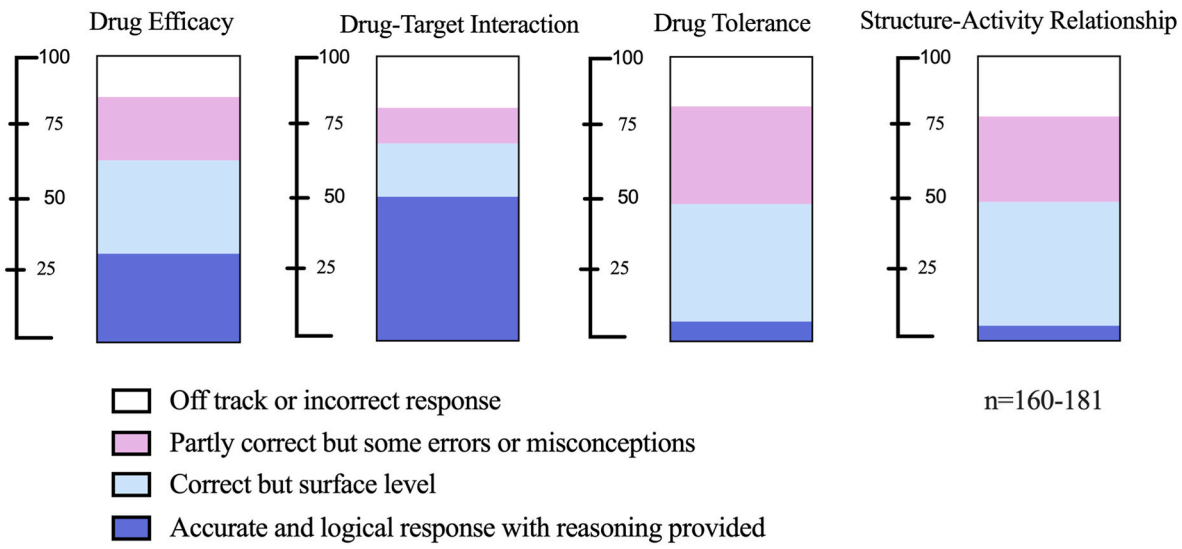

Fig. 3. Expert ratings of the responses to the application tasks for each core concept. n = 160–181.

Table 4
Thematic analysis of student questions regarding *drug target interaction.*

Misconception (n)	Source Question*	Exemplar
All drug targets are receptors (51)	conception	*"How the drug interacts with its target receptors"*
All drug targets are proteins (11)	conception	*"The drug molecule forms reversible (electrostatic interactions, hydrophobic interactions) or irreversible (covalent bonds) bonds with the binding pocket of a protein target."*
Confusing drug-target interaction with dose-response (6)	conception	*"The effect of a drug based on its concentration"*
Confusing drug target with target tissue (6)	conception	*"The interaction between the drug molecule and the target site of action that results in an effect"*
Includes factors involved in PK when the question is focused on PD (38)	Application	*"The ADME (absorption, distribution, metabolism, excretion)"*
Drugs must have efficacy to be effective (10)	Application	*"Drug exerts agonist activity and cascade of events occur"*
Only considering one component in drug-target interaction (drug or target rather than both) (5)	Application	*"The bioactivity of the drug"*
Focused on downstream signalling which is not the main focus of *drug-target interaction* (5)	Application	*"The conformational change which is induces in the receptor and the downstream signalling pathway which is activated"*

3.6. Summary of misconceptions findings

Supplementary Table 1 shows the complete list of apparent misconceptions identified by the analysis team. Overall, there were 55 misconception themes coded in a total of 480 instances.

For *drug efficacy*, there were 9 themes in total, with 3 themes for the conception task and 6 themes for the application task, coded 47 times. For *drug-target interaction*, there were 29 themes in total, with 17 themes for the conception task and 12 themes for the application task, coded 172 times. For *drug tolerance*, there were 8 themes in total with 3 themes for the conception task and 5 themes for the application task, coded 51 times. For *structure-activity relationship*, there were 9 themes in total, with 5 themes for the conception task and 4 themes for the application task, coded 200 times.

