ARTICLE
A Critical Thinking Activity on Drug Tolerance for Undergraduate Neuroscience Courses

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Active teaching techniques that involve critical thinking and analysis lead to better learning and retention, and there is growing need for learner-centered classroom activities in the neurosciences. This article presents a critical thinking activity that offers context and meaning to basic principles of synaptic pharmacology. Students analyze fictional datasets to identify major characteristics of drug tolerance. Students' self-reported perceptions and ungraded quiz scores suggest that this activity was an enjoyable and impactful way to deepen students' understanding and engage them with the course material. This activity was developed for a 300-level psychopharmacology course that included majors from various science departments, but could be used and/or modified for specialized seminars or other undergraduate courses in psychology or biology.

Key words: drug; tolerance; neuropharmacology; psychopharmacology; active learning; classroom activity

BACKGROUND

Core competencies for undergraduate neuroscience programs include basic neuroscience knowledge and an ability to think critically and integratively (Kerchner et al., 2012). The American Association for the Advancement of Science (AAAS, 2010), Association of American Medical Colleges and Howard Hughes Medical Institute (AAMC-HHMI, 2009) have each identified similar goals for undergraduate STEM education. These competencies guide our development of course goals and learning objectives, and help to dictate the pedagogical approaches that we implement in the classroom. Learning activities that incorporate questions of mechanism and encourage creative problem solving can be used to help students realize these objectives (Olivares, 2005; Lo, 2010).

Active learning techniques are an effective way to promote critical thinking in undergraduate courses. Such techniques typically encourage students to use higher-order cognitive skills (Bloom, 1956), engage in activities beyond just listening (e.g., discussion, group work), and work on developing translatable skills (Bonwell and Eison, 1991). Active learning opportunities in undergraduate STEM classrooms improve higher-order problem-solving skills (Hake, 1998; Armbruster, 2009), student attitudes (Armbruster, 2009), and exam scores (Armbruster, 2009; Freeman et al., 2014), and reduce failure rates (Freeman et al., 2014). These techniques also promote student engagement in the learning process (Barkley, 2010). Opportunities to interact with course material outside of traditional lecture formats promote enduring, transferable learning (Halpern and Hakel, 2003).

There is growing interest in publically available educational resources in the neurosciences. Many outstanding laboratory activities, demonstrations, and multimedia resources are available via the *Journal for Undergraduate Neuroscience Education* and the online database Educational Resources in Neuroscience (ERiN; http://erin.sfn.org/), hosted by the Society for Neuroscience. Far fewer problem-based learning activities or case studies are available that can be facilitated easily in a variety of classroom settings (e.g., Meil, 2007; Roesch and Frenzel, 2016; see Weirtelak et al., 2016).

A fundamental topic in basic pharmacology is drug tolerance. Tolerance and sensitization are typically covered early in pharmacology courses, and often incorporate an overview and comparison of different forms of tolerance, e.g., metabolic versus pharmacokinetic. Drug tolerance is also often covered, to varying degrees, in collateral courses in psychology, neuroscience and biology, and is a crucial topic for pre-health courses.

The present activity requires that students apply their understanding of drug tolerance to interpret fabricated datasets. The activity was designed to help students apply their understanding of major characteristics of drug tolerance (Meyer and Quenzer, 2013, Table 1.8) to analyze and evaluate fictional datasets. The scenario of this activity is that a mystery drug, Drug X, has been identified and needs to be characterized; fictional data from rodent experiments using Drug X are presented in five parts. Students must (a) develop a working definition of tolerance, (b) think creatively about potential factors contributing to tolerance, (c) compare/contrast the rate at which tolerance develops to different drug effects, (d) evaluate how medical practitioners must consider drug tolerance when determining the type/dose of drug to administer to a patient, (e) identify conditions under which tolerance can be reversed, (f) synthesize data to identify cross-tolerance to different classes of drugs and (g) compare/contrast chemical structures of different drug classes to predict the drug class that Drug X belongs to.

The ability to analyze and interpret data is considered an essential goal of undergraduate neuroscience education (Kerchner et al., 2012), and practice reading and interpreting figures is important to scientific literacy. Further, an understanding of drug tolerance is not only useful to understanding behavioral and neurobiological factors that contribute to escalating drug use and addiction, but it also informs drug administration and monitoring

practices by healthcare professionals as well as by patients prescribed drugs associated with rapid tolerance (e.g., analgesic narcotics). This activity was used in a 300-level neuropsychopharmacology course that included majors from various science departments, but could be used and/or modified for specialized seminars or other undergraduate courses in neuroscience, psychology, or biology.

