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# Buprenorphine Pharmacokinetics Following Intravenous Administration in Gestating Sheep

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## Abstract

Pregnant women who are addicted on opioids are frequently treated with buprenorphine, a semi-synthetic opioid. Pregnancy-related buprenorphine pharmacokinetics is little studied. To find out the pharmacokinetics of intravenous buprenorphine in pregnant sheep, we performed a pharmacokinetic study. An intravenous bolus injection containing 10 μg/kg of buprenorphine was administered to 14 pregnant sheep with late gestation. Plasma samples were taken for up to 48 hours following administration. Using an LC/MS/MS approach, the levels of buprenorphine and its metabolite, nor buprenorphine, were measured in plasma. The lower limits of quantification for each drug were 0.01μg/L and 0.04μg/L, respectively. Non-compartmental analysis was used to calculate the pharma-cokinetic parameters. The median (minimum–maximum) pharmacokinetic characteristics were: Cmax 4.31 μg/L (1.93–15.5), AUCinf 2.89 h*μg/L (1.72–40.2), and CL 3.39 L/h/kg (0.25–Vss 8.04 L/kg (1.05–49.3), terminal t½ 1.75 h (1.07–31.0), and 6.02. Norbuprenorphine was not found in any of the plasma samples. Compared to non-pregnant sheep and male human participants, the median clearance in pregnant sheep was greater. Six subjects had extended terminal half-lives, and a high degree of between-subject variability was found in the sample population using our sensitive analytical approach. Statement of significance: Pregnant women with opioid use disorder are frequently treated with buprenorphine. Nevertheless, there is a paucity of information regarding the pharmacokinetics of buprenorphine in pregnancy. We performed a study on pregnant sheep because this kind of research cannot be done on humans for ethical reasons. The pharmacokinetic information on buprenorphine in pregnant sheep provided by this study aids in our comprehension of the drug's pharmacokinetics in humans.

**Keywords:** Buprenorphine • Pharmacokinetics • Pregnancy • Sheep

## Introduction

Buprenorphine (BUP) exhibits antagonistic actions at the δ- and κ-opioid receptors while functioning as a partial agonist at the μ-opioid receptor [1,2]. The antinociceptive effect may potentially be attributed to antagonistic interactions with the opioid receptor-like 1 receptor [1,3]. BUP is categorized as a long-acting opioid because of its strong affinity and slow rate of dissociation from the opioid receptors [1,4]. BUP is a tiny, very lipophilic molecule that has a 96% binding strength to plasma proteins. BUP is N-dealkylated into norbuprenorphine (NBUP), its primary active metabolite, in the liver by CYP3A4. Uridine 5'-diphospho-glucuronosyltransferase (UGT) UGT1A1, UGT1A3 and UGT2B7 further glucuronidate BUP and NBUP to form BUP-3-glucuronide and NBUP-3-glucuronide. The majority of BUP and its metabolites are excreted in feces, with water-soluble metabolites accounting for 10-15% of the dose that is excreted in urine [5]. Since 1996, buprenorphine has been used to treat opioid use disorder and moderate-to-severe pain. BUP is frequently used in the therapy of opioid replacement for pregnant women who are addicted to opioids; however it is not advised for the management of pain during pregnancy. The pharmacokinetics of BUP during pregnancy is not well characterized, despite its widespread use. Pregnancy can cause a number of physiological and body composition changes that may impact (Figure 1).

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## Materials and Methods

### BUP's pharmacokinetics

These include modifications in the expression and activity of metabolizing enzymes (CYP3A4 and UGTs), decreased protein binding and increases in cardiac output, plasma volume, total body water, and glomerular filtration rate [6]. Women using BUP for replacement treatment of opioid dependency have lower BUP exposure (area under the plasma concentration curve, AUC) during pregnancy than postpartum after sublingual dose [7,8]. In Human BUP metabolic ratios, or the AUC of BUP divided by the AUC of NBUP and NBUP-glucuronide are higher during pregnancy than they are during the postpartum phase. these results might point to a higher BUP systemic clearance during pregnancy. There are, however, few pharmacokinetic studies on BUP during pregnancy. The primary goal of this study was to determine the basic pharmacokinetic parameters of BUP in pregnant sheep following intravenous (IV) administration. These parameters will be useful for understanding BUP

