Chapter 3: How We Adapt to Drugs—Tolerance, Sensitization, and Expectation

Chapter Overview

In this chapter, we show how principles of traditional learning theory (classical and operant conditioning) can be applied in order to understand behavioral pharmacological phenomena such as drug tolerance and withdrawal. Students are presented with various mechanisms, both physiological and behavioral, that underlie the diminishment of a drug's effects with repeated use. That tolerance develops to the effects of a drug, and not to the substance itself, is an important distinction for students to comprehend. Likewise, the conditioning of compensatory responses—physiological changes that are opposite those produced by the drug itself—is an important concept that will aid students in understanding why drug-associated cues can, in the absence of drug administration, elicit symptoms of withdrawal. The concept of sensitization, or reverse tolerance, is also introduced in this chapter as preliminary background preparation for a much broader discussion and application of sensitization to theories of addiction, covered in Chapter 5. This chapter closes by revisiting the placebo effect, introducing the nocebo effect, and discussing the importance of expectancy and context in mediating drug effects.

Chapter Outline/Notes

- ✧ Drug tolerance is defined either as the decreased effectiveness (or potency) of a drug that results with repeated administrations, or as the necessity of increasing the dose of a drug in order to maintain its effectiveness after repeated administrations.
- ✧ Tolerance to some effects of a drug may develop or dissipate rapidly, whereas others may develop or dissipate slowly or not at all. This suggests that drug tolerance is the result of multiple mechanisms.
- ✧ Cross-tolerance occurs when tolerance to one drug diminishes the effects of another.
- ✧ Acute tolerance develops during a single drug-taking session, so that the perceived effects of a drug are diminished as blood concentrations are falling compared to when blood concentrations were rising.
- ✧ Pharmacokinetic tolerance arises from an increase in the rate or ability of the body to metabolize a drug, resulting in fewer drug molecules reaching their sites of action. For the most part, pharmacokinetic tolerance is due to enzyme induction—an increase in the level of an enzyme the body uses to break down the drug.
- ✧ Pharmacodynamic tolerance arises from adjustments made by the body to compensate for an effect caused by the continued presence of a drug. These adjustments are brought about through homeostasis—a process by which the body attempts to maintain stability over fluctuation.
- ✧ Tolerance develops only in a circumstance where a drug places a demand on an organism's homeostatic mechanisms; if the drug effect is of no biological or functional significance to the organism, tolerance will not develop.
- ✧ Behavioral tolerance arises from conditioned changes in behavior that compensate for the effects of a drug.
- ✧ Withdrawal symptoms are physiological changes that occur when the use of a drug is discontinued or the dosage reduced. They are thought of as expressions of the compensatory adjustment that homeostatic mechanisms have made to the repeated effects of a drug.
- ✧ Drug dependence is somewhat of an ambiguous term, as it has been used to refer to both the state in which discontinuation of a drug causes withdrawal symptoms and the state in which a person compulsively takes a drug (which is also often described as addiction).
- ✧ Solomon and Corbit's (1974) opponent process theory proposes that drugs of abuse stimulate an "A" process that creates a euphoric (pleasant) *a* state, but that soon after, a compensatory "B" process is evoked that creates a dysphoric (unpleasant) *b* state.

- ✧ Solomon and Corbit's (1974) opponent process theory can be used to explain acute tolerance and hangover that result from a single drug administration, as well as chronic tolerance and withdrawal symptoms that occur with repeated drug administration.
- ✧ Stimuli paired with drug administration will eventually come to elicit effects through classical conditioning processes. Quite often, the effect that becomes conditioned is not that of the drug itself but of the physiological responses triggered to oppose the unconditioned effects of the drug—that is, conditioned compensatory responses.
- ✧ Conditional tolerance is dependent upon the presence of environmental cues predictive of drug administration. These cues elicit conditioned compensatory responses that diminish the effects of the drug. In the absence of drug administration, conditioned compensatory responses are expressed as conditioned withdrawal symptoms.
- ✧ If a drug interferes with an organism's ability to obtain reinforcement, behavioral tolerance will develop. If the ability to compensate for the effect of a drug is not reinforced, tolerance may not develop. Similarly, tolerance to some drug effects develops only if the organism is reinforced for demonstrating compensatory operant responding.
- ✧ Sensitization is the increase in a drug's effect with repeated administrations. It is often measured in terms of a drug's behavioral-activating effects. Like tolerance, sensitization can be conditioned to a particular environment and cross-sensitization may occur across different drugs.
- ✧ The placebo effect—the expectations individuals have regarding the effects of a drug—exerts great influence on the drug experience. Brain regions and pathways have been identified that mediate this expectancy effect.
- ✧ The nocebo effect is a placebo's capacity to generate adverse side-effects. This stems from knowledge the individual has pertaining to the negative effects of the particular drug being replaced by the placebo.
- ✧ The context in which a drug is administered can influence its effects. This includes whether the individual self-administers the drug or has no control over its delivery. The environment, whether familiar or novel, also modifies a drug's effects.

