

## Homework Assignment 7: Due at the beginning of class 2/22/02



Figure 1: OxyContin (R) tablets.

In May 1996, the Food and Drug Administration (FDA) approved the prescription medication OxyContin<sup>®1</sup> for use in the treatment of moderate to severe pain which requires treatment for more than a few days, such as the pain associated with musculoskeletal conditions<sup>2</sup> (see Figure 1<sup>3</sup>). OxyContin<sup>®</sup> was developed and is marketed by Purdue Pharma L.P. (see Figure 2<sup>4</sup>).

Nick-named “hillbilly heroin”<sup>5</sup> this prescription medicine became controversial in the late 1990’s as rumors of rampant abuse (especially in rural areas of Eastern and Southern states<sup>6</sup>) and OxyContin<sup>®</sup>-related deaths were reported in the popular media. (When OxyContin<sup>®</sup> tablets are powdered and either snorted or injected, the drug produces a heroin-like high<sup>7</sup>. Figure 3<sup>8</sup> shows the molecular similarities between oxycodone and heroin.)

Federal officials<sup>9</sup> are reported to have described OxyContin<sup>®</sup> as “the most widely abused prescription drug ... in the last twenty years.” The temperature of this controversy has recently been increased by DEA Administrator Asa Hutchinson’s

testimony before congress<sup>10</sup> on December 11, 2001. In his testimony, Administrator Hutchinson implicated<sup>11</sup> Purdue Pharma L.P. in the “escalating abuse and diversion of the drug.” Hutchinson charged:

“Disproportionate abuse of OxyContin<sup>®</sup> may be partially due to aggressive marketing and promotion ... Due to concern that pharmaceutical companies are now marketing directly to consumers, DEA is communicating to the pharmaceutical industry our belief that direct to consumer advertising of controlled substances is contrary to the public interest.”

<sup>1</sup> OxyContin<sup>®</sup> is a registered trade mark of Purdue Pharma L.P. Any reference to OxyContin<sup>®</sup> in this document that does **not** include the symbol ® reflects an omission of this symbol in the original document quoted.

<sup>2</sup> Source: *CenterWatch*<sup>TM</sup> Clinical Trials Listing Service. <http://www.centerwatch.com/>

<sup>3</sup> Image source: <http://www.npr.org/>

<sup>4</sup> Image source: <http://www.purduepharma.com/>

<sup>5</sup> Source: CNN. (2001) “States work to control OxyContin abuse.” July 20, 2001.

<sup>6</sup> Source: <http://www.oxyabusekills.com/>

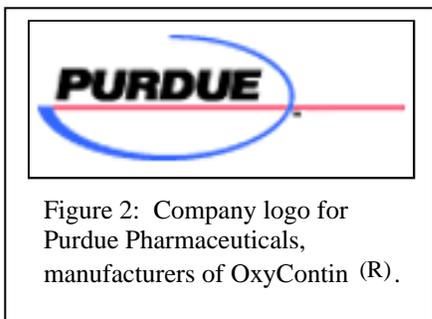
<sup>7</sup> Source: Nancy Zuckerbrod, Associated Press. (2001) “DEA Reproves OxyContin Maker.” *Sun News*, Thursday 13 December, 2001.

<sup>8</sup> Image sources: <http://www.purduepharma.com/> and <http://www.ch.ic.ac.uk/>

<sup>9</sup> Source: <http://www.oxyabusekills.com/>

<sup>10</sup> Source: The full text of Administrator Hutchinson’s testimony can be found on-line at: <http://www.usdoj.gov/dea/pubs/testimony.htm>

<sup>11</sup> Certain other marketing practices of Purdue Pharma L.P. have come under intensive scrutiny due to the OxyContin<sup>®</sup> controversy. Included at the end of this homework assignment is a report from the *South Carolina Sun News* detailing some of Purdue Pharma’s questionable practices.



In response to the abuse of OxyContin<sup>®</sup> Purdue Pharma L.P. (in cooperation with the FDA and DEA) have included strong warnings in the printed inserts that they are required (by law) to include with shipments of OxyContin<sup>®</sup>. Part of the text of this strengthened warning is shown below. OxyContin<sup>®</sup> is the best-selling drug in it's category. In 2000, approximately six million prescriptions were written generating revenues for Purdue Pharma in excess of one billion dollars<sup>12</sup>.