3.7. Student performance by course of study, first language and prior exposure to pharmacology

This study was not designed to test hypotheses regarding possible relationships between programs of study, first language, or the number of pharmacological courses that students had previously taken. Nonetheless, comparison of student performance by binning data using these variables was considered worthwhile to inform future studies of any causative relationships. Supplementary Tables 1–6 show similar performance between pharmacy and pharmaceutical science students with respect to conceptions and application tasks, students whose first language was not English and students whose first language was English and finally students who had taken two or more courses of pharmacology compared to those who had taken less than 2.

4. Discussion

4.1. Summary of major findings

This study provides major insights into students' understanding of four key PD concepts. Taken together, students vary markedly in their understanding of what is meant by *drug efficacy*, *drug-target interaction*, *drug tolerance*, and *structure-activity relationship* (RQ1), with highly variable alignment with expert expectations (RQ2). By contrast, students were better able to apply the concepts to novel scenarios or to use them to predict outcomes (RQ3), though their ability to do so was much better for the concept of *drug-target interaction*. Unexpectedly misconceptions relating to drug efficacy were evident in responses to questions relating to the *drug efficacy* questions but also the *drug-target interaction* and *structure activity relationship* questions (RQ4).

4.2. Understandings of PD core concepts

4.2.1. Drug efficacy

For *drug efficacy*, there were inconsistencies between the data from the conception task and the application task. Key themes arising from the text-mining analysis were broadly consistent with the core concept definition outlined by Guilding et al. (2024); "Drug efficacy is the ability of a drug to elicit a response once bound to a drug target". However, this consistency was not reflected in the element analysis of student conceptions, with less than 20% of students fully including the EE. This may reflect a surface level understanding of the concept, in which students know the correct words but don't fully understand them. This

Table 5
N-grams analysis of student questions regarding *drug tolerance*.

PD Concept	Common Themes	Common Terms (n) – Concept	Common Terms (n) – Application
Drug tolerance	Higher dose required	*higher dose (8), higher dose is needed/required (2) more drug (7) more medicine (2)*	
	Produce the same effect	*the same effect (8), required to produce (3) to achieve the same (7) same level of (4)*	
	Reduced response to repeated administration	*reduced reaction/effect (7), repeated use/administration/exposure (10)*	
	Different medicine is needed	*different medicine is needed (3)*	
	The body gets used to the drug	*used to (14), gets used to (6)*	*Body gets used to (2)*
	Side effects	*side effects (11)*	
	Desensitisation		*desensitisation (27)*
	Receptor internalisation		*internalis(z)ation (15), internalisation of receptors (3)*
	Downregulation/receptor expression		*downregulation (3), receptor expression (4), number of receptors (4)*
	Increased metabolism		*metabolise, metabolic, (4), accelerated metabolism (2)*

Table 6
Thematic analysis of student questions regarding *drug tolerance*.

Misconception (n)	Source Question*	Exemplar
Patient's ability to withstand adverse drug reactions (28)	conception	*Drug tolerance is how well a patient tolerates a drug, it has to do with adverse effects and how many of them a patient has*
Confusion with drug dependence/addiction (3)	conception	*A repetitive exposure to a drug that has developed tolerance. As a result, can cause addiction*
Patients develop drug resistance analogous to antimicrobial resistance (8)	conception	*It is the ability of a cell to resist or generate mechanisms against the exogenous action of drugs*
Drug tolerance is a form of resistance (9)	Application	*"Antibiotic resistance"* *"Use medicine (antibiotic) when not needed"* *"… the ability of the body to have resistance over the drug …"*
Humanisation of processes happening in cells (9)	Application	"***Exhaustion*** *of receptors due to overstimulation"* "*Decreased response to stimulation* via ***fatigue****/overuse …* ""*… where receptors* ***die*** *and the number becomes lower therefore needing more drug to activate*"

interpretation does not tally with the fact that, for the application question, approximately 40% of students provided an accurate and logical answer with reasoning.

Text-mining of the application task, which required students to consider *drug efficacy* in terms of a full and partial agonist, revealed common terms relating to *lower efficacy* and *less activation of the receptor* by a partial agonist, and to a lesser extent, *conformational change*. This suggests that for this concept, at least some students are thinking about efficacy at the molecular level as described in the subconcepts described by Guilding et al. (2024); "Efficacy depends on the drug's ability to favour stabilisation of active conformational states of the agonist-bound receptor."

