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Research Article

Clinical Therapy Dose Optimization of Sublingual Buprenorphine in Poorly Adherent Pregnant Patients: A PBPK Translational Modelling Study

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Abstract

Plasma levels of sublingual buprenorphine utilized in the therapy of opioid use disorder, has been demonstrated to undergo gestation-associated decline in vivo, to an extent influenced by upheavals physiologically across gestational trimesters. However, based on extant literature, a dearth of knowledge exists in the optimization of buprenorphine therapeutic modalities, pharmacokinetic interactions and posological scrutiny, necessary for successful regimen adherence. A physiologically-based pharmacokinetic modelling methodology in a virtual clinical trial premise was utilized to investigate gestational upheavals in peak plasma buprenorphine concentrations, followed by a pharmacokinetic drug-drug interaction investigation and dose optimization strategy, to maintain buprenorphine levels above proposed thresholds of 1ng/ml and below 22.2ng/ml adjudicated as a fatality limit. A fold decline (> 1.3fold) in buprenorphine mean peak plasma concentration (92% - 74%) was evident for the model predicted buprenorphine metrics across selected gestational weeks to term in line with the model predicted increases in physiological upheavals occurring across gestation which may influence the changes. The rifampicin mediated drug-drug interaction on buprenorphine levels initially resulted in fold decreases (>1.5 fold) over a twenty-four hour duration, in concert with escalating physiological metrics across gestational trimesters. The interaction perpetrated with Clarithromycin dosing resulted in fold increases (> 2-fold) in the plasma concentration as well as an increase in other metrics associated with buprenorphine kinetics. The dose optimization approach maintained majority of subjects (>90%) with the extensive metabolizer (EM) phenotype above 1ng/ml and below 22.2ng/ml in the 8mg – 24mg dose ranges albeit with 1% and 3% in the 28mg and 32mg doses above the fatality limit respectively. This study demonstrates the utility of physiologically based pharmacokinetic methods to predict the time course of administered buprenorphine in plasma during gestation which could aid clinician decisions in a translational manner, in order to optimize therapeutic modalities in the therapy of opioid use disorder.

Keywords

Buprenorphine, Drug Interactions, Dose, Optimization, Pharmacokinetics, Phenotype, Pregnancy, PBPK

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1. Introduction

1.1. Background

Historical evidence suggests that cohabitation with psychotherapeutic substances has been a part of human existence since antiquity. Both natural and artificial substances that have an impact on the body or mind have been abused at some point. According to Gossop [1], "the desire to experience some altered state of consciousness appears to be an inherent part of the human condition... and we are surrounded by xenobiotics... the cup of tea and coffee, the glasses of beer, wine, and whiskey, the cigarettes, the snorts of cocaine, the joints, the tablets of acid, the fixes of heroin, and the ubiquitous tranquillizers and sleeping pills."

It is vital to define precisely what is denoted by "substance abuse." The U.S. Food and Drug Administration (FDA) [2] defines substance abuse as the deliberate utilization of an unprescribed or non-prescribed xenobiotic. Substances such as cocaine, heroin, opiates, alcohol, and are customarily abused. Overdosing, failing to refill prescriptions, incorrectly interpreting medical advice, administering insufficient doses, and ingesting xenobiotics at the wrong time are examples of xenobiotic misuse [3].

Inappropriate or excessive utilization of these therapeutics may produce undesirable health or social outcomes [4]. In addition, repeated, sustained utilization of these xenobiotics at escalating doses and/or for longer durations perpetrates a distinct illness that can be diagnosed, hampers optimal functioning, and may necessitate peculiar care. This illness is called substance use disorder. These disorders can span from being mild and transitory to severe and intractable. Addictions are a colloquial term for severe and unabating substance use disorders. Unfortunately, unlike other chronic conditions, substance use disorders have never been as carefully monitored, controlled, or insured [4]. According to a study published by Smith et al. [5], having a pre-existing substance use disorder doubles the probability of developing severe and expensive medical conditions such as asthma, stroke, diabetes, chronic pain, and hypertension. Xenobiotic misuse can result in complications that are either generic, in that they are caused by the misuse, or specific to a particular xenobiotic [4]. In the absence of perceptual or chronic symptomatology of a particular xenobiotic, such complications may be the first indication of a substance abuse problem. Some instances of these complications include osteomyelitis, septicemia, dental decay, necrotizing fasciitis, cellulitis, and varicose ulcers. Environmental and genetic factors can promote a person's predisposition for substance abuse [4]. Misuse can be consequent to adverse outcomes such as, sexual violence, automobile crashes, overdose demise and self- immolation [4]. Healthcare professionals frequently fail to identify women who abuse substances during gestation [6, 7] and tend to delay seeking antenatal care, if they do at all, because they are afraid of being reported to infant wellbeing authorities and express doubts about the effectiveness of care [8].