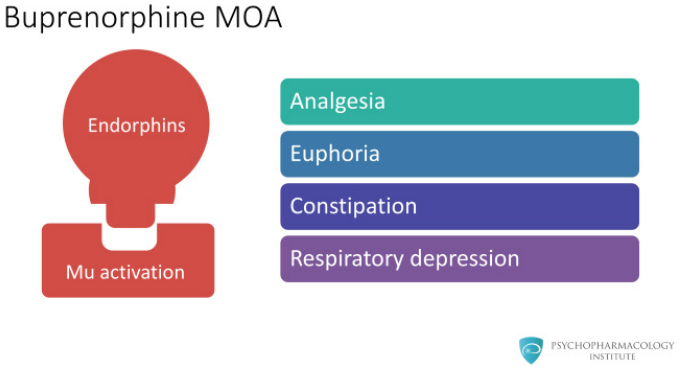


**Figure 1.** The buprenorphine mechanisms of action and rationale for therapeutic use in the brain, naturally produced opioids called endorphins is released in the synapse and activate the opioid receptors producing a classic mu-opioid response. The effects include: analgesia, euphoria, constipation and respiratory depression.

pharmacokinetics in humans during pregnancy as well as for future reference in subsequent studies on BUP central nervous system permeation in the sheep model. Since it was unethical to perform this kind of Figure investigation on humans, we employed a pregnant sheep model (Figure 2). Fourteen sheep in this investigation were nearing the end of their pregnancies. Sheep are similar to humans in size and weight; hence they were selected as the study's animal model. Furthermore, the sheep fetus is comparable in size and weight to the human fetus in the latter stages of gestation, although having a half the duration of the human gestation period. The animal's size facilitates cannulation and allows for the collection of enough blood samples from it. Sheep also have the advantage of quickly adapting to the handling and laboratory setting, displaying little to no stress throughout acclimatization and research. When compared to rat species, these characteristics provide notable advantages in obstetric investigations. But no animal model is precisely like a human being. Despite the fact that the fundamental purpose of While the placental interface varies between species and can impact a medication's pharmacokinetics, the placenta's functions during pregnancy are comparable to those of all mammals, including hormone production, drug transfer, and the transfer of nutrients and pharmaceuticals. In contrast to humans, where the placenta consists of only one layer of trophoblasts to separate the maternal blood from the fetal circulation (hemomonochorial placenta), sheep have a placenta made up of one layer of maternal uterine endothelium and one layer of trophoblasts to separate the maternal and fetal circulation [9]. As far as we are aware, there have been no reports on the IV pharmacokinetics of BUP in pregnant sheep. Studies on the pharmacokinetics of IV BUP in non-pregnant sheep have been conducted; however they have some drawbacks, chief among them being brief research duration (Figure 3). In Nolan and colleagues' investigation with only six hours after injecting 6 µg/kg BUP intravenously (IV), plasma samples from six adult female sheep were obtained in the Lindhardt K, study, 3 sheep were sampled for one hour [10]. Neither study was able to capture the genuine BUP elimination phases due to the short sampling duration. Our study's objective was to measure the amounts of BUP and NBUP in pregnant sheep following a single IV bolus treatment. BUP and NBUP were measured using a very sensitive LC/MS/MS technique on plasma samples that were obtained up to 48 hours after dosing. Each unique pharmacokinetic parameter was found using no compartmental analysis. Pregnancy raises the systemic clearance (CL) of BUP in comparison to no pregnant sheep, according to our study hypothesis.