The most common misconceptions emerging from the *drug efficacy* questions were very similar, centring around a conflation of *drug efficacy* with drug affinity (amount of receptor binding or increased affinity led to increased efficacy) and drug potency (either defining drug efficacy as drug potency or suggesting that higher potency led to higher intrinsic efficacy). This points to the importance of using active learning tasks to encourage students to think about the distinction between these two ideas. The application task uncovered additional misconceptions relating *drug efficacy* to the way in which a drug binds to a receptor, with suggestions that a partial agonist binds to fewer receptors or does not fully bind/binds less tightly/binds partially or is more amenable to displacement. There are a number of potential reasons for this confusion. First, this might reveal weaknesses in students' chemistry understanding, that is their understanding of molecular level events and suggests the need for further research on the impact of prior chemistry knowledge and understanding on pharmacology. Second, efficacy can be described at the macro- or observable level or the micro – molecular level (Fig. 4). At the macro/observable level (panel C), a drug with less efficacy i.e. a partial agonist will have a lower maximum response than a drug with higher efficacy i.e. a full agonist in a concentration-effect graph. At the micro- or molecular level (panel B) *drug efficacy* is described as the ability of a drug to activate a receptor once it is bound. *Drug efficacy* can also be portrayed in a symbolic manner using chemical equations (panel A). It is well accepted throughout biology that students have difficulty moving between different levels of organisation (Verhoeff et al., 2008) and in chemistry education research, difficulties in moving between symbolic, molecular and macroscopic representations are known as Johnstone's triangle (Johnstone, 1991). Connecting macro-, micro- and symbolic representations can provide a powerful framework for developing explanations (Petillion and McNeil, 2020).

Notably, there are different schools of thought in the literature with respect to the mathematical and conceptual aspects of *drug efficacy*, and these may account for the different interpretations seen in student

Table 7
N-grams analysis of student questions regarding *Structure-activity relationships*.

PD Concept	Common Themes	Common Terms (n) – Concept	Common Terms (n) – Application
Structure activity-relationships	Site of interaction	*chemical (33), chemical structure (24), functional groups (5), active site (5), site (8), receptors (13), parts of a drug (2)*	
	Binding	*binding (14), affinity, binding to (6), connection (3)*	
	Biological activity/ response	*biological activity (20), the activity (13), response (8)*	
	No idea/not sure	*Not sure (5), no idea (5)*	
	Drug characteristics - chemical		*chemical (15), lipophilicity (9), structure (8), hydrophobic (2)*
	Drug properties		*affinity (40, affinity for the target (3), efficacy (33), potency (32), binding (26), specific (12), specific target (7), specificity (6)*
	Effect on the body		*response (12)*

Table 8
Thematic analysis of student questions regarding *structure–activity relationships*.

Misconception (n)	Source Question*	Exemplar
SAR is only related to drug structure (98)	conception	*"The effect a specific drug has when it binds to a specific receptor because of its shape"*
SAR is linked to receptor targets (30)	conception	*"Depending on the structure of the receptor, the activity of the biological response due to drug will vary"*
SAR is like a lock and key system/enzymes (7)	conception	*"It is like a lock and key system, drug can only binds to structures that can be recognized in order to be effective" or "When the substrate fits the enzyme's active site, the enzyme elicits its activity"*
SAR is only related to target structure (7)	conception	*"The structure of a given receptor allows and restricts its activation or initiation by chemical mediators"*
SAR relates to therapeutic response/effects (6)	conception	*"The relationship between the physicochemical structure of the drug and its target receptor, with the magnitude of the resultant biologic and therapeutic effect"*
Effective drugs have efficacy or having efficacy is the only way to be an effective drug (32)	Application	*"The ability to bind to receptor, the time can be effective without breaking down by enzyme, the efficacy" or "Whether drug B is an agonist. If it is an antagonist then it has no efficacy. Other factors, binding affinity, selectivity, specificity"*
Drug effectiveness is largely dependent on PD (9)	Application	*"potency, specificity, PD profile (dose-response curve)"*