1.2. Prevalence of Substance Misuse

According to the 2016 National Survey on Drug Use and Health [9], encompassing 265 million individuals aged 12 or older, approximately 17 percent of the populace aged 12 and older (or 44 million people) asserted using an illicit xenobiotic, using a stipulated xenobiotic non-therapeutically, or drinking excessively in the prior year. In the nationwide survey, nearly 15 million people admitted to using prescription xenobiotics outside of their intended medical purpose (5.5 percent of the population). Brand-name prescribed opioid painkillers (such as Oxycontin and Vicodin) accounted for 69 percent of rampancy in this group (10 million people), followed by sedatives (such as Valium®) or psychostimulants (such as Adderall®), each of which 4 million people reported using. Additionally, 3 million people, or 6% of the population in the UK, use at least one illegal xenobiotic each year [10].

According to a 2003–2004 national regiment research in America, 4.7 percent and 10 percent of expectant mothers, respectively, admitted to using illegal xenobiotics or alcohol in the previous 30 days [11], and latter pregnancies did not remarkably reduce illegal xenobiotic utilization [12].

Abuse of alcohol or other drugs during pregnancy is also a sign of risky social behaviors and living conditions [13]. Despite prior studies on obstetrical substance abuse treatments in antenatal health centers showing it to minimize the negative pediatric consequences, the lifelong implications on these women and their relatives are elusive [14-16].

Opiate addicts are acclaimed to have inferior possibilities for medical and psychological, outcomes. In a British study, Nutt et al., compared the harmfulness of legal and illicit substances to individuals and society, and established that opiate misuse, specifically heroin misutilization, was chiefly detrimental to a person [17]. In addition to physical harm, accidents, overdose, and suicide, substance abuse is associated with mental health problems such as depressive episodes, social phobia, and borderline personality disorder. Injection-based drug abuse can also spread blood-borne viruses akin to HIV, Hepatitis B and C [17, 18]. Further, Hernandez-Avila et al., has demonstrated that women who regularly abuse opioids are more susceptible to negative outcomes than men, such as a quicker progression to dependence and a higher incidence of health issues [19]. Likewise, it has been reported that psychiatric co-morbidities, depressive disorders, are more prevalent and complement substance use disorders in women more regularly than in men. [20, 21]. Pregnancy-related mental or physical health issues affect most opioid-dependent women [22].

Marijuana, alcohol, cocaine, and opiate use has been linked to menstrual irregularities, anovulation, and spontaneous abortion, in addition to pregnancy complications, despite the

paucity of data on the subject and the controversy surrounding the conclusions [23, 24]. People with substance abuse problems frequently engage in non-medical use as well as problematic xenobiotic use, especially when it comes to analgesics and sedatives. [25].

1.3. Pharmacology of Opioids

Opiates are alkaloids, such like morphine and codeine, discovered in the juice of the poppy plant's seed capsule, as well as compound of a synthetic nature that closely mimic morphine. All substances that act on opioid receptors are referred to as opioids, including endogenous opioids, also known as endorphins [26]. When exposed to noxious stimuli, the endogenous opioids are produced. The central nervous system uses opioids and endogenous opioids as neurotransmitters. Endogenous opioids act as organic trophic inhibitors, blocking DNA synthesis and mitosis in the growing brain. Selective σ-receptor agonists have been identified to impair neurogenesis, whilst selective μ-receptor activation has been shown to neuronal cell multiplication [27]. The release of neurotransmitters is inhibited by opioids presynaptically and generally opioids' postsynaptic actions are inhibitory [28].

The peripheral tissues and the central nervous system both contain three classical opioid receptors. Opioid receptors found on the cell membranes of neurons mediate the effects of opioids. Like many other membrane receptors, the G-proteins, which bind guanine nucleotides, are connected to the opioid receptors. G-proteins have three subunits (A, B and G). Subunit A becomes decoupled and forms a complex when the receptor is occupied, which in turn interacts with systems at a cellular level to elicit an outcome [28]. Respiratory depression, dyspnea, sedation, constipation, anorexia, miosis, dependence, dysphoria, and are all linked to receptor stimulation. Psychomimetic and dysphoric effects may also be caused by opioid receptor stimulation, but these effects have not yet been thoroughly researched [26].

Opioids activate the presynaptic receptor sites on gamma-aminobutyric acid (GABA) nerve cells, resulting in a GABA release decline in the ventral tegmental area and ultimately resulting a boosted dopamine release. The brain interprets the extra dopamine in the nucleus accumbens as being intrinsically positive and rewarding. These enjoyable feelings encourage repeating the behavior by serving as reinforcement [29]. In the striatum, as well as the nucleus accumbens, opiates and other addictive substances have the same impact on dopamine signaling as non-addictive rewards (such as food). The effect is more strongly reinforcing the faster dopamine levels rise in the striatum. Dopamine is essential for the onset of addiction and acute reward [30]. Reduced dopamine release and fewer dopamine receptors in the striatum are linked to addiction development. The cingulate gyrus and the orbitofrontal cortex both exhibit decreased activity when the number of receptors in the striatum increases. This suggests that by dysregulating the frontal regions, dopamine is probably liable for the loss of control and compulsive xenobiotic utilization that exemplify addiction. [30-32].

1.4. Withdrawal Symptoms and Dependence Linked to Opioid Misuse

The acute therapeutic effects of opioid utilization include autonomic downregulation, analgesia and inebriation (feeling "high"). With continued utilization, the individual will eventually require higher doses to maintain health, as withdrawal symptoms would otherwise develop [29]. Tolerance is described as the requirement for a higher opiate dose regimen to achieve the same outcome. An opioid abuser can use one hundred times more than a naïve individual and these doses are potentially lethal for first-time users and those experiencing withdrawal [33].

When an individual stops using opioids abruptly, they experience withdrawal symptoms, which are a sign of physical dependence. These are thought to be caused, at least in part, by neuroadaptation. Noradrenergic stimulation, which exacerbates opioid withdrawal symptoms, also directly impacts placental perfusion by changing pulse rate and blood pressure, tangentially impact the growth and welfare of the fetus. After stopping the use of opiates, sweating, lacrimation, yawning, and restlessness appear. After 18 to 24 hours, chills, hot flashes, muscular rigidity, enlarging of the pupils, and chest pain appear. 30 to 36 hours onwards, symptoms such as gastroenteritis, vomiting, growing agitation, hypertension, and a rapid heart rate start to manifest. Within 7–10 days, the symptoms mostly go away. Additionally, adults in good health are not in danger of dying from withdrawal [34]. When a person stops using a psychoactive substance, they may experience emotional or motivational symptoms known as psychological dependence. It is most likely the most potent predictor of opiate addiction [35]. These symptoms encompass, control loss over xenobiotic self-administration, an overwhelming desire, drug utilization and compelling drug seeking, in spite of harmful repercussions. Adverse medical, legal, and social implications are linked to opioid addiction and dependence. Hematogenic illnesses such as "puffy hands" syndrome, HIV, long-lasting hepatitis B and C, septicemia, as well as endocarditis, are the health problems associated with injection usage that are most particularly pronounced. Individuals who misuse opioids are at an escalated propensity for ischemic- hypoxic brain abnormalities [36]. Theoretically, the temporary hypoxia caused by respiratory depression, thrombosis, vasculitis, or hypotension led to the ischemia. Heroin users also frequently have other neurological side effects include psychosis, oculogyric crisis, epilepsy, myelopathy, neural infections, and polyneuropathy.

Cardiac issues and hypotension are commonplace. According to estimates, opiate users have a death rate that is roughly 13 times higher than that of the populace generally [37]. Furthermore, opioid misuse is typically associated with

exclusion, violence, a disordered criminal lifestyle, and prostitution [38]. Its societal repercussions include homelessness, poor housing, and lack of psychosocial assistance.

Substance abuse during gestation is dangerous and tend to perpetrate extensive repercussions on the offspring. It is a widespread pre-emptive cause of adverse neonatal, and pre-adolescent consequences in contemporary economies. In the UK, 2% of expectant mothers were discovered to have utilized opiates before becoming pregnant [39]. According to an American epidemiological study [40], the preponderance of opiate usage during gestation ranged from 1.2 percent (maternal expositions) to 2.3 percent (fecal matter analyses).

Misuse of opiates prenatally, has been linked to poor gestational outcomes. The escalated possibility of obstetric complications, such as intrauterine growth retardation, prenatal hemorrhaging, preterm membrane rupture, spontaneous abortions, puerperal morbidity, and fetal distress as well as intricacies to the neonate, such as small head perimeter, opiate withdrawal, fetal growth insufficiency, cognitive and motor issues, increased neonatal demise, and preterm delivery, have been addressed [41-45]. An anarchic lifestyle and poly-xenobiotic utilization, involving tobacco and alcohol, are also prevalent in this group (pregnant women) and are thought to be confounders in the event of a poor gestational aftermath [46]. Opiates have been reported to promote disordered eating behaviors and impair the nutritional status of the user, resulting in negative effects on the fetus [47].

According to several studies [48, 49], substance abuse may be construed as a proxy indicator for a cluster of circumstances including low socioeconomic status, subpar levels of education, malnourishment, and an absence of social support that may transcend to an impoverished gestational outcome in general [50].

1.4.1. Fetal Repercussions Associated with Opioid Misutilization

In the course of analyzing xenobiotic transfer to the fetus, the physiochemical characteristics and potential placental biotransformation of a medication are of interest and “passive diffusion” has been implicated as the primary mechanism [51, 52]. Small molecules (less than 500 Dalton) such as buprenorphine that are neutral, unbound, and lipophilic are known to pass easily through the placenta. Heroin diffuses considerably more efficiently across the blood-brain barrier and the placenta due to its incredible lipid solubility [53]. Abuse-related drugs alter the way intracellular mediators and neurotransmitter networks signal. The same neurotransmitters also act as chemicals that control cell migration, circuit creation, survival, and proliferation [54]. It is established that maternal opiate use has neurological system depressant effects on the fetus. These effects are clinically evident in decreased fetal body movements, breathing patterns, and pulse rate unevenness [55-57]. Intrauterine drug exposure can result in stunted fetal growth, fetal discomfort, stillbirth, preterm membrane rupture, birth abnormalities, and early birth [58-60]. Even when used for controlled purposes, such as pain relief during early labor, opioids cause hypoxia and respiratory depression [61, 62], which can result to neonatal death, and poor neurological implications are all significantly influenced by perinatal hypoxia [63]. As a consequence, oxygen fortification is requisite [64].

1.4.2. Effects of Substance Misuse on the Neonate

Though opioids traverse the placenta, they possess potential to induce physical dependence in the developing embryo. This manifests as neonatal abstinence syndrome (NAS) described as “a generalized disorder denoted by symptoms and signs indicating dysfunction of the autonomic nervous system, respiratory system, and gastrointestinal tract” [65]. The occurrence of neonatal abstinence syndrome (NAS) may manifest from the substance's discontinuation at birth. 55%–94% of opiate-exposed opioid-sensitized newborns develop NAS [66, 67]. NAS is manifested by different forms of nervous system and digestive disorder as well as, reflex, metabolic and lung perturbations, including shrill crying, overactive reflexes, muscle spasms, hypertension, seizures, frenzied fist-suckling, malnutrition, emesis, gastroenteritis, fluid loss, rhinorrhea, sultriness of the nasal mucosa, perspiration, discoloration of the skin, pyrexia [68, 69]. It resembles ischemic-hypoxic encephalopathy clinically. NAS is ephemeral, but it can result in an extended hospitalization [70].

Clinical documentation of the enormity of NAS is possible utilizing verified point systems akin to that of the Neonatal Abstinence Scoring System (Finnegan score). The neonatal abstinence score comprises three components as per the Finnegan score: nervous system perturbations, respiratory-metabolic-vasomotor irregularities, and digestive issues. Opiates tend to be a more advantageous therapy alternative for the management of acute NAS symptoms caused by prenatal opiate sensitization [71-73]. Arguments have been proposed regarding the consequences of opiate sensitization on the prospective maturation of neonates. However, escalated rates of absent-mindedness, agitation, and behavioral challenges were found in the sensitized populace [74]. Intra - uterine sensitization to opiate utilization has been associated with a higher possibility of sudden infant death syndrome (SIDS) in previous research [75, 76], despite the presence of extraneous variables including tobacco use, intra-uterine growth retardation, and preterm birth [77]. Further, a narrowed consequence of opiate utilization on maturation of the respiration core has been previously hypothesized [78].

1.5. Substance Misuse Treatment

Once substance use is established, it frequently advances to substance abuse and then substance dependence [79]. There are numerous treatment options available for substance abuse. These can be implemented from a pharmacological and non-pharmacologic modality. The non-pharmacologic component of therapy of substance misuse includes psychotherapy;

– delineated as, treatment comprising communications between client and therapist aiming to ameliorate the client's malady. Also, Motivational Enhancement Therapy [80] developed by William Miller in 1982 as a "client-centered and directive" approach has been implemented as a nonpharmacologic therapy option for xenobiotic misuse. Furthermore, Cognitive Behavioral Therapy (CBT) [81] and Complementary /Alternative Medicine (CAM) [82] have been utilized in the treatment of substance misuse. The principles heralding CBT therapy can be applied to substance misuse [83] whereas CAM therapies, which are increasingly popular, lack sufficient data that tacitly augment criticality for its exact role in substance misuse management.

Detoxification, on the other hand, can be thought of as a form of therapy designed to reduce the temporary psychological and medical volatility that follows a period of heavy and protracted substance utilization. It may be implemented in a hospital, community setting, or patient's residence allowing the individual, a chance to contemplate on the negative repercussions linked to their substance misutilization and adopt adjuvant offers of interventions. Several case reports of primal infant death [84] and fetal desolation [85] as a result of opiate withdrawal have reignited the debate about the efficacy of detoxification [66, 86, 87] and highlighted the criticality of opioid substitution therapy during gestation.

1.5.1. Opioid Substitution Therapy (OST): Buprenorphine & Methadone

The justification for this form of therapy aims to enhance the dependent individual's social and psychological performance along with their functional status [88, 89]. Opiates tend to be only illegal prescription xenobiotics for which there is currently a recognized potential therapeutic replacement therapy [90]. Typically, psychosocial therapy is added to substitution therapeutic interventions, which has proven to expand the proportion of respondents who abstain at later investigations [91, 92]. Contingency management (CM), a form of psychosocial therapy is demonstrated to be effective in promoting abstinence in stimulant and cannabis users, as well as in opioid substitution therapy participants who still utilize illicit xenobiotics, according to an increasing number of research studies [93]. Opioid drug substitution therapy has been shown to be more effective at keeping patients in therapy (retention) and reducing heroin utilization than xenobiotic-free therapeutic approaches [94].

Buprenorphine is an increasingly lipophilic partial agonist of the mu opioid receptor (MOR) and a kappa opioid receptor (KOR) antagonist. Semi-synthetically derived from thebaine, a naturally occurring alkaloid of the opium poppy; *Papaver somniferum*, it is 20 - 55 times more potent than morphine [95]. It exhibits a 'ceiling effect', that is, above the recommended dose, it seizes to exert an increased pharmacodynamic effect. Buprenorphine has a limited intrinsic activity in terms of its partial agonistic property and exhibits antagonistic effects when combined with a full opiate agonist, such as morphine. These characteristics increase its efficacy in the treatment of opioid dependence and withdrawal. It has a duration of action of up to 12 hours at low doses (2mg - 4mg) and up to 48-72 hours for high doses (16mg to 32mg). Due to its pharmacological properties, buprenorphine can be consolidated with other mu-opioid receptor agonists to produce additive effects [96, 97].

The summary of product characteristics of buprenorphine stipulates its indications for "substitution therapy for opioid xenobiotic dependence, within a scheme of medical, social and psychological therapy" [79]. Buprenorphine, like all opioids, is susceptible to abuse [98]. In contrast to methadone, buprenorphine espouses both partial opioid agonist and opioid antagonist activity and has a milder, less euphoric, and less tranquillizing effect than full opioid agonists such as methadone [79]. Moreover, the high binding affinity of buprenorphine for opioid receptors suggests that it has a prolonged duration of action at increased doses, allowing for alternate-day dosing [79]. Buprenorphine maintenance therapy (BMT) has been widely utilized in France since 1996, including for expectant women [99]. Despite this, missed doses and poor adherence are common, which can precipitate 'withdrawal symptoms', and puts the patient at risk of further illicit drugs use and the number of pregnant women treated with buprenorphine is still negligible, according to published research [100].

On the contrary, the pharmacologic attributes of methadone, a full opioid agonist, are comparable that of morphine. Despite being a racemate, methadone's levo-isomer (L-Methadone) has an analgesic effect that is 8 to 50 times stronger than that of the dextro-isomer (D- Methadone) [95]. Methadone implementation in the substitution of opioid therapy has been in vogue since the 1960s [101]. Methadone maintenance treatment has a relatively long history of utility in the United States [102] and is inclusive of the therapy of expectant mothers [89]. Twenty-four hourly administration of this opioid agonist (methadone) is part of the methadone maintenance therapy (MMT) [89].

MMT has been shown to be superior to methadone-assisted detoxification in context of improving therapy engagement and drastically reducing heroin utilization as well as attenuating the spread of infectious diseases like hepatitis B, C and HIV [103, 104]. However, concerns regarding overdose-related issues have been significantly escalated due to methadone's pure agonistic nature [105]. Methadone utilization has also been linked to other severe health risks, such as the probability of ventricular tachycardia and QT prolongation [106, 107]. According to Strain et al. methadone dosage in MMT is effective if it impedes cessation, diminishes or eradicates drug yearning, and hampers narcotic euphoria [108].

The pharmacological profile of methadone ascribes a criterion for its utilization as a maintenance drug. The summary of product characteristics (SPC) of methadone states that, it is indicated for "use in the treatment of opioid drug addictions as

a suppressant of the narcotic abstinence syndrome" [79]. Amidst its reverence as the "gold standard" in gestational opioid substitution therapy, methadone's utility in MMT has balanced lifestyle choices, decreased hazardous conduct, decreased the occurrence of premature conception and intra-uterine growth retardation [90, 109].

1.5.2. Pharmacokinetics of Buprenorphine

Buprenorphine's exceptional intrinsic effects are due to its pharmacokinetic properties. Due to its extensive first-pass metabolism, buprenorphine's oral bioavailability (F) is diminished. [110]. Its sublingual bioavailability expedites the administration route for opioid dependence therapy treatment [110]. Additionally, pH ionization constitutes a factor influencing sublingual absorption and bioavailability. Furthermore, variability in the time to maximum plasma concentration (t_{max}) ranges from 40 minutes to 3.5 hours [111]. Buprenorphine is predominantly bound to α- and β-globulin [112]. Buprenorphine traverses the blood-brain barrier. It passes easily through the placenta and freely through mother's milk with similar concentrations in maternal plasma. Its distribution attribute (V_d, 188 – 335L) emerges in harmony with its lipophilicity upon intravenous administration. The liver is responsible for the biotransformation of buprenorphine, and the by-products are eliminated via bile [113]. As well, the elimination half-life of buprenorphine is 20 – 73 hours [113]. The elimination half-life estimates tend to be extended for sublingual buprenorphine formulations than for the intravenous formulation [110]. The metabolism of buprenorphine follows non-saturable Michaelis-Menten kinetics [114]. Two metabolic pathways are implicated in the biotransformation of buprenorphine. Buprenorphine undergoes N-dealkylation catalyzed by CYP3A4 and glucuronidation resulting in three metabolites: buprenorphine-3-glucuronide (B3G), N-dealkylbuprenorphine and norbuprenorphine-3-glucuronide (N3G) [115]. The half-life of buprenorphine ($t_{1/2}$) is resultant of the administration methodology with 2 hours (F = 100%) for intravenous, 26 hours (F = 15%) for a transdermal patch, 28 hours (F = 46 - 65%) for buccal film, and 37 hours (F = 28 - 51%) for the sublingual tablet [115, 116].

1.6. Buprenorphine Formulation Systems

Formulation systems containing buprenorphine or buprenorphine in combination with naloxone have been created and are available commercially. These systems include generic Buprenorphine Sublingual Tablets in 0.4mg, 2mg, and 8mg dosage strengths. The active substance in this system is dissolved within three to five minutes; however, residual buprenorphine could be evident for ten to fifteen minutes after administration but in negligible amounts. The combination of buprenorphine and naloxone is also available in sublingual tablet form. The opioid antagonist naloxone is co-formulated solely to discourage injecting where there is cause for concern, reducing the likelihood of abuse and diversion. Buprenorphine is also formulated as a buccal film that confers increased efficacy and tolerance in opioid naïve patients.

A freeze-dried wafer formulation of buprenorphine available as 2mg and 8mg lyophilizate offers the benefit of enhanced bioavailability with rapid degradation (less than 15 seconds) when subsumed on the tongue, although this can be affected by personal cases commensurate with dryness or moisture of the mouth. [117]. Also, Buprenorphine Transdermal System (BTDS), Butrans® CIII, is a 7-day transdermal formulation of buprenorphine endorsed for the management of extensive opioid use disorders for which substitute therapy choices are inadequate [118].

The U.S. FDA 2016 approved an extended-release subdermal implant (Probuphine; Braeburn Pharmaceuticals, Princeton, NJ, USA) containing 90 mg of buprenorphine uniformly blended with a biologically compatible non-biologically degradable form of ethylene-vinyl acetate polymer and extruded into a 26 × 2.5 mm rod shape for the treatment of opioid use disorder, with an efficacy comparable to an 8mg daily dosage of buprenorphine [119]. Further, a buprenorphine depot formulation (RBP-6000; Indivior, Richmond, VA, USA) has been developed for dispensation [120]. It contains 200 mg/mL of buprenorphine base in a precipitation delivery system of biologically compatible solvent (N- methyl pyrrolidone) and biologically degradable polylactide-glycolide polymer that, at the periphery in the subcutaneous space, solidifies in proximity to water [120] and provides prolonged release of buprenorphine over 28 days through polymer degradation and diffusion [121].

1.7. Gestational Upheavals Influencing Xenobiotic Pharmacokinetics

Gestation involves a prodigious myriad of physiologic upheavals which effectuate changes in the pharmacokinetic attributes of several xenobiotics. These gestational upheavals tend to offset the total body composition. As a result, the maternal body undergoes adaptations. Some of the changes include, for instance, increased cardiac output, maternal blood volume, and perfusion to the kidney, as well as the uterine and placental unit. In addition, the total body water and maternal fat are escalated. Furthermore, the maternal blood volume dilatation takes place at an enormous ratio to the rise in erythrocyte quantity, resulting in hemodilution and anemia. Other physiological changes include slowed gastrointestinal motility, altered activities of hepatic biotransformation enzymes, and an increase in capillary hydrostatic pressure. During gestation, anatomical adjustments in organ compartments are also influenced by fluctuations in estrogenic and progesterone levels. These changes may influence the absorption, biodistribution, and elimination of xenobiotics, and thus their pharmacodynamic properties during pregnancy.

From a pharmacokinetic viewpoint, the bioavailability of xenobiotics administered orally are variably capped, hence

limiting the amount reaching the systemic circulation. Also, the bioavailability is influenced by first-pass metabolism and the amount absorbed across the intestinal epithelium. These upheavals alter the bioavailability parameters like C_{max} and t_{max} of orally administered xenobiotics [122]. This stir concerns for xenobiotics that are ingested as a single dose. In addition, xenobiotic absorption is diminished by nausea and vomiting in early gestation, resulting in lower plasma levels of xenobiotics [123]. Moreover, the escalating occurrence of constipation and the utility of opiates to alleviate nociception during labor retard duodenal xenobiotic absorption and lengthen gastrointestinal kinetics. This may result in elevated xenobiotic levels after postpartum. [124]. Furthermore, the rise in gastric pH may increase the ionization of weak acids, limiting their absorption [125].

In gestation, the volume of distribution (V_d) is subject to changes as there is an increased volume of fluid (total body water and plasma) traversing between the maternal and embryonic compartments. The V_d of a xenobiotic is useful in approximating the dose required to attain a given plasma concentration [125]. Xenobiotics that have increased binding affinity to tissues, with a minute portion left in the intravascular space, have a high V_d. By juxtaposition, xenobiotics that are highly bound to plasma proteins and/or have a large molecular weight, tend to concentrate intravascularly and elucidate low V_d [125]. Clinically, a larger V_d may necessitate an increased initial and maintenance dose of hydrophilic xenobiotics to attain therapeutic plasma levels. Alternatively, plasma protein binding of xenobiotics decreases during pregnancy due to diminished concentration of both alpha-1-acid glycoprotein and albumin [126-128]. Diminished protein binding leads to increased concentrations of free xenobiotics, thus, favoring more distribution into tissues.

In the liver, biphasic biotransformation (Phases I & II) in gestation influences the pharmacokinetics of administered xenobiotics. Oxidative phase I biotransformation is majorly perpetrated by the cytochrome P450 (CYP) family of enzymes differing in their substrate specificity and is a major biotransformation route of many xenobiotics [129]. The activities of CYP3A4, CYP2A6, CYP2D6, and CYP2C9 are increased in pregnancy [129]. Conversely, most CYP isoforms show decreased activity in gestation. Also, phase II enzymatic activity is altered [129]. Doses of xenobiotics profoundly biotransformed by these isoenzymes may need to be increased during pregnancy to avoid loss of efficacy.

The gestational disposition of most xenobiotics incites concern. This is augmented by increased renal perfusion and glomerular filtration rate by 50%, as early as 14 weeks of pregnancy [130]. The surge in renal clearance can have a profound increase in the disposition of renally cleared xenobiotics leading to short half-lives [127]. Also, volume expansion, occurring due to aldosterone-mediated sodium reabsorption [131], which retains water, causes a decrease in apex serum concentrations (C_{max}) of hydrophilic xenobiotics.

1.8. Impact of Gestation on Buprenorphine Pharmacokinetics

Physiological changes and a myriad of gestational dyadic modifications at the maternal- fetal level affect the pharmacokinetics of buprenorphine. However, there are consequences of the use of illicit opioids in the fetus. Additionally, pensive diseases that emerge as an outcome of pregnancy, such as gestational diabetes, and preeclampsia, require some form of restorative therapy, but still lack elemental information about the disposition and response to optimize treatment decisions in the patient. Biotransformation upheavals are a crucial factor that influences buprenorphine exposure between gestational and postpartum women. Prenatal exposure with buprenorphine seizes to alter developmental milestones [132]. Buprenorphine is disposed of from the body through biotransformation involving CYP3A4 and Uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes [110].

In vivo, investigative studies show increased gestational activity of cytochrome P450 enzymes such as CYP3A4, the primary enzyme responsible for the biotransformation of buprenorphine to its metabolites. Polypharmacy with inducers of CYP3A4 such as rifampicin adversely influences the plasma concentration of buprenorphine. In pregnancy, protein levels decrease and maternal body fat increases, leading to a larger volume of distribution for xenobiotics such as buprenorphine [129]. The activity of glucuronide conjugating enzymes has also been shown to increase during pregnancy, specifically UGT1A and UGT2B enzymes [133]; hence these upward physiologic escalations influence buprenorphine pharmacokinetics resulting in heightened drug biotransformation and decreased plasma levels in vivo.

Furthermore, the absorption and dissolution of sublingual buprenorphine could be affected by salivary pH, which decreases in pregnancy [134]. A low salivary pH can reduce absorption, as less drug would be unionized, and thus contