Supplementary material to "A Critical Thinking ctivity on Drug Tolerance for Undergraduate Neuroscience Courses"
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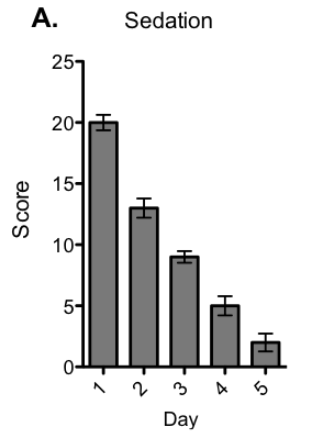
Activity – Drug Tolerance

Background: A new street drug was discovered in Seattle, WA. It did not match the description of any known drugs, so they decided to refer to it as Drug X. Little is known about its characteristics. The research team developed a series of experiments in rodents to investigate its properties.

PART 1: A group of rats were given a subcutaneous injection of Drug X at the same time each day for five consecutive days. The dose of each injection of Drug X was always the same (10mg/kg). After each injection, rats' sedative response (calmness/sleepiness) to Drug X were measured by researchers and scored on a scale. The data are located to the left:

Fig.1



a. Briefly explain what happens with rats' sedation in response to Drug X over time.

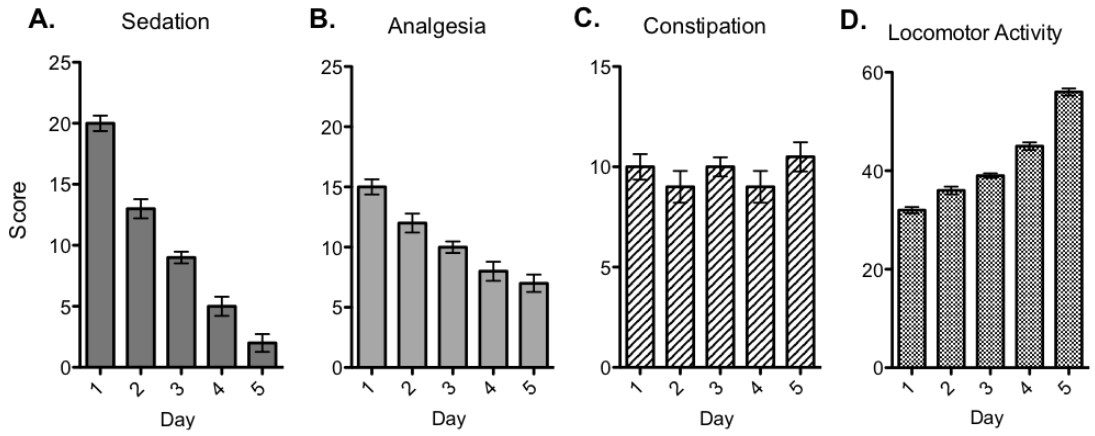
b. What is the term for this pattern in behavior?

c. Provide a definition of this phenomenon here:

d. Based on the information provided and your knowledge thus far, brainstorm <u>at least two potential factors</u> that could be contributing to this change in drug response over time. In other words, consider how this pattern of behavior might be attributed to metabolic, pharmacodynamic or behavioral factors. Not much is known about Drug X,, so think creatively and speculate, based on what you know. What types of factors could be contributing to this pattern of behavior?

PART 2: Researchers wanted to learn more about Drug X, so they monitored three other behavioral responses: analgesia (pain prevention/relief), constipation and locomotion. Fig.1 depicts these new data, alongside the sedation data from Part 1.

Fig.1



1. Does tolerance occur in any other behavioral response measured here? If so, which one(s)?

2. What is the primary difference between the patterns of sedation (Fig.1A) and analgesia (Fig.1B)?

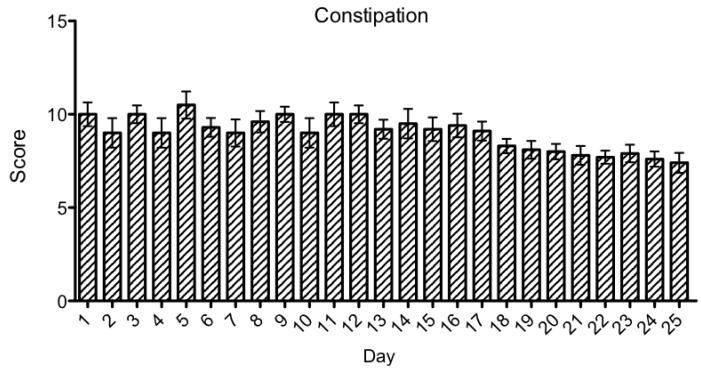
3. What is the primary difference between the patterns of sedation and analgesia and the pattern of constipation?