Multiple Choice Questions

3-1. Which of the following is an indicator of drug *tolerance*? a. A decrease in the effectiveness of a drug resulting from repeated administrations. b. A decrease in the potency of a drug resulting from repeated administrations. c. The necessity to increase the dose of a drug in order to achieve the same effect after repeated administrations. d. A shift to the right in a drug's dose–response curve resulting from repeated administrations. e. All of the above are indicators of drug tolerance.	***Answer:*** E ***Objective:*** ***Topic/Section:*** Tolerance ***Difficulty:*** ***Bloom's level:***

3-2. Tolerance to the various effects of a drug develops at different rates. This means that a. researchers cannot study tolerance using scientific protocols. b. researchers cannot predict when drug tolerance will occur in an individual. c. there must be more than one mechanism responsible for the development of tolerance. d. overdose deaths can be attributed to a sudden drop in the rate of tolerance development. e. eventually, all drug effects will show complete tolerance.	***Answer:*** C ***Objective:*** ***Topic/Section:*** Tolerance ***Difficulty:*** ***Bloom's level:***

3-3. When she was a teenager, Joan fell off a horse and shattered her pelvis. She has been taking the opioid pain medication oxycodone ever since. Last week, Joan was in a car accident	***Answer:*** B ***Objective:***

and the emergency-room physician administered morphine to treat Joan's pain. What would you expect to have happened, in this case?	***Topic/Section:*** Tolerance ***Difficulty:*** ***Bloom's level:***
a. Joan's body is accustomed to opioid medications, and so the morphine would be a highly effective pain reliever.	
b. Joan's body is accustomed to opioid medications, and so the morphine would be a poorly effective pain reliever.	
c. Joan's body is unaccustomed to morphine, and so morphine would be a highly effective pain reliever.	
d. Joan's body is accustomed only to oxycodone, and so that's what the physician should have administered to treat her pain.	
e. Joan must not be taking her oxycodone as prescribed, otherwise she would not have had any pain following the car accident.	

3-4. Tolerance can develop to the effects of a drug during a single administration. This is known as	***Answer:*** A ***Objective:*** ***Topic/Section:*** Tolerance ***Difficulty:*** ***Bloom's level:***
a. acute tolerance.	
b. cross-tolerance.	
c. chronic tolerance.	
d. sustained tolerance.	
e. Mithridatism.	

3-5. When a drug effect is greater at a specific blood level when the concentration in the blood is rising, compared to at that same blood level when the concentration in the blood is falling, this is called	***Answer:*** C ***Objective:*** ***Topic/Section:*** Tolerance ***Difficulty:*** ***Bloom's level:***
a. physiological tolerance.	
b. metabolic tolerance.	
c. acute tolerance.	
d. dispositional tolerance.	
e. behavioral tolerance.	

3-6. Mark is having a house party to celebrate landing a new job. He's been drinking alcohol fairly steadily since early in the evening, and it is now 3:00 a.m. Mark's friends are having trouble hailing a cab, so Mark offers to drive them home. When they remind Mark that he's had a lot to drink, he agrees that he was really drunk a couple of hours ago but says he feels pretty sober now. He suspects he can drive perfectly fine. What is likely happening to Mark?	***Answer:*** B ***Objective:*** ***Topic/Section:*** Tolerance ***Difficulty:*** ***Bloom's level:***
a. Mark's body has eliminated the alcohol from his system and he is now nearly sober.	
b. Mark is showing acute tolerance to the subjective effects of alcohol.	
c. Mark is showing cross-tolerance to the subjective effects of alcohol.	
d. Mark is showing pharmacokinetic tolerance to the subjective effects of alcohol.	
e. Mark is showing pharmacodynamic tolerance to the subjective effects of alcohol.	

3-7. Tolerance that arises from an increase in the rate or ability of the body to metabolize a drug, resulting in fewer drug molecules reaching their sites of action, is known as	***Answer:*** D ***Objective:*** ***Topic/Section:*** Mechanisms of Tolerance ***Difficulty:*** ***Bloom's level:***
a. pharmacodynamic tolerance.	
b. physiological tolerance.	
c. cellular tolerance.	
d. pharmacokinetic tolerance.	
e. All of a., b., and c.	