## Results and Discussion

To the best of our knowledge, this study is the first to investigate the pharmacokinetics of intravenous BUP in pregnant sheep and the first to collect blood samples from sheep up to 48 hours after IV BUP administration. We were able to gather more accurate pharmacokinetic data during the elimination phase because to an extended sampling interval and an extremely sensitive quantification technique. Pregnant lambs were used because they offered the nonclinical data required to evaluate potential dangers to expectant mothers and foetuses (Figure 4). Without previous nonclinical data, this kind of study could not be conducted in humans for ethical reasons. There was significant inter-subject variation in the pharmacokinetic characteristics, which was partially caused by the rapid drop in plasma buprenorphine concentrations below the LLOQ in the first seven hours following injection in eight out of fourteen lambs. All plasma samples lacked NBUP, indicating that NBUP concentrations are insignificant following a single intravenous dosage of BUP (10 µg/kg) in sheep. Because BUP pharmacokinetic studies frequently show considerable inter individual variability, we used 14 sheep for the study in order to boost the power of the findings [11]. We created a highly sensitive LC/MS/MS approach for BUP and NBUP quantification from sheep plasma, which was able to precisely measure BUP content at and above 0.01 µg/L with an upper limit of linearity of 25.0 µg/L. This allowed us to identify very low amounts at late time periods. Plasma concentrations were obtained in this investigation up to 48 hours following IV injection, which demonstrated be sufficient to record the actual removal stage for individuals with detectable plasma concentrations at later time periods. Compared to those who only displayed detectable plasma concentrations up to 7 hours after injection (median 1.65 hours), these people had a terminal half-life that was significantly longer (median 15.2 hours). We

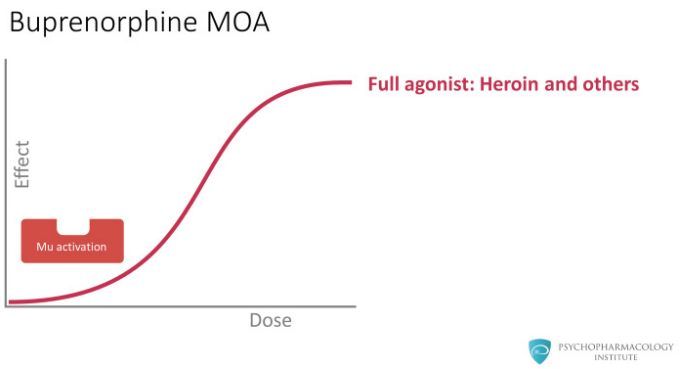


**Figure 2.** When exogenous opioids like heroin are ingested and enter the brain, it will also activate the same receptors producing the same results. Because heroin is a full mu-opioid agonist, at some dose, the receptors are fully activated to a theoretical 100% maximal effect.

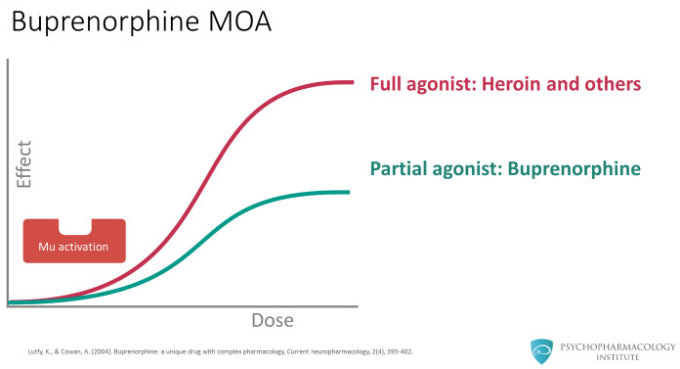


**Figure 3.** There are two main issues of buprenorphine that make it unique from other full agonist opioids. The first is that buprenorphine is a partial agonist. It activates the mu-opioid receptors producing the same results: analgesia, euphoria, constipation and respiratory depression. But it does so to a certain limit.

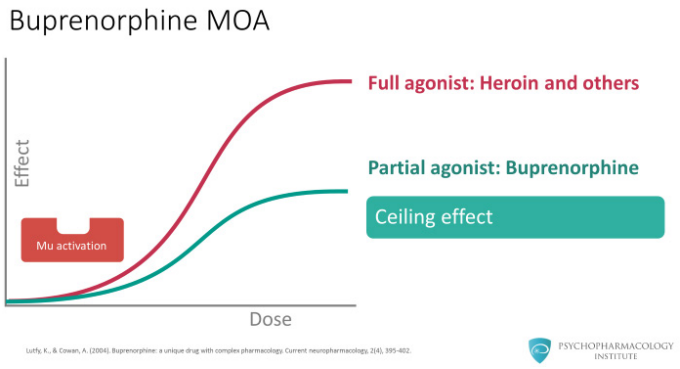


**Figure 4.** We call this a ceiling effect, because even if you increase the dose of buprenorphine, these effects do not go above our theoretical ceiling limit. If we were to say 50%, no matter how much buprenorphine we provide, the level of analgesia or euphoria or respiratory depression will not go above these limits.

performed a post hoc study to compute the partial AUC0–7 for every sheep and found that, while the results of the AUCinf computation varied greatly, most of the findings were similar (Figure 5). Consequently, a more accurate estimate of the between-subject variability in this study is revealed by the extended sample duration. The exact calculation of the pharmacokinetic parameters for IV BUP and the detection of the genuine BUP elimination pattern were made possible by the extended sample duration and the extremely sensitive approach. For sheep that are pregnant in the past, researchers Lindhardt and Nolan have examined the pharmacokinetics of IV BUP in sheep that are not pregnant [12]. There are restrictions on the results of these earlier investigations. Since Lindhardt and colleagues' investigation focused on the bioavailability of an intranasal formulation rather than the complete pharmacokinetic profile of IV BUP in sheep, they only monitored the plasma concentrations for one hour.

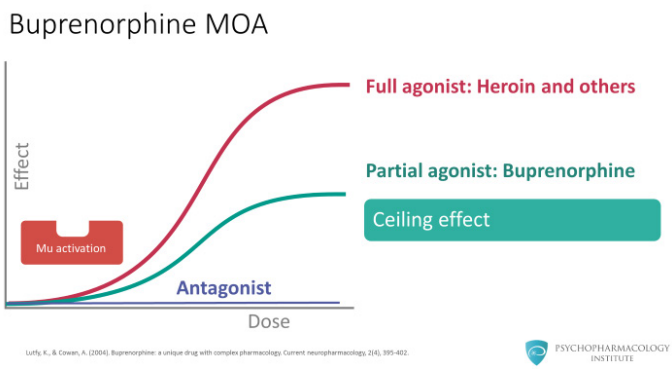


**Figure 5.** Antagonists attach to receptors but never actually activate the receptors. Therefore, antagonists unlike either partial or full agonist never activate the receptors.

After an IV injection, Nolan monitored the plasma concentrations for six hours and found that the elimination t½ (mean 2.03 h, range 0.73–5.83) had significant between-subject variability. Both of these investigations did not fully capture the terminal elimination phase of BUP due to the short sampling duration. This study likewise showed high variability in t½, primarily because of a rapid drop lower than LLOQ in numerous cases. Although t½ in this investigation increased significantly when able to quantify plasma concentrations for a longer period of time, the sheep that showed plasma concentrations above the LLOQ up to 7 h had t½ close to that seen by Nolan and collaborators. This study found that BUP had a high CL. In nonpregnant sheep, the mean CL was roughly twice as high as that reported by Nolan (3.40 *vs.* 1.78 L/h/kg). Increased glomerular filtration rate and increased activity of metabolizing enzymes (Figure 6), as well as physiological differences between pregnant and nonpregnant sheep, could account for higher CL. These physiological differences could also be explained by variations in sheep features and experimental circumstances. Human studies have demonstrated by Bastian. The AUC of BUP exposure is almost 50% lower during pregnancy than postpartum, which aligns well with our observation of elevated CL in pregnant sheep and suggests that our sheep model for BUP pharmacokinetic investigations is feasible. These results show that many of our results, as well as those of Nolan and associates, based on the terminal phase of the concentration-time curve (AUCinf, CL, Vz, Vss), are not very precise because of the rapid decline below LLOQ. Moreover, a long sampling regimen and a sensitive method are required to capture the true terminal elimination phase of BUP. The plasma concentrations in the two earlier nonpregnant sheep trials were measured by radioimmunoassay, which does not distinguish between BUP and NBUP, and the BUP results could be impacted by the presence of NBUP. This doesn't seem feasible, though, given our findings, as NBUP remained undetected in all plasma samples following a single IV administration.

Although there is significant between-subject variability in CL in our pregnant sheep, overall the results are significantly greater (mean 194 L/h for 57 kg sheep) than in non-pregnant human research. For example, Huestis and colleagues found that in five male participants (mean weight 75 kg) sampled up to 72 hours after receiving a 2 mg BUP IV injection, mean human CL was 49.8 L/h, t½ was 21.8 h, and Vz was 743 L.22 In a previous assessment of the literature, Upton discovered that sheep (who are not pregnant) had a higher percentage of cardiac output that passes into the liver (47% compared to 23%) than do humans (Figure 7). The percentages roughly correspond to 87 L/h in a 69 kg human and 155 L/h in a 45 kg sheep's liver. Given that more blood in sheep reaches the liver per unit of time and can be cleansed of the medication in the systemic circulation, this variation may help to partially explain the greater CL seen in this study. The observed difference in BUP CL between pregnant sheep and humans is supported by a prior IV pharmacokinetic research for oxycodone conducted in a similar study environment, which revealed notably high CL.24 Similarities between the results of Huestis and our pregnant sheep non compartmental analysis may be seen in the pharmacokinetic values t½ and Vz. High distribution levels were noted for both humans and mean Vz of 1722 L for 57 kg and 743 L for 75 kg, respectively, for pregnant sheep. In the event that we could track plasma concentrations over an extended duration, the observed mean t½—17.6 hours in sheep as opposed to 21.8 hours in humans—is comparable to that of Huestis.

The primary human metabolite, NBUP, was absent from every sample of sheep plasma. Prior research conducted by Jensen and Zullian also shown that sheep did not exhibit any detectable levels of NBUP following an IV infusion of 40 µg/kg and a subcutaneous injection of 50 µg/kg of BUP, respectively (Figure 8). IV BUP pharmacokinetic studies conducted in humans by Huestis MA, et al. [13] showed that NBUP was detectable 10–15 minutes after injection, and

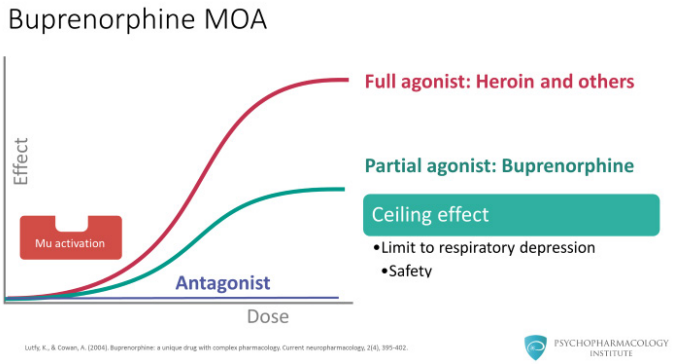


**Figure 6.** The ceiling effect of buprenorphine means that there is a limit on the respiratory depression. This is one of the reasons why this medication can be safely prescribed.

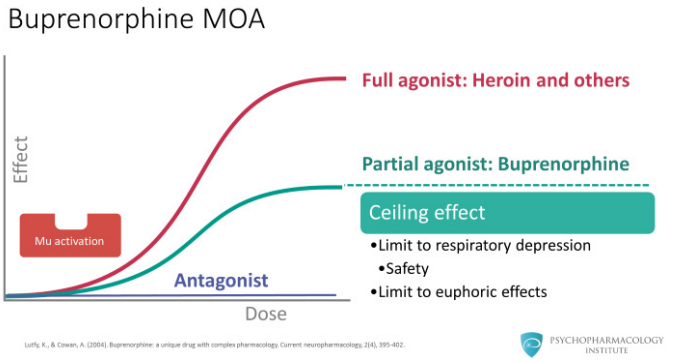


**Figure 7.** What this also means is that taking more buprenorphine does not lead to additional euphoric effects. This is very different from other full agonist opioids (oxycodone, heroin or morphine) where taking additional doses generally means you get additional euphoria. This is exactly why patients can be trusted to take one or two tablets a day and refrain from taking additional tablets.

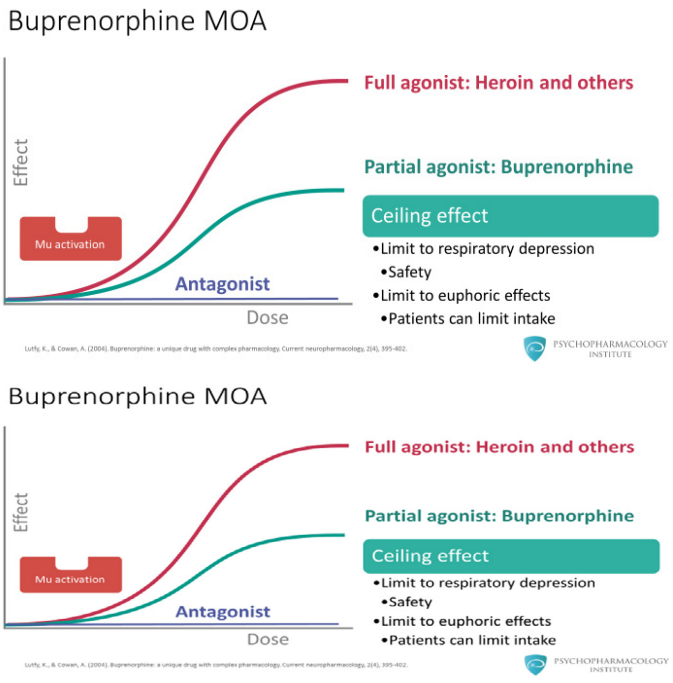


**Figure 8.** For patients who are addicted to opioids, by definition they are unable to control their opioid intake. However, for buprenorphine, because of its partial agonism, they are able to limit their intake to what is recommended and prescribed.

NBUP AUC was 18% of the BUP AUC on average (Figure 9). Our findings may point to either the absence of BUP biotransformation into NBUP in sheep or the extremely effective glucuronidation of NBUP that has been shown in other species. Our study has certain limitations. Owing to practicalities related to the study site, we were unable to conduct the study at different points throughout the pregnancy, before the pregnancy, or after labour. In our study cohort, this would have given us a better knowledge of how pregnancy affects the pharmacokinetics of BUP. Furthermore, at the time of the IV research, we were unable to identify the prenatal exposure to BUP following the injection since we did not have access to the fetus. The preliminary nature of the pilot study's findings warrants further investigation in a therapeutic context is utilized cautiously. Our ability to assess plasma concentration over an extended length of time and obtain a more accurate picture of the pharmacokinetics of BUP in pregnant sheep was made possible by our study's highly sensitive analytical approach with a comparatively low LLOQ and long sampling period (Figures 10-12).

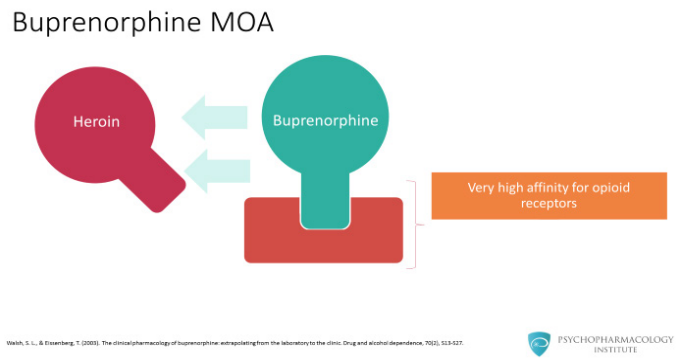


**Figure 9.** The second issue about buprenorphine is that it has a very high affinity for the opioid receptor, which means that it binds very tightly to the receptors. If buprenorphine is attached to the receptor, other full agonists typically used such as heroin, oxycodone, morphine will not displace buprenorphine.

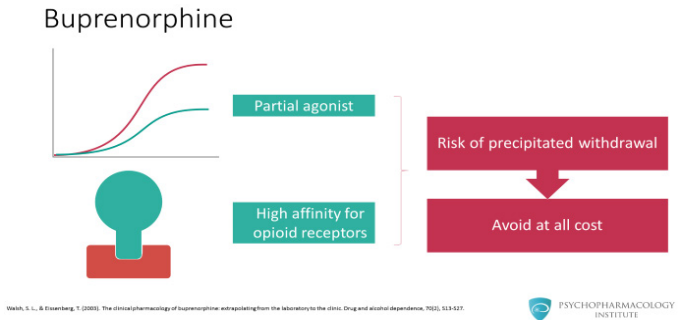


**Figure 10.** For patients who are addicted to opioids, by definition they are unable to control their opioid intake. However, for buprenorphine, because of its partial agonism, they are able to limit their intake to what is recommended and prescribed.

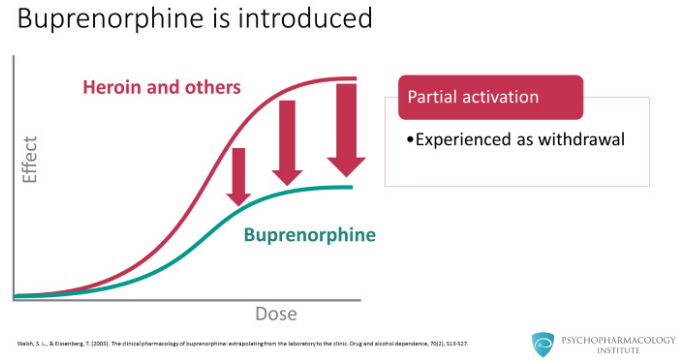


**Figure 11.** On the other hand, if heroin is already on the receptor and then buprenorphine is introduced, because buprenorphine has a high affinity for the receptor, buprenorphine will displace the heroin. Once this happens, this displacement will cause a sudden drop in the receptor activation going from a full activation to partial activation. This sudden drop in activation is experienced as withdrawal.

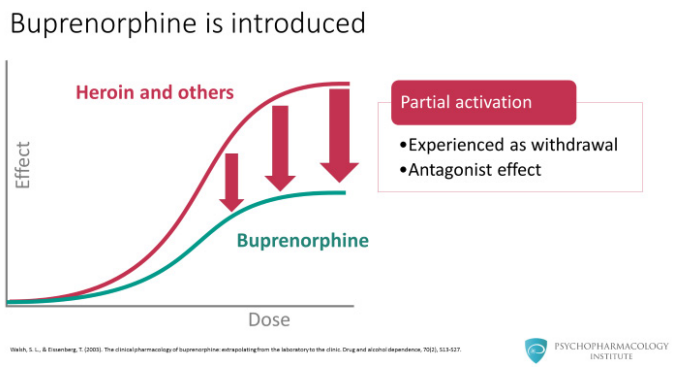


**Figure 12.** For patients who are addicted to opioids, by definition they are unable to control their opioid intake. However, for buprenorphine, because of its partial agonism, they are able to limit their intake to what is recommended and prescribed.

## Conclusion

We have elucidated the fundamental pharmacokinetics of BUP in gestating sheep following a single intravenous administration. This information can also be applied to future research on the transplacental transfer of BUP to the fetus in the pregnant sheep model, which will expand our understanding of the safe use of BUP during pregnancy. Using 14 pregnant sheep in the current pharmacokinetic study, we have demonstrated that the systemic CL of BUP in pregnant sheep is higher than in nonpregnant sheep and human (male) subjects. We have also shown that a long sampling period and a sensitive analytical method are essential for identifying the true elimination phase of BUP. Following a single IV dose, all plasma samples showed no signs of NBUP, the primary metabolite in humans 10 µg/kg.

## Conflict of Interest

The authors declare no conflicts of interest.

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