4. Given these data:
   (a) does tolerance develop to all drug effects?

   (b) does tolerance always develop at the same rate?

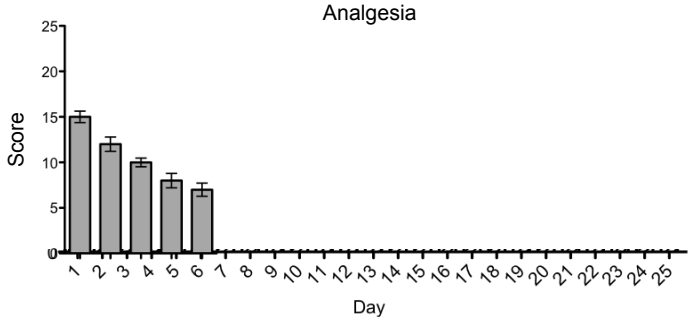
PART 3: The research team was intrigued by the lack of change in constipation after five consecutive days of drug exposure (Fig.1C). They decided to continue administering Drug X for twenty more days. Fig.2 depicts these data.

Fig.2



1. Is the response pattern seen in Fig.2 consistent with your general statement from Part 2 Q4 (above)? Why/why not?

2. What do you think would happen to analgesia if Drug X was administered for 20 more days? Complete the graph to the right.

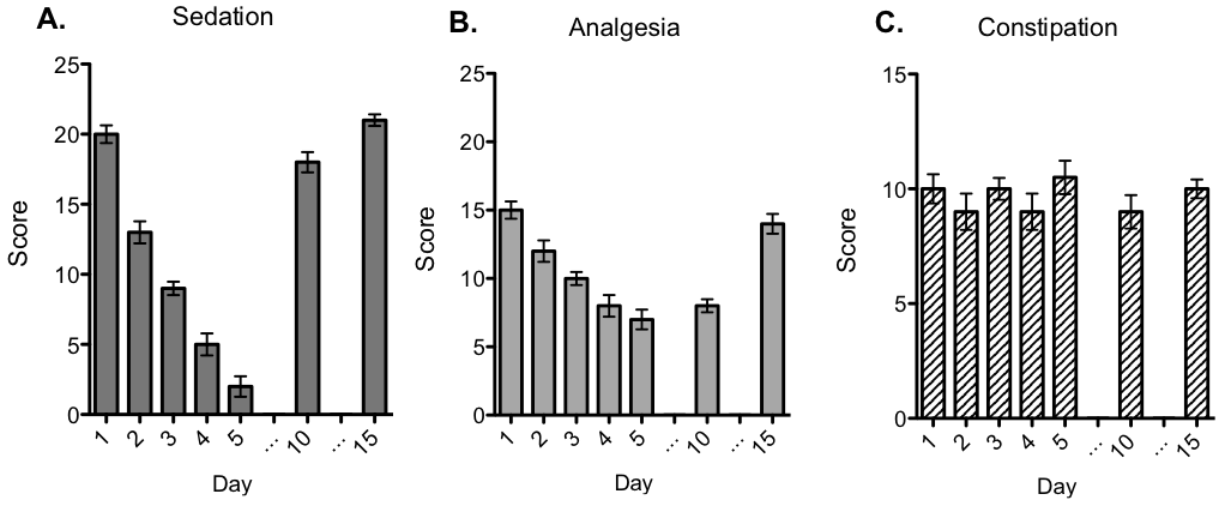


3. Would Drug X be a good painkiller to administer patients with chronic pain? Why/why not?

4. If you were a doctor who could only administer Drug X to help somebody in chronic pain, what would you need to do to ensure that they were receiving adequate pain relief after weeks or months of taking Drug X?