3-8. Enzyme induction	***Answer:*** A

a. is important in the development of pharmacokinetic tolerance. b. is caused by an enzyme blocker, such as disulfiram. c. slows the metabolism of drugs in younger members of a species. d. accounts for the different levels of an enzyme in different species. e. is a principal cause of accidental drug overdose.	***Objective:*** ***Topic/Section:*** Mechanisms of Tolerance ***Difficulty:*** ***Bloom's level:***

3-9. Tolerance that arises from adjustments made by the body to compensate for an effect caused by the continued presence of a drug is known as a. pharmacokinetic tolerance. b. metabolic tolerance. c. dispositional tolerance. d. pharmacodynamic tolerance. e. All of a., b., and c.	***Answer:*** D ***Objective:*** ***Topic/Section:*** Mechanisms of Tolerance ***Difficulty:*** ***Bloom's level:***

3-10. Which of the following forms of drug tolerance is attributed to the process of *homeostasis*? a. Pharmacodynamic tolerance b. Physiological tolerance c. Cellular tolerance d. Metabolic tolerance e. All of a., b., and c.	***Answer:*** E ***Objective:*** ***Topic/Section:*** Mechanisms of Tolerance ***Difficulty:*** ***Bloom's level:***

3-11. The *upregulation* or *downregulation* of neurotransmitter receptor sites can lead to a. pharmacokinetic tolerance. b. pharmacodynamic tolerance. c. acute tolerance. d. behavioral tolerance. e. all of the above forms of tolerance.	***Answer:*** B ***Objective:*** ***Topic/Section:*** Mechanisms of Tolerance ***Difficulty:*** ***Bloom's level:***

3-12. Tolerance to the anorexic effects of amphetamine will develop in rats whenever a. the drug is repeatedly administered. b. the drug is repeatedly administered to satiated animals in the presence of food. c. the drug is repeatedly administered to satiated animals in the absence of food. d. the drug is repeatedly administered to hungry animals in the presence of food. e. the drug is repeatedly administered to hungry animals in the absence of food.	***Answer:*** D ***Objective:*** ***Topic/Section:*** Mechanisms of Tolerance ***Difficulty:*** ***Bloom's level:***

3-13. Tolerance that develops as a result of learning to compensate for the effect of a drug is called a. cross-tolerance. b. acute tolerance. c. behavioral tolerance. d. dispositional tolerance. e. physiological tolerance.	***Answer:*** C ***Objective:*** ***Topic/Section:*** Mechanisms of Tolerance ***Difficulty:*** ***Bloom's level:***

3-14. _____ symptoms are physiological changes that occur when the use of a drug is stopped or the dosage is decreased. a. Compensatory	***Answer:*** D ***Objective:***

b. Diversionary	***Topic/Section:*** Withdrawal ***Difficulty:*** ***Bloom's level:***
c. Sensitization	
d. Withdrawal	
e. Tolerance	

3-15. When physiological changes occur in response to the discontinuation of a repeatedly administered drug, this indicates a state of	***Answer:*** C ***Objective:*** ***Topic/Section:*** Withdrawal ***Difficulty:*** ***Bloom's level:***
a. acute tolerance.	
b. behavioral tolerance.	
c. dependence.	
d. habituation.	
e. sensitization.	

3-16. Greg is a compulsive cannabis user. He smokes cannabis nearly every day, and often multiple times per day. What do we know for certain about Greg?	***Answer:*** E ***Objective:*** ***Topic/Section:*** Withdrawal ***Difficulty:*** ***Bloom's level:***
a. Greg will definitely experience withdrawal symptoms if he cuts down on his cannabis use.	
b. Greg is definitely dependent upon cannabis.	
c. Greg is definitely addicted to cannabis.	
d. We know for certain that all of a., b., and c. are true about Greg.	
e. We don't know for certain if any of a., b., or c. are true about Greg.	

3-17. The physiological changes that take place during withdrawal are often in the direction opposite to those caused by taking the drug. This indicates that	***Answer:*** A ***Objective:*** ***Topic/Section:*** Withdrawal ***Difficulty:*** ***Bloom's level:***
a. the body is readjusting to the absence of the drug.	
b. the body is responding to a metabolite of the drug.	
c. withdrawal symptoms are independent of the direct effects of the drug.	
d. there is nothing a person can do to avoid drug withdrawal.	
e. withdrawal symptoms will last longer if a drug is taken intermittently.	

3-18. According to Solomon and Corbit's (1974) *opponent process theory*,	***Answer:*** E ***Objective:*** ***Topic/Section:*** Withdrawal ***Difficulty:*** ***Bloom's level:***
a. abused drugs stimulate an A process that creates a euphoric or pleasant *a* state.	
b. soon after a drug is administered, a B process is evoked that creates a dysphoric or unpleasant *b* state.	
c. as a drug's effects wear off, the A process dissipates but the B process endures.	
d. acute tolerance results from the effects of the B process in cancelling out those of the A process.	
e. all of the above are true.	

3-19. Which behavioral paradigm was used by Barrett and Smith (2005) to demonstrate the opponent processes involved in the development of anxiety in rats as a conditioned compensatory response to a tranquilizer?	***Answer:*** B ***Objective:*** ***Topic/Section:*** Box 3-1 Anxiety as a Conditioned Compensatory Response to a Tranquilizer ***Difficulty:*** ***Bloom's level:***
a. Classical conditioning	
b. Drug discrimination	
c. Dissociation	
d. Progressive ratio schedule of reinforcement	
e. Conditioned place preference	

3-20. In Barrett and Smith's (2005) rat study of anxiety as a conditioned compensatory response to a tranquilizer, _____ was the *a* state and _____ was the *b* state.	***Answer:*** C ***Objective:*** ***Topic/Section:*** Box 3-1 Anxiety as a Conditioned Compensatory Response to a Tranquilizer ***Difficulty:*** ***Bloom's level:***
a. the anxiolytic; the anxiogenic	
b. the anxiogenic; the anxiolytic	
c. relaxation; anxiety	
d. anxiety; relaxation	
e. chlordiazepoxide; pentylenetetrazol	

3-21. Which of the following forms of tolerance would be <u>least</u> likely to lead to the development of withdrawal symptoms, when drug administration is discontinued?	***Answer:*** A ***Objective:*** ***Topic/Section:*** Mechanisms of Tolerance/Withdrawal ***Difficulty:*** ***Bloom's level:***
a. Behavioral tolerance	
b. Physiological tolerance	
c. Cellular tolerance	
d. Pharmacodynamic tolerance	
e. All forms of tolerance lead to the development of withdrawal symptoms.	

3-22. In an experiment conducted by Ivan Pavlov's colleague, Dr. Podkopaev, a dog was injected with a small dose of the nauseating drug *apomorphine* and a tone was played in the background. After numerous conditioning trials, the tone alone elicited outwardly visible signs of nausea in the drug-free animal. In this experiment, the apomorphine acted as	***Answer:*** B ***Objective:*** ***Topic/Section:*** Conditioning of Drug Effects ***Difficulty:*** ***Bloom's level:***
a. a neutral stimulus.	
b. an unconditioned stimulus.	
c. a conditioned stimulus.	
d. an unconditioned response.	
e. a conditioned response.	

3-23. In an experiment conducted by Ivan Pavlov's colleague, Dr. Podkopaev, a dog was injected with a small dose of the nauseating drug *apomorphine* and a tone was played in the background. After numerous conditioning trials, the tone alone elicited outwardly visible signs of nausea in the drug-free animal. In this experiment, the tone acted as	***Answer:*** E ***Objective:*** ***Topic/Section:*** Conditioning of Drug Effects ***Difficulty:*** ***Bloom's level:***
a. a neutral stimulus.	
b. an unconditioned stimulus.	
c. a conditioned stimulus.	
d. a conditioned response.	
e. both a. and c.	

3-24. Conditioned drug effects	***Answer:*** C ***Objective:*** ***Topic/Section:*** Conditioning of Drug Effects ***Difficulty:*** ***Bloom's level:***
a. are usually more intense than the effects of the drug.	
b. are very difficult to demonstrate experimentally.	
c. are usually in the direction opposite to those of the drug.	
d. are very short in duration.	
e. are nearly identical to those of the drug.	

3-25. In a classic experiment, Shepard Siegel (1975) demonstrated that the expression of tolerance to the analgesic effect of morphine depended upon the novelty of the environment in which the rats were tested. This is an example of	***Answer:*** C ***Objective:***

a. metabolic tolerance. b. physiological tolerance. c. behavioral tolerance. d. sensitization. e. habituation.	***Topic/Section:*** Conditioning of Drug Effects ***Difficulty:*** ***Bloom's level:***

3-26. In a classic experiment, Shepard Siegel (1975) repeatedly injected rats with morphine and tested their analgesic response using the hot plate test. He discovered that the rats quickly developed tolerance to morphine's analgesic effect. When Siegel later injected these rats with saline and tested their analgesic response on the hot plate, he found that a. their tolerance continued to build. b. the rats showed a strong analgesic response. c. the rats showed a weak analgesic response d. the rats showed a hyperalgesic response. e. the rats' paw-lick latencies were much longer than they were at the end of training.	***Answer:*** D ***Objective:*** ***Topic/Section:*** Conditioning of Drug Effects ***Difficulty:*** ***Bloom's level:***

3-27. Shepard Siegel's (1975) finding that rats' tolerance to the analgesic effect of morphine was evident only in the environment in which the drug had been experienced supports the notion of a. conditional tolerance. b. state-dependent learning. c. operant conditioning. d. conditioned place preference. e. sensitization.	***Answer:*** A ***Objective:*** ***Topic/Section:*** Conditioning of Drug Effects ***Difficulty:*** ***Bloom's level:***

3-28. A person who consumes the same number of identical alcoholic beverages will, all things being equal, likely feel least cognitively impaired under which of the following conditions? a. When a novel alcoholic beverage is consumed in a novel setting b. When a novel alcoholic beverage is consumed in a familiar setting c. When a familiar alcoholic beverage is consumed in a novel setting d. When a familiar alcoholic beverage is consumed in a familiar setting e. The familiarity of the alcoholic beverage and the setting in which it is consumed are irrelevant to a person's subjective level of cognitive impairment caused by alcohol.	***Answer:*** D ***Objective:*** ***Topic/Section:*** Conditioning of Drug Effects ***Difficulty:*** ***Bloom's level:***

3-29. Which of the following factors greatly diminishes the effects of *conditional tolerance*? a. The route of drug administration b. The blood concentration of a drug c. The environment in which the drug is administered d. The rate at which a drug is infused e. All of the above factors affect conditional tolerance	***Answer:*** C ***Objective:*** ***Topic/Section:*** Box 3-2 The Mystery of Heroin Overdose ***Difficulty:*** ***Bloom's level:***

3-30. Shepard Siegel has suggested that unexplained heroin overdose may be caused by a. a loss of metabolic tolerance resulting from damage to the liver. b. a loss of conditional tolerance resulting from taking heroin in a new environment. c. a sudden decrease in the potency of the drug resulting from conditioned drug effects. d. accidentally injecting the drug into an artery rather than a vein. e. none of the above. Heroin overdoses are always explained by taking too much heroin.	***Answer:*** B ***Objective:*** ***Topic/Section:*** Box 3-2 The Mystery of Heroin Overdose ***Difficulty:*** ***Bloom's level:***

3-31. When an animal is placed in an environment where heroin has been repeatedly administered, the animal will likely a. show a conditioned compensatory response. b. experience physiological changes opposite to those caused by the drug. c. demonstrate symptoms of withdrawal. d. experience what Solomon and Corbit (1974) label the B process. e. experience all of the above.	***Answer:*** E ***Objective:*** ***Topic/Section:*** Conditioning of Drug Effects ***Difficulty:*** ***Bloom's level:***

3-32. Conditioned withdrawal symptoms a. do not contribute to drug relapse. b. disappear when physical withdrawal has ended. c. can, in some cases, be used to explain drug relapse. d. only go away through the process of extinction. e. both c. and d. are true.	***Answer:*** E ***Objective:*** ***Topic/Section:*** Conditioning of Drug Effects ***Difficulty:*** ***Bloom's level:***

3-33. Your little sister talks constantly. She interrupts your conversations with friends and asks a million questions. You find her incessant talking extremely irritating, yet you don't want to ignore her and risk hurting her feelings. Plus, every now and then she says something interesting. You decide to use your knowledge of operant conditioning to alter her behavior. Which schedule of reinforcement might you choose to employ in an attempt to decrease your sister's chattiness? a. A differential reinforcement of low rates (DRL) schedule b. A variable ratio (VR) schedule c. A fixed ratio (FR) schedule d. A fixed interval (FI) schedule e. None of the above schedules will have any impact on a chatty little sister.	***Answer:*** A ***Objective:*** ***Topic/Section:*** Operant conditioning of drug effects ***Difficulty:*** ***Bloom's level:***

3-34. Campbell and Seiden (1973) trained rats to respond for food reinforcement in a Skinner box on a *differential reinforcement of low rates* (DRL) schedule. They found that rats could overcome the effects of amphetamine on responding if they had been allowed to practice the DRL schedule under the influence of the drug. This is an example of a. dispositional tolerance. b. habituation. c. behavioral tolerance based on operant conditioning. d. behavioral tolerance based on classical conditioning. e. reverse tolerance.	***Answer:*** C ***Objective:*** ***Topic/Section:*** Conditioning of Drug Effects ***Difficulty:*** ***Bloom's level:***

3-35. Why would rats exhibit tolerance to the motor-stimulating effects of amphetamine when trained to respond for food reinforcement on a *differential reinforcement of low rates* (DRL) schedule, but not on a *fixed interval* (FI) schedule of reinforcement? a. Responding on an FI schedule is prone to ceiling effects, even in the absence of amphetamine, which is not the case for responding on a DRL schedule. b. Rats reinforced on an FI schedule receive immediate feedback on their performance, whereas feedback is delayed on a DRL schedule. c. Responding too quickly on a DRL schedule causes rats to lose reinforcements, but this is not the case on an FI schedule. d. Too few reinforcements are available when responding on an FI schedule, which slows learning; this is not true of a DRL schedule.	***Answer:*** C ***Objective:*** ***Topic/Section:*** Conditioning of Drug Effects ***Difficulty:*** ***Bloom's level:***

e. Amphetamine has no effect on performance on an FI schedule, but speeds performance on a DRL schedule.	