**WARNING<sup>13</sup>:**

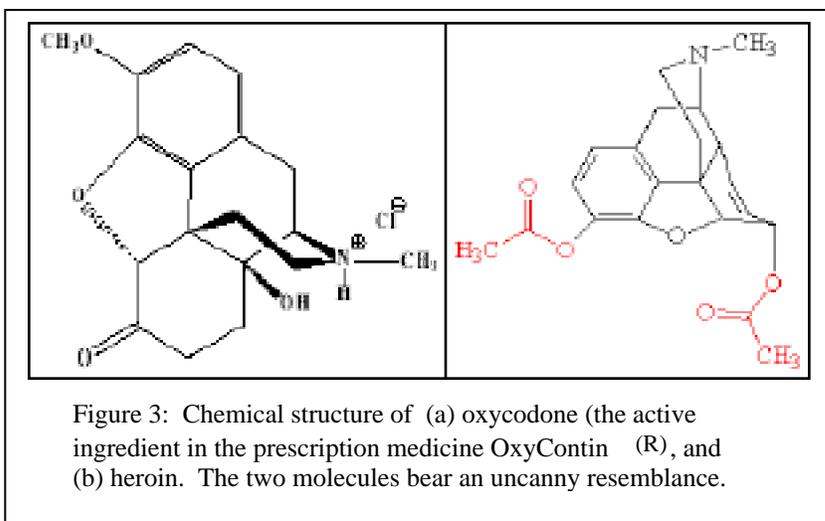
**OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.**

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

**OxyContin Tablets are a controlled-release formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.**

**OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY.** These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

**OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.**



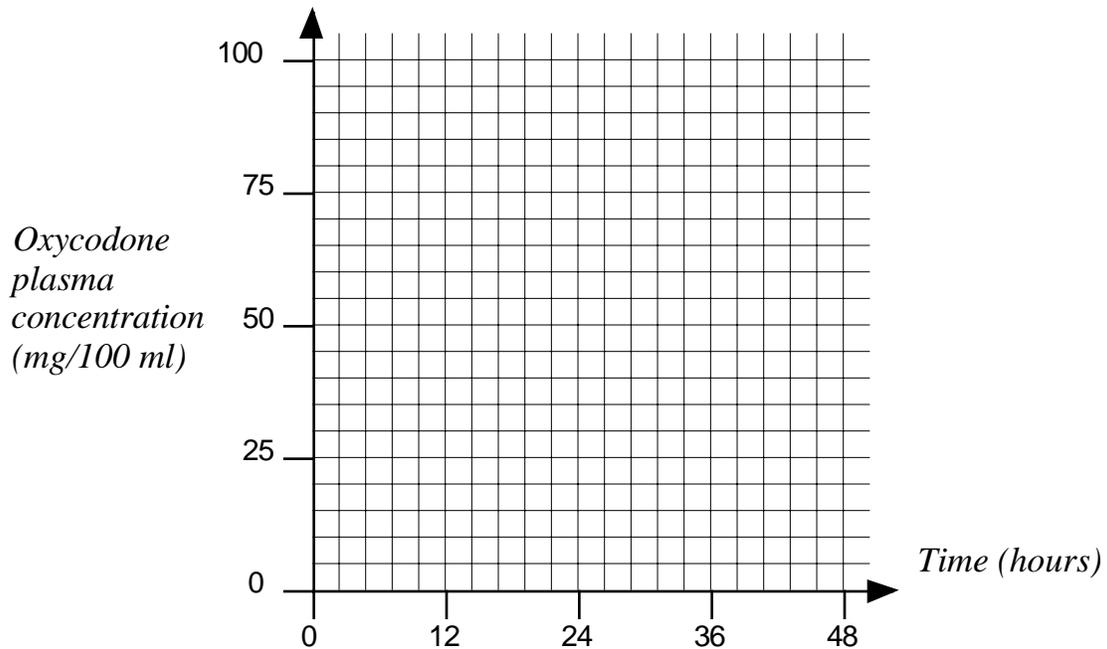
The text of the packet insert goes on to give the elimination half-life<sup>14</sup> of oxycodone (on average, it is 3.2 hours) and the suggested dosage (one tablet every 12 hours).