PART 4: The research team was curious how the rats would respond after they were re-exposed to drug after a drug-free period. After Day 5 of drug treatment, Drug X was withheld and rats remained in their homecage without any drug until Day 10, when they received an injection of Drug X. They again remained drug-free until Day 15, when they received a second injection of Drug X. Both of these Drug X injections used the same dose/ route as the first five days.

Fig.3



1. Describe rats' levels of <u>sedation</u> upon drug re-exposure on Day 10. Consider how Day 10 levels compare to, say, levels on Day 1 and Day 5. How would you interpret this?

2. How does the rats' sedation change, if at all, upon re-exposure at Day 15? Why do you think this is?

3. Is tolerance permanent? Under what conditions might it persist?

4. Describe rats' levels of analgesia upon drug re-exposure on Day 10. Consider how Day 10 levels compare to levels on Day 1 and Day 5. How would you interpret this?

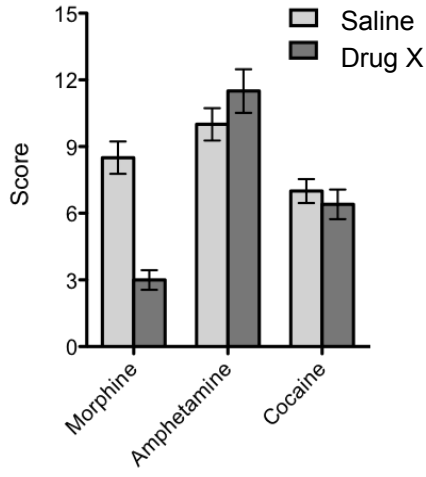
5. How does the rats' analgesia change, if at all, upon re-exposure at Day 15? Why do you think this is?

6. Under what conditions does it seem that tolerance might be reversed?

PART 5: Researchers wanted to compare the sedative effects of Drug X with other abused drugs. However, their only remaining cohorts of rats had already been exposed to Drug X or saline for five consecutive days. The researchers gave a single injection of a different drug (either morphine, amphetamine or cocaine) to rats that had previously received Drug X or saline, then measured the rats' sedation. Fig.4 depicts these data.

1. Describe how rats responded to morphine after receiving prior exposure to saline or to Drug X.

Fig.4 Sedation

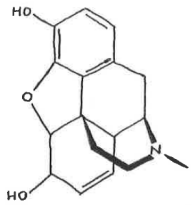


2. Why do you think that rats' level of sedation in response to morphine differed based on their previous Drug X exposure? What is the term that describes this phenomenon?

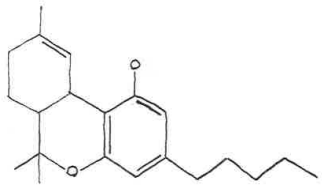
3. Why do you think that rats' level of sedation in response to amphetamine or cocaine did *not* differ based on whether their previous exposure to saline or Drug X?

4. Look at the chemical structures of the drugs below. Circle the drugs that you predict would produce a sedative response that would <u>differ</u> between rats that had previously been exposed to saline and those that had been exposed to Drug X, similar to the data shown in Fig.4. Why did you choose these drugs?

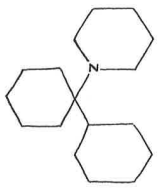
Morphine



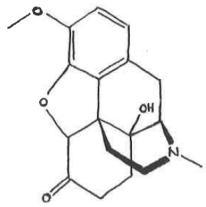
THC



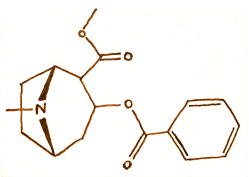
PCP



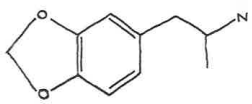
Oxycodone



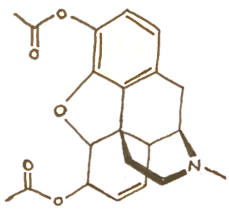
Cocaine



MDMA (Ecstasy)



Heroin



Thanks to L. Paul Sands for drawing the chemical structures.