3-36. If one word could be used to describe the cause of the 1997 car crash that killed Britain's Princess Diana, what would that word be?	***Answer:*** A ***Objective:*** ***Topic/Section:*** Box 3-3 Did Alcohol Kill Princess Diana? ***Difficulty:*** ***Bloom's level:***
a. Inexperience	
b. Drunkenness	
c. Carelessness	
d. Speeding	
e. Paparazzi	

3-37. *Sensitization* is also known as *reverse tolerance*. Sensitization and tolerance differ, however, in that	***Answer:*** D ***Objective:*** ***Topic/Section:*** Sensitization ***Difficulty:*** ***Bloom's level:***
a. sensitization does not occur in humans, whereas tolerance does.	
b. sensitization can only be demonstrated with amphetamines and other stimulant drugs, whereas tolerance results from the use of many different drug classes.	
c. sensitization cannot be classically conditioned to neutral stimuli present in the drug-taking environment, whereas tolerance can.	
d. compared to tolerance, sensitization may last for a much longer period of time.	
e. there is no such thing as cross-sensitization, whereas cross-tolerance is well-established in behavioral pharmacology research.	

3-38. *Sensitization* is most often demonstrated in which of the following drug effects?	***Answer:*** E ***Objective:*** ***Topic/Section:*** Sensitization ***Difficulty:*** ***Bloom's level:***
a. The effects of drugs on DRL responding.	
b. The effects of drugs on analgesia.	
c. The effects of drugs on body temperature.	
d. The effects of drugs on cognitive performance.	
e. The effects of drugs on behavioral activation.	

3-39. The sensitization of which brain pathway is believed to be responsible for the excessive craving or 'wanting' exhibited in drug addiction?	***Answer:*** B ***Objective:*** ***Topic/Section:*** Sensitization ***Difficulty:*** ***Bloom's level:***
a. The nigrostriatal dopamine pathway	
b. The mesolimbic dopamine pathway	
c. The tuberoinfundibular dopamine pathway	
d. The mesocortical dopamine pathway	
e. Sensitization of all of the above pathways is responsible for eliciting craving.	

3-40. The sensitization of which brain pathway is thought to be responsible for the emergence of stereotyped behaviors with excessive, long-term drug administration?	***Answer:*** A ***Objective:*** ***Topic/Section:*** Sensitization ***Difficulty:*** ***Bloom's level:***
a. The nigrostriatal dopamine pathway	
b. The mesolimbic dopamine pathway	
c. The tuberoinfundibular dopamine pathway	
d. The mesocortical dopamine pathway	
e. Sensitization of all of the above pathways is responsible for the emergence of stereotyped behaviors.	

3-41. If an animal with a history of cocaine administration demonstrates increased behavioral activation following an injection of morphine, this is evidence for	***Answer:*** D ***Objective:*** ***Topic/Section:*** Sensitization
a. behavioral tolerance.	
b. generalization.	

c. cross tolerance. d. cross sensitization. e. none of the above. Cocaine and morphine belong to different drug classes and cannot influence one another.	***Difficulty:*** ***Bloom's level:***

3-42. The *placebo effect* a. plays a minimal role in behavioral pharmacology research. b. may be responsible for up to 75% of the effectiveness of antidepressant drugs. c. may be responsible for up to 50% of the effectiveness of pain relievers. d. is an important consideration in designing behavioral pharmacology research studies. e. relates to all of b., c., and d. above.	***Answer:*** E ***Objective:*** ***Topic/Section:*** Expectancy and Context ***Difficulty:*** ***Bloom's level:***

3-43. Inclusion of which of the following research groups convinced Benedetti, Amanzio, and Maggi (1995) that the drug *proglumide* is not an effective pain killer. a. Natural History group b. Hidden Drug group c. Placebo group d. Open Drug group e. None of the above—the researchers determined that proglumide is, in fact, an effective pain killer.	***Answer:*** B ***Objective:*** ***Topic/Section:*** Expectancy and Context ***Difficulty:*** ***Bloom's level:***

3-44. Italian researchers Benedetti, Amanzio, and Maggi (1995) included an uncommon control group in their study of the analgesic effect of *proglumide* in post-surgical patients. What was this group? a. Patients who received saline, but did not know it. b. Patients who received proglumide, but did not know it. c. Patients who were told they were receiving saline. d. Patients who were told they were receiving proglumide. e. None of the above groups is uncommon in analgesic drug research.	***Answer:*** B ***Objective:*** ***Topic/Section:*** Expectancy and Context ***Difficulty:*** ***Bloom's level:***

3-45. According to Colloca and Benedetti (2005), the analgesic response of participants receiving the drug *proglumide* was greater than that of participants receiving a placebo because a. proglumide is an effective pain-killer. b. placebos have no effect on pain. c. patients' expectation of receiving proglumide activated an *expectation mechanism*. d. the administration of a placebo failed to activate an *expectation mechanism*. e. all of the above are true.	***Answer:*** C ***Objective:*** ***Topic/Section:*** Expectancy and Context ***Difficulty:*** ***Bloom's level:***

3-46. Which of the following is <u>false</u>, regarding the *placebo effect*? a. The endogenous opioid system plays an important role in placebo analgesia. b. The placebo analgesic effect involves the same pain control mechanisms as those of morphine and other opioids. c. The placebo analgesic effect can be produced by more than one brain system. d. Conditioned placebo effects are blocked by the opioid antagonist, naloxone. e. Unconditioned placebo effects are blocked by the opioid antagonist, naloxone.	***Answer:*** D ***Objective:*** ***Topic/Section:*** Expectancy and Context ***Difficulty:*** ***Bloom's level:***

3-47. Using positron emission tomography (PET) to image the brain, Volkow and colleagues (2003) found that the effects of methylphenidate (Ritalin) on brain metabolism and on participants' reports of feeling 'high' were greater when participants	***Answer:*** B ***Objective:*** ***Topic/Section:*** Expectancy and Context ***Difficulty:*** ***Bloom's level:***
a. were not expecting the drug.	
b. were expecting the drug.	
c. administered the drug themselves.	
d. were administered the drug by a researcher.	
e. were in a highly distracting environment.	

3-48. In a study investigating the effectiveness of a placebo in the treatment of irritable bowel syndrome (IBS) symptoms, Kaptchuk and colleagues (2010) discovered that	***Answer:*** C ***Objective:*** ***Topic/Section:*** Expectancy and Context ***Difficulty:*** ***Bloom's level:***
a. patients who knowingly took a placebo reported no improvement in IBS symptoms.	
b. patients who knowingly took IBS medication reported no improvement in IBS symptoms.	
c. patients who knowingly took a placebo reported improvement in IBS symptoms.	
d. patients who knowingly took IBS medication reported improvement in IBS symptoms.	
e. control-group patients who received no treatment reported improvement in IBS symptoms.	

3-49. What is the *nocebo effect*?	***Answer:*** D ***Objective:*** ***Topic/Section:*** Expectancy and Context ***Difficulty:*** ***Bloom's level:***
a. It is the failure to find any placebo effect in drug research.	
b. It is the failure to find a large placebo effect in drug research.	
c. It is the ability of a placebo to produce therapeutic effects in drug research.	
d. It is the ability of a placebo to produce adverse side effects in drug research.	
e. It is the ability of a pharmaceutical drug to produce a placebo effect.	

3-50. A 1997 study by Hemby and colleagues found that levels of dopamine in the nucleus accumbens were higher in rats that	***Answer:*** A ***Objective:*** ***Topic/Section:*** Expectancy and Context ***Difficulty:*** ***Bloom's level:***
a. were allowed to actively self-administer cocaine by pressing a lever.	
b. were passively injected with cocaine by a researcher.	
c. were injected with cocaine every time rats in the yoked condition received a cocaine injection.	
d. worked for cocaine on variable ratio (VR) schedule of reinforcement.	
e. worked for cocaine on a fixed interval (FI) schedule of reinforcement.	

Short Answer Questions

3-1. Compare and contrast *pharmacokinetic* and *pharmacodynamic* tolerance.	***Topic/Section Containing Answer:*** Mechanisms of Tolerance—Pharmacokinetic Tolerance/Pharmacodynamic Tolerance

3-2. Explain how the process of *homeostasis* can influence the effectiveness of a drug.	***Topic/Section Containing Answer:*** Mechanisms of Tolerance—Pharmacodynamic Tolerance

3-3. Describe the importance of *functional disturbances* in the development of tolerance to drug effects. Cite research that supports your answer.	***Topic/Section Containing Answer:*** Mechanisms of Tolerance—Functional Disturbances

3-4. Explain why use of the term *dependence* can be confusing. What is the relationship between dependence, withdrawal, and addiction?	***Topic/Section Containing Answer:*** Withdrawal—Dependence

3-5. Applying what you have learned about Solomon and Corbit's (1974) *opponent process theory*, explain why a person may feel drunk at a given blood alcohol level while alcohol concentration in the body is rising, but feel sober at that same blood alcohol level while alcohol concentration in the body is falling.	***Topic/Section Containing Answer:*** Tolerance—Acute Tolerance/Withdrawal—Opponent Process Theory

3-6. Describe the reason for a *hangover*, in the context of Solomon and Corbit's (1974) *opponent process theory*.	***Topic/Section Containing Answer:*** Withdrawal—Opponent Process Theory

3-7. Define *conditional tolerance*. Briefly describe the methodology and outline the results of Shepard Siegel's (1975) experiment in which rats were tested for the development of conditional tolerance to morphine's analgesic effects.	***Topic/Section Containing Answer:*** Conditioning of Drug Effects—Classical Conditioning of Drug Tolerance

3-8. Chronic heroin users are able to survive self-administering doses of the drug that would prove lethal in a non-tolerant individual. Yet, some of these individuals 'mysteriously' die from overdose after taking an amount of heroin that is similar or lower than doses they regularly used. Why might this be the case?	***Topic/Section Containing Answer:*** Box 3-2 The Mystery of Heroin Overdose

3-9. Shepard Siegel and colleagues were interested in explaining how it is possible for a chronic heroin user to die of drug overdose after taking an amount heroin that was readily tolerated previously. The researchers reasoned that tolerance to heroin is partly conditioned to the environment in which the drug is normally administered. To test their theory, the researchers conducted an experiment with rats. Describe the methodology and outline the results of this Siegel et al. (1982) study.	***Topic/Section Containing Answer:*** Box 3-2 The Mystery of Heroin Overdose

3-10. One piece of advice often offered to a person recovering from alcoholism is to stay away from bars or places where he or she often consumed alcohol. Why is this a common piece of advice? Do you agree with this advice?	***Topic/Section Containing Answer:*** Conditioning of Drug Effects—Classical Conditioning of Withdrawal

3-11. Briefly describe the methodology and outline the results of Judith Campbell and Lewis Seiden's (1973) experiment in which rats were tested for the effects of operant conditioning on tolerance to amphetamine's motor-stimulating effects.	***Topic/Section Containing Answer:*** Conditioning of Drug Effects—Operant Conditioning of Drug Effects

3-12. List two similarities and two differences between drug *tolerance* and *sensitization*.	***Topic/Section Containing Answer:*** Sensitization

3-13. Describe the experimental design and research outcomes of the 1995 study conducted by Italian researchers Benedetti, Amanzio, and Maggi who investigated the analgesic properties of the drug *proglumide*.	***Topic/Section Containing Answer:*** Expectancy and Context

3-14. For the past two months, Annie has been suffering from tension headaches. She doesn't want to take medications daily, and decides to visit an acupuncturist. Under what circumstances is Annie most likely to experience benefit from acupuncture and alleviation of her headaches?	***Topic/Section Containing Answer:*** Expectancy and Context—The Placebo Effect in Medical Treatment

3-15. How are the *placebo effect* and the *nocebo effect* similar to one another, and how are they different?	***Topic/Section Containing Answer:*** Expectancy and Context—The Placebo Effect/The Nocebo Effect

Essay Questions

3-1. Illustrate Solomon and Corbit's (1974) *opponent process theory* in the form of a graph that represents the effects of a single drug administration. Label the axes and lines appropriately. Making reference to the graph, explain how this theory can account for both acute tolerance and symptoms of hangover. Extend your discussion by adding further information to the graph, this time depicting the opponent process theory in relation to the effects of chronic drug administration. How does this theory account for the development of drug tolerance and the withdrawal symptoms that emerge in drug dependency?	***Topic/Section Containing Answer:*** Withdrawal

3-2. Describe how classical conditioning can influence the emergence of drug tolerance and risk of drug overdose. Outline research evidence to support your explanations.	***Topic/Section Containing Answer:*** Conditioning of Drug Effects—Classical Conditioning of Drug Tolerance/Box 3-2 The Mystery of Heroin Overdose

3-3. The work of researcher Shepard Siegel has significantly advanced our understanding of the important role contextual cues play in the development and expression of drug tolerance and the risk of drug overdose. Describe Siegel's work with laboratory animals, and discuss the implications arising from his findings as they relate to the human drug user.	***Topic/Section Containing Answer:*** Conditioning of Drug Effects—Classical Conditioning of Drug Tolerance/Box 3-2 The Mystery of Heroin Overdose

3-4. Compare and contrast drug *tolerance* and *sensitization*.	***Topic/Section Containing Answer:*** Tolerance/Sensitization

3-5. Is it ethical for physicians to prescribe a placebo as treatment, unbeknownst to their patients? Support your opinion with research evidence.	***Topic/Section Containing Answer:*** Expectancy and Context