<sup>12</sup> Source: Josh White. (2001) "OxyContin Abuse is Increasing, DEA Says." *The Washington Post*, Wednesday December 12, 2001.

<sup>13</sup> This warning is from the package insert that Purdue Pharma is required (by law) to include with shipments of OxyContin<sup>®</sup>.

<sup>14</sup> This is the amount of time that it takes for a person's body to eliminate half of the amount of oxycodone present in the body. This is a lot like the "half life" in a radioactive decay problem.

1. The most commonly<sup>15</sup> prescribed dosage of OxyContin<sup>®</sup> quickly establishes an oxycodone plasma concentration<sup>16</sup> of 20 mg/100ml. That is, each 100 ml of the patient's blood will contain 20 mg of oxycodone. Let  $t$  represent the number of hours since a patient was given an OxyContin<sup>®</sup> tablet and  $M(t)$  represent the oxycodone plasma concentration. Find an equation for  $M(t)$ .
2. According to the equation that you have found in Question 1, what is the oxycodone plasma concentration twelve hours after the patient was given the OxyContin<sup>®</sup> tablet?
3. The dosage guide for OxyContin<sup>®17</sup> suggests that the dose should be repeated every 12 hours. Use the axes shown below to sketch the oxycodone plasma concentration of a person who is given an OxyContin<sup>®</sup> tablet every 12 hours, as suggested.



**NOTE:** You should hand in a completed graph as part of your work for this assignment.

<sup>15</sup> Source: <http://www.purduepharma.com/IP/Oxycontin.pdf>

<sup>16</sup> This is the concentration of oxycodone in the patient's blood.

<sup>17</sup> Source: <http://www.purduepharma.com/IP/Oxycontin.pdf>

4. Using your graph from Question 3 (and other understandings of what is going on) complete the table shown below.

Time since OxyContin <sup>®</sup> treatment started (hours)	0	12	24	36	48	96	144	192
Oxycodone Plasma Concentration (mg/100ml)								

**NOTE:** You should hand in a completed table as part of your work for this assignment.

5. Suppose that the patient who is receiving OxyContin<sup>®</sup> continues to take the drug indefinitely. The lethal dose of oxycodone is estimated<sup>18</sup> to be between 100 mg/100ml and 200 mg/100ml. Generally speaking death in the case of oxycodone overdose is due to severe respiratory arrest. Use a geometric series to express the oxycodone plasma concentration of the patient and determine whether the patient will be at risk for receiving a lethal dose of oxycodone<sup>19</sup> if they continue to take the suggested dose of OxyContin<sup>®</sup> indefinitely.

**Extra Credit (Up to 10 additional points available):**

Suppose that a person (who is not opioid tolerant) takes an OxyContin<sup>®</sup> tablet every twelve hours, as suggested by the packet insert that accompanies the drug. What is the minimum level of oxycodone plasma concentration that an OxyContin<sup>®</sup> should deliver in order to *eventually* cause a lethal dose of oxycodone? Use your result to explain why Purdue Pharma L.P. stipulates that the 80 mg/100ml and 160 mg/100ml OxyContin<sup>®</sup> tablets should only be prescribed to patients who are opioid tolerant.

<sup>18</sup> Source: <http://ash.xanthia.com/> The oxycodone plasma concentrations given are for people who are not accustomed to opiates. For people who are tolerant of or accustomed to opiates, these lethal doses may be higher. This dosage is called the LD-50. "LD-50" stands for "Lethal Dose 50%" which means the dose at which 50% of people who were exposed would be expected to die. This figure is estimated because the FDA generally does not permit clinical trials in which a pool of patients are exposed to steadily higher levels of the substance until 50% of them are dead.

<sup>19</sup> People who crush and either snort or inject OxyContin<sup>®</sup> can achieve oxycodone plasma concentrations that are this high. Complete inhalation of the powder obtained from crushing one 80 mg/100ml OxyContin<sup>®</sup> tablet may deliver a oxycodone plasma concentration of 100-200 mg/100ml.