ACTIVITY ON DRUG TOLERANCE

During the third week of the course, students were assigned to read the portion of Chapter 1 (Principles of Pharmacology) of the course textbook (Meyer and Quenzer, 2013) that focused on drug tolerance. The activity on drug tolerance was completed during two consecutive class sessions that week. Students worked in randomly assigned small groups of 2-3 students to answer activity questions. After each part of the activity, groups shared their thinking/answers with the class and I presented a mini-lecture on related content.

In Part 1, students develop a working definition of tolerance and think creatively about potential factors contributing to tolerance. Students spent ~10min on this part, after which I asked volunteers to share their thinking, provided a definition of tolerance and gave a mini-lecture on four types of tolerance (acute, metabolic, pharmacodynamics, behavioral) that included figures from Meyer and Quenzer (2013) and supplementary examples.

In Parts 2-3, students compared/contrasted the rate at which tolerance develops to different drug effects, and evaluated how a medical practitioner might consider tolerance to analgesic effects when administering an analgesic narcotic to a pain patient. Students spent about ~15min on each section, after which I asked volunteers to describe their thinking and sketch data on the whiteboard that were consistent with their answer (Part 3). We then held a brief discussion of the subjective nature of pain and various drug- and non-drug based approaches to helping pain patients manage/treat their pain.

In Part 4, students compared how long tolerance to certain drug effects persisted and identified conditions under which tolerance could be reversed. Students spent ~20-30min on this part, during which I circulated around to answer questions and stimulate thinking. After students shared their answers, I gave a mini-lecture on research that examined how long receptor downregulation persisted in chronic cannabis smokers (Hirvonen et al., 2012).

In Part 5, students synthesized data intended to show cross-tolerance to a certain class of drugs, then compared and contrasted chemical structures of different drug classes to predict the drug class that Drug X belongs to. Students spent ~10-15min on this part, with the majority of that time spent interpreting the cross-tolerance graph.

STUDENT RESPONSES TO THE ACTIVITY

Methods. Participants were undergraduate students, aged 18-22, enrolled in a 300-level psychopharmacology course at a small liberal arts university located in Tennessee. The course was comprised of sophomores, juniors and seniors and required a prerequisite introductory neuroscience course. Most students (73%) were psychology majors and 33% were neuroscience minors. To participate in the study, students must have participated in the small-group activity on drug tolerance (see Supplementary Material). No other inclusion/exclusion criteria were used. This study was approved by the Institutional Review Board of The University of the South, and informed consent was received from all participants.

Study participants were recruited orally at the end of the second session; a written announcement containing the Qualtrics link was also posted to the course Blackboard website. The Qualtrics link contained an informed consent form. After consenting to participate, participants completed a brief online questionnaire and a short, ungraded quiz via Qualtrics.

The questionnaire included both Likert-type and open response questions. Open-response questions provided a source of qualitative data on subjective interest and perception. The Likert-type scale ranged from 1 (strongly disagree) to 9 (strongly agree), with 4 being neutral. N/A was also an option but was not selected on any question. These questions are listed in Figures 1-2, though phrasing may have been slightly altered for presentation purposes.

The quiz consisted of true-false and open response questions. Open response questions were graded out of two points, mimicking how a similar exam question might be graded (0-incorrect; 1-partial credit; 2-full credit). Questions are listed in Table 1.

Participants were not aware that study outcomes would include declarative knowledge resulting from this activity, and were debriefed after completing the study. Participation was voluntary and all data remained anonymous. In order to enhance participant privacy, demographic information, including gender and major, was not collected from this sample. Participants that opted to receive compensation received a gift card to a local coffee shop. Compensation was handled by a departmental colleague so participants' identities would not be revealed to the course instructor. Students were able to participate for two weeks after the Qualtrics link was distributed.

Results. Two-thirds of the class (*n*=10) participated in the study. Most students (55%) participated on the first day that the Qualtrics link was available; all but one student participated within a week.

Data on students' self-reported perceptions and interest in the tolerance activity are presented in Figure 1. The overall rating of this activity, on a scale of 1 (low) to 10 (high) was a mean of 8.90 +/- 0.31, with a median score of 9. Students' responses to the question "What did you enjoy most about this activity?" that addressed the activity's content included:

"[This activity] helped give context to the factual information we were learning to provide a deeper understanding."

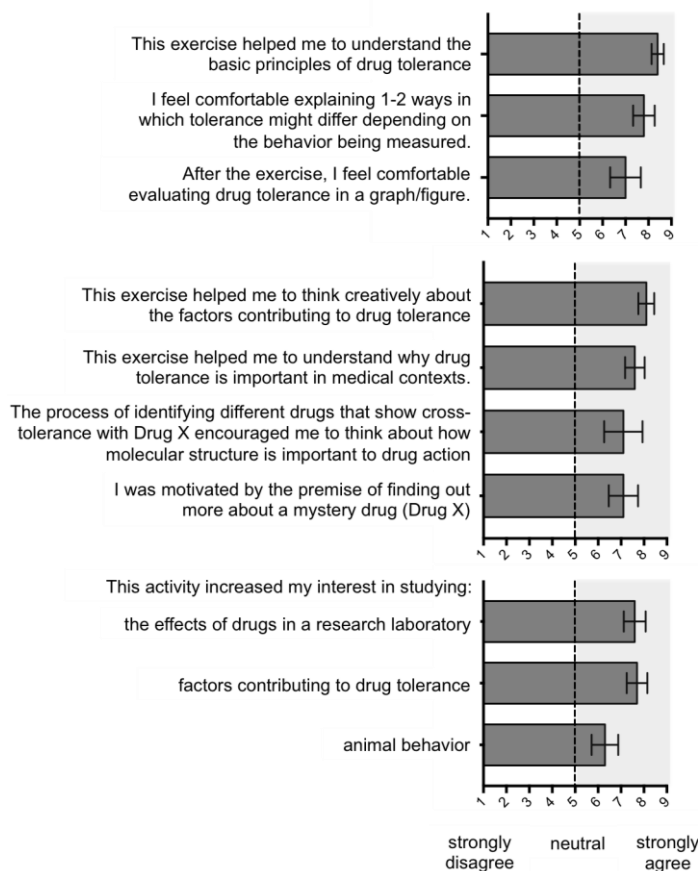*"I liked going over the material and then immediately being able to apply [it]"*

Figure 1. Students' self-reported perceptions and interest in the content of the tolerance activity. Grey shading reflects scores suggesting positive experiences. Data are presented as mean +/- SEM.

"Applying the material we learned about tolerance ensured that we were really grasping the concepts."

"Comparing and understanding graphs"

Data on students' responses to the structure and presentation of the tolerance activity are presented in Figure 2. Students' responses to the question "What did you enjoy most about this activity?" that addressed these aspects of the activity included:

"I enjoyed working in groups to answer questions because sometimes a graph may have shown more than one [possible] answer and working in groups helps raise more than one possibility."

"I enjoyed the interactive nature of this activity"

"I loved how we were able to take breaks in between each part to come together as a class and discuss answers. It really allowed me to feel as if I were caught up, versus falling behind if we either didn't go over them or if we went over them all at once."

"I liked that it was easy to follow and that [the instructor] explained the answers during the breaks."
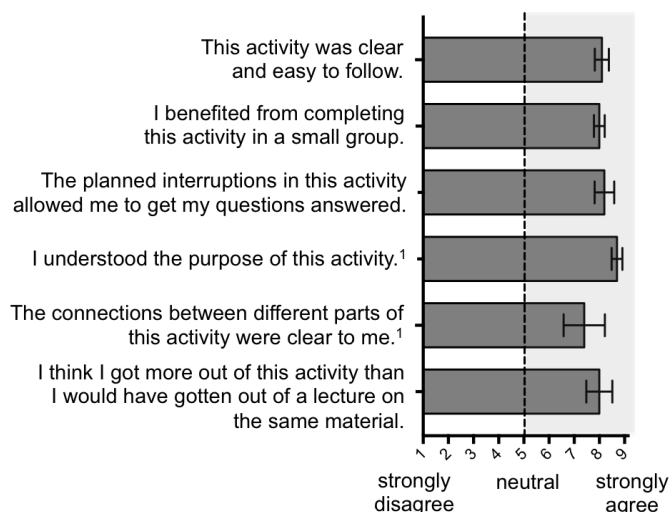

Figure 2. Students' responses to the structure and presentation of the tolerance activity. Grey shading reflects scores that suggest positive experiences. Data are presented as mean +/- SEM. [1] denotes questions that were reverse-coded in the original questionnaire.

Participants also performed well on declarative knowledge questions. Each participant got all true/false questions correct, and most participants received full points on the short-answer questions (Table 1). These questions addressed lower-order learning outcomes (Bloom, 1956), to avoid potential conflict with existing course exam questions. Given the small size of the class, tolerance-related questions on course exams could not be assessed while maintaining participant privacy. However, students' contributions during class discussions were relevant, insightful, and demonstrated their deep thinking about the activity. While participants' identities remain anonymous, it seemed that most students interacted thoughtfully with the material and successfully analyzed and evaluated the fictional datasets.

DISCUSSION

This activity was built into a unit on basic pharmacology, which occurred relatively early in this neuropsychopharmacology course (Week 2-3). It was presented like an interrupted case study, with small groups sharing their thinking and answers with the class after each of five parts.

Many aspects of this activity could be expanded upon, depending on the particular course and learning objectives. For instance, pre-health classes might devote more class time discussing pain diagnosis and drug-based and non-pharmacological approaches to pain management. The topic of cross-tolerance also seemed to interest students, and additional discussion time and/or an expanded lecture on relevant empirical research could easily be incorporated into this unit.

The topic of cross-tolerance also seemed to be one of the more challenging aspects of the activity (Part 5). Some groups of students spent a long time thinking about and interpreting the cross-tolerance graph, while a few caught

on relatively quickly. It might be useful to pair groups that understand and finish early with groups that are struggling, as an opportunity for collaborative learning and peer-led instruction. Further, only a few students in the present course had taken college-level biochemistry and/or were familiar with molecular structures, so I encouraged students to approach the second portion of Part 5 by simply looking for similarities in the shapes of the drug structures. Students responded positively to this part of the activity, as it seemed to empower them to make logical decisions about a set of unfamiliar (and potentially intimidating) data. This part also served as a useful reminder to students that a drug's chemical structure dictates much about its mechanism(s) of action.

When this activity was implemented, we ran out of time while students were working on Part 4. We ended up discussing this part at the beginning of the second class, so additional time was given to students to revisit/review their work on Part 4 before beginning the discussion. If possible, it would be ideal to start and complete each part within a single class period.

Planned interruptions between each part of this activity allowed students to share thinking and answers, and helped ensure that everyone stayed on the same page. Indeed, reporting their group's findings out to the class can incentivize students' engagement in these types of activities (Armbruster, 2009). Findings could also be shared between groups by breaking up and rearranging the small groups in a version of a jigsaw (Barkley, 2010). This activity could also be done outside of class, as the nature of active learning activities, rather than whether they are administered during or outside of class, contribute to improvements in low- and higher-order learning outcomes (Jensen et al., 2015), though information-sharing and discussion in the classroom setting seemed to enhance students' enjoyment of and engagement with the activity.

While this activity could be completed individually, activities involving the use of evidence, interpretation and logic, such as the present activity, are particularly amenable to collaborative group work (Olivares, 2005). Participation in small-group activities has been associated with higher exam grades and higher perceived level of deep learning (Lo, 2010). Indeed, students that studied collaboratively performed better on higher-order thinking questions than did students who studied independently (Gokhale, 1995), and students reported that working in small groups increased their understanding, stimulated thinking, provided feedback, and offered different/new perspectives (Gokhale, 1995; Lo, 2010). Such reactions were reiterated in students' qualitative feedback on this activity.

Higher-order thinking activities can affect students' educational experience in other ways. Active learning activities promote re-engagement midway through a lecture, when retention of material can dip (Johnston and Calhoun, 1969). Further, higher-order thinking activities are positively associated with students' social integration

	Declarative knowledge questions	Points earned		
		0	1	2
Short Answer	What is tolerance? Provide a brief definition here.	0%	20%	80%
	In what type of situation might a medical practitioner care about drug tolerance?	10%	10%	80%
	If a rat shows tolerance to a certain drug, how might we determine if he is tolerant to a different drug?	20%	10%	70%
True/False	Tolerance develops to all drug effects.	0%	100%	--
	Tolerance always develops at the same rate (e.g., takes the same number of days).	0%	100%	--
	Tolerance is permanent.	0%	100%	--
	If an individual shows tolerance to one drug, s/he may show tolerance to structurally similar drugs.	0%	100%	--

Table 1.   Students' performance on declarative knowledge questions in the online quiz.   Data are the percentage of participants in each category.

within their academic institution, measured via peer relations and out-of-class interactions with faculty (Braxton, 2000); in turn, social integration is linked to students' commitment to the institution and likelihood that they will stay after their first year (Tinto, 1975; Braxton, 2000, 2008).

In a 2009 survey of FUN mentors, nearly two-thirds of undergraduates who received a FUN Travel Award were currently enrolled in, or planning to enroll in, a PhD or MD/PhD program (Hardwick and Smith, 2010). Learning objectives for medical schools set forth by the AAMC include the ability to "assess and critique, at a fundamental level, research as it is reported in major medical journals, based on an understanding of how data are derived" (AAMC, 2010). While this activity is not derived from real-life data, it was intended to replicate the types of figures found in peer-reviewed publications.

One limitation to the present study was the inability to assess how this activity impacted the longer-term retention of higher-order skills without "giving away" exam questions used in the course. It would have been ideal to include in the IRB proposal an option for students to submit their answers to relevant exam questions to the study; this may have also reduced selection bias in the sample studied. This option was considered but was logistically complicated, given the need to maintain students' anonymity, given the small university and class size. The impact of this activity on students' long-term retention of higher-order skills might be studied creatively in a different setting (e.g., larger university with teaching assistants to provide consistent and anonymous grading).

Overall, this critical thinking activity offers an engaging means of emphasizing key principles of drug tolerance and is particularly amenable to undergraduate courses in psychopharmacology, neuroscience, psychology and biology.

The full activity is included as supplementary material to this article. For a copy of the key and/or to discuss ideas for its implementation, please contact the author (kmcammac@sewanee.edu).

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