responses. This complexity makes it extremely challenging for students and indeed educators to navigate the literature on *drug efficacy*. Older ideas persist, including the notion that drug response is proportional to the fraction of receptors occupied and the ability of the drug to produce a response (intrinsic efficacy) which ranged from 0 to 1 (Ariens, 1954). This is problematic because it does not explain the situation where spare receptors exist, among other things. Stephenson's (1956) addition of a tissue-dependent element in the response, the subsequent two-state models of Del Castillo and Katz (1957) and the operational model of Black and Leff (1997), provide more sophisticated mathematical models which link the micro or molecular level concept of efficacy with the macro or observable level concept of efficacy. Students who want a fuller understanding of the observed magnitude of response to an agonist need to understand the molecular (microscopic) property of a drug and also factor in system-dependent properties such as the receptor number, amplification and number of spare receptors. While an introductory course in pharmacology may not need to include this depth of explanation, it is important that all lecturers within a course/programme are on the same page and consistent in their approach to teaching this concept. Otherwise, there is a risk that student learning will be negatively impacted. An introductory course might simply explain that efficacy can be thought of at the micro-level and at the macro-level as shown in Fig. 4. Graduate research students are more likely to need to engage with the two levels through use of mathematical modelling.

4.2.2. *Drug-target interaction*

For *drug-target interaction*, the key themes arising from text-mining of the student conceptions task were the nature of the drug, the nature of the interaction and the effect of target interaction. Although this generally aligns well with the lecturer-identified EEs only a minority of students included the biological effects or an understanding of drug-target in their explanations of what the term meant to them, and only about half highlighted the specific nature of the interaction. This could signal surface level understanding, but approximately 50% of students were able to provide accurate and logical responses to the application question. This is interesting because Khurshid et al. identified drug-receptor interaction as a threshold concept in pharmacology and indicated that students have difficulty in areas of acquisition and automation relating to this concept.

Key misconceptions for drug-target interaction relate to the nature and role of key players/events involved, such as the drug, the target, the interaction, the response/effect, which students seem to misunderstand or omit. In terms of the drug and the drug target, many students included one or the other but not both. The term "drug target", seemed to be problematic for students, with some of the most highly ranked misconceptions being "all drug targets are proteins" or "all drug targets are receptors". While the understanding that "all drug targets are proteins"

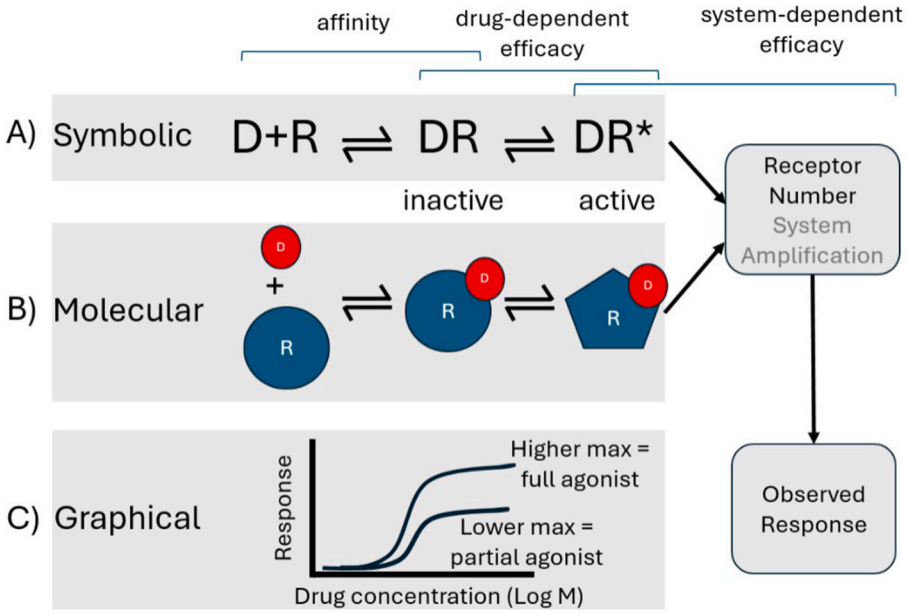

Fig. 4. Different representations of *drug efficacy*: *Drug efficacy* can be portrayed in A) a symbolic manner, B) at the molecular level C) at the macro/observable level (panel C).

may be more defensible, it is outdated considering the number of non-protein drug targets. The misunderstanding that all drug targets are receptors may result from a focus on receptor pharmacology over other targets, such as transporters, ion channels, enzymes and nucleic acids within some programmes. Considering these "other targets" constitute a large proportion of those targeted by drugs, it is important for students to have a broader understanding of what a drug target is (Santos et al., 2017). It is also possible that students may be understanding the word "receptor" in its everyday sense as something that receives and accepts signals and thus encompasses all drug targets. However, in pharmacology the term receptor takes on a more nuanced meaning. This type of misconception is called a vernacular misconception. These are a "… result of language confusion where mistaking everyday speech lexemes for scientific terms leads to erroneous interpretation of phenomena." (Chrzanowski et al., 2018). For pharmacology students, this may be confounded by the fact that the definition of a receptor in disciplines such as physiology is slightly broader, referring to both cellular receptors and sensory receptors. Therefore it is important that introductory courses in pharmacology are updated to emphasise other drug targets as well as the fact that nucleotide drug targets exist. Students were also confused about the difference between a drug target and a target tissue. This has the potential to cause confusion for students going forward and should, therefore, be addressed early in programmes. While biological effects or the word "effect" may have come up often in the text-mining, it is clear from the analysis of student responses that some students did not make the connection between the interaction and the response. Overall, it is clear that students need a better understanding of both the individual elements and the role that each element plays in *drug-target interactions.*

Other apparent misconceptions included a focus on PK when drug-receptor interaction is a PD process, and an assumption that a drug must have efficacy to be effective. Despite the fact that the question focused on the binding of a drug to its target, many student answers focused on pharmacokinetics (PK). While this emphasis on PK might suggest that students have a better understanding of PK than PD, several studies suggest that students tend to do better in PD assessments than PK (Pandit et al., 2021). Many answers to the PD application question focused on agonist activity. This may have stemmed from the fact that the question asked about the effect on the biological outcome. The students may have associated this biological outcome with efficacy at the drug target; however, although an antagonist has no efficacy at the drug target, its binding can lead to a biological outcome.

4.2.3. Drug tolerance

For *drug tolerance*, different key themes arose from the text-mining analysis of the conception and application tasks. From the conception task, key themes included higher dose required, produce the same effect and reduced response to repeated administration, all in alignment with the EEs identified for this concept. Despite this, only ~60% of respondents fully or partially identified EE1, and only ~40% of respondents fully or partially identified EE2 in their responses, highlighting gaps in understanding. Again, students seem to know the words but not the deeper meaning. The application task required students to consider mechanisms of *drug tolerance*, which provided different themes, including desensitisation, receptor internalisation, down-regulation and increased metabolism.

A range of misconceptions arose from the conception and application tasks, with some overlap in these misconceptions across both tasks. From the conception task, the major misconceptions arising revolved around *drug tolerance* as being able to tolerate adverse drug reactions, and confusion with drug dependence/addiction. Interestingly, a previous report has also identified similar misconceptions about the differences between *tolerance*, physical dependence, and addiction in the health care professions, which they attributed to use of incomplete and inconsistent terminologies (Buhler et al., 2024). Common to both the conception and application tasks emerged the misconception of *drug tolerance* as a form of resistance analogous to antimicrobial resistance, or that antibiotic resistance is a mechanism of *drug tolerance*. There is a clear need to integrate more robust and detailed content on *drug tolerance* into pharmacology curricula. This should include not only the meaning and mechanisms of *drug tolerance* but also the distinctions between *drug tolerance*, dependence, addiction, and resistance. It will also be important to ensure that lecturers within a programme are using consistent terminology when teaching students. Interactive and practical learning approaches, such as case studies and problem-based learning, may help students better understand and apply these concepts in real-world scenarios.

4.2.4. Structure-activity relationships

For *structure activity relationships*, the key themes arising from text-mining were reflective of the educator-identified key components of the definition, with students mentioning structures within drug targets and drugs, the binding itself and the response. Despite these words being frequently seen in student conceptions, most student answers only mentioned structures/properties of the drug with a minority acknowledging the structure of the drug target as being important. This is reflected in the application question where students more frequently included the importance of the properties of the drug, while the properties of the drug target itself were not mentioned. This is in line with what we saw for the concept of *drug-target interaction*, whereby students also focused on either the target or the drug as being important but the connectivity between the two were minimally explained. While other disciplines have looked at misconceptions around student understandings of the "shape of the molecules (Behera, 2019) and substrate enzyme interaction (Bretz and Linenberger, 2012), the misconception here, that it is only the structure of either the drug or the drug target that is important, may be limited to Pharmacology. Concept mapping was identified as a way to improve student understanding of concepts and to address misconceptions (Behera, 2019).

Overall, the misconceptions for structure activity relationships are very similar to those for drug-target interaction, which is probably not surprising since the key players/events involved are similar. What is different is the focus of each. While drug-target interaction focuses on the ways in which drugs and drug targets interact (e.g. competitively or otherwise, irreversibly or reversibly, as an agonist or antagonist), structure activity relationship focuses on the effect of the structure of the drug and the structure of the drug target on their interaction and hence the response (Guilding et al., 2024). While studies of structure activity relationship in the past may have focused on the structure of many potential drug compounds with only one drug target, potentially emphasising drug structure to students, the advent of newer tools like proteochemometrics, means that now we can assess the relationship between multiple drug compounds with multiple proteins at one time (van Westen et al., 2011). Highlighting the importance of the structure of both the drug and drug target at an early stage of learning will lay a strong foundation for understanding more complex concepts later.

One apparent misconception that seems to be unique to *structure activity relationships* is that it is like a lock and key system analogous to that described for enzymes. Whether this is a misconception or not is open to debate. Even among researchers, the lock and key idea has "dominated the philosophical underpinnings of molecular docking (which is one way of looking at structure activity relationships experimentally) (Tripathi and Bankaitis, 2017). However, more evolved theories of how drugs interact with drug targets have emerged and while the lock and key model and even the 'induced fit model' might be suitable for entry-level pharmacology students, more senior pharmacology students should understand more advanced models.

4.3. Conception vs application

Our results highlight a mismatch between students' ability to explain the meaning of, and apply, core concepts. While text mining revealed

close alignment between the themes seen in student conceptions and those of experts, the alignment between students and expert definitions varied markedly, with less than 25% of students able to explicitly identify the EEs for *drug efficacy*, although almost all students could at least partially describe EE2, and at least 50% correctly defined 2 elements for *drug-target interactions*. The lack of alignment with expert definitions, may suggest that the students don't understand the concepts, but it should be noted that the expert definitions were reached by consensus, not agreement, which suggests that even experts do not fully agree on these definitions. For example, after the 3-month process to create these definitions and two days of in person refinement only 93% of educators endorsed the definition for *drug efficacy*, only 89% endorsed the definition for *drug-target interaction*, 96% endorsed the definition for *structure-activity relationship* and 100% endorsed the definition of *drug tolerance* (Guilding et al., 2024). Despite the fact that the definition for *drug tolerance* is the one that reached the highest agreement among experts, some students who did not even attempt the conception task for *drug tolerance*, attempted the application task. As mentioned for each of the concepts above, application of knowledge to the application/interpretation question showed a very different pattern. More than 75% of students were able to answer these questions at least partially correctly, although less than 10% provided an accurate response along with a reasonable rationale for the *drug tolerance* and *structure-activity relationship* questions. This suggests a disconnect between students' ability to explicitly explain the core concepts and to apply them to a novel scenario. The reason(s) for this dichotomy remains to be elucidated. Given the increasing focus on active learning at institutions worldwide, it is possible that students did not accurately identify the essential elements of the concept because this is not the way in which they acquire their knowledge and understanding. By contrast, it may indicate a real difficulty that students have in understanding these concepts and the need for a curriculum that places a greater focus on pharmacology core concepts and their application.

4.4. Influence of course/first language and prior learning

As mentioned, this study was not designed to test hypotheses regarding possible relationships between student demographics and understandings of PD core concepts. However, the analysis provides some insights for further investigation. Overall, the performance of students was similar on conception and application tasks when binned using these variables.

4.5. Limitations

There were several limitations to this study. Firstly, student responses to the tasks provided were usually one or two sentences. It was therefore challenging at times to distinguish between true misconceptions and incomplete understandings or even appropriate understanding but poor communication or mixing up the name for one concept with that of another e.g. efficacy mixed up with potency or drug-target interaction mixed up with drug-drug interaction. Some authors (e.g. Halim et al., 2018) consider inaccurate use of terminology as a misconception. Future studies using think aloud protocols (Cheung, 2009) or similar deeper investigations (Taber, 2002; Halim et al., 2018) are required to fully confirm the apparent misconceptions in this study. It is possible that some of the misconceptions identified may be due to knowledge gaps (or missing conceptions), where students have missing or incomplete knowledge about a topic, rather than misconceptions where the knowledge they hold regarding a concept is in conflict with what is expected (Chi, 2009). While knowledge gaps may be easier to address than misconceptions, as conceptual change is not an issue, knowledge gaps in core concepts of pharmacology do need to be addressed. Therefore, we feel that both are useful to include as distractors in our concept inventories. Secondly, context will always play a role in teaching, learning and assessment. At different universities and even in different programmes within the same university, students are exposed to different lecturers, have different peer groups and study different co/prerequisites. There are several contextual factors which may have affected our results. Each concept may have been taught differently in different institutions and this likely accounts for some of the variability in the explanations provided by students. For example, the largest cohort of students hailed from one Australian University and so the results could be skewed in one direction or the other by this large cohort with a shared context. This study was not designed to determine the impact of factors such as curriculum type and teaching method on student understanding of the core concepts of pharmacology. However, the concept inventories that will be created using the data from this study will be invaluable tools in future studies evaluating the impact of such factors on pharmacology education. Also, the timing of the quiz in relation to which aspect of pharmacology the students had studied most recently may have affected either their interpretation of questions and/or their answers. It is possible that this is what happened for the drug-target interaction question, where the largest misconception was the idea that pharmacokinetic related factors would influence drug-target interaction when the drug was already at the target. These students may have recently had a lecture on the importance of pharmacokinetics in the response to drug treatment which biased their answers. Unfortunately, because this was a survey study, we were unable to collect this depth of data. Therefore, when confirming these findings, it will be important to incorporate greater contextual detail. Finally, the limited time allowed for students to complete the quiz may be responsible for some of the omissions or surface level responses provided by students. Further research, using some of the qualitative methods described above should allow us to validate our identified misconception.

4.6. Guide to educators

In this study, key gaps in student understanding and common misconceptions around the concepts of drug efficacy, drug-target interaction, drug tolerance, and structure-activity relationship, were identified. For each concept we have compiled some suggestions for teaching (Table 9).

5. Conclusions and next steps

This paper shared some similar findings with its companion paper by Babey et al. (submitted to this special issue). Most notably, many students struggled to define or apply the core concepts investigated and analysis of their responses revealed many misconceptions. Also, there was a tendency for stronger application of the concepts than the meaning of the concepts with both PK and PD concepts. This study was not designed to determine the impact of factors such as curriculum type and teaching method on student understanding of the core concepts of pharmacology. However, the concept inventories that will be created using the data from this study will be invaluable tools in future studies evaluating the impact of such factors on pharmacology education.

This study identified 55 misconception themes, and many gaps in understanding and application of the core concepts were held by a broad range of students across different programs and in different countries. Pharmacology educators may be able to improve student learning of these difficult concepts by focusing on the specific deficits identified in this study. Ultimately, the identified misconceptions will be used to create the distractors for multiple choice questions in the Core Concepts of Pharmacology Concept Inventory. The Concept Inventory will allow educators around the world to test and refine the applied understanding of core concepts held by their students.

CRediT authorship contribution statement

Roisin Kelly-Laubscher: Writing – review & editing, Writing –

Table 9
Suggestions for teaching pharmacodynamic core concepts.

Topic	Suggestions
Consistency in Teaching Approaches	Some concepts (e.g. efficacy, drug-target interaction) can be taught in different ways. Instructors should agree on a consistent approach at the start of a course/ program to avoid student confusion caused by differing representations.
Drug Efficacy	Activities which enhance student understanding of the differences and relationships between drug efficacy, drug potency and drug affinity should be incorporated into all introductory courses.
Drug-Target Interaction	The broad scope of what constitutes a drug target should be introduced to students at the beginning of any introductory course in pharmacology. Activities that enhance student understanding of both the nature of the individual elements and the role each plays in drug target interaction should be included in all introductory courses.
Drug Tolerance	Ensure consistent use of terminology by lecturers within a programme regarding tolerance, addiction, dependence and resistance. Activities should be created that allow students to actively learn the differences between drug tolerance, addiction, dependence and resistance.
Structure-Activity Relationship:	Activities that enhance student understanding of both the nature of the individual elements and the role each plays in structure activity relationships should be included in all introductory courses.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: No additional relationships to declare If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejphar.2025.177257.

Data availability

Data will be made available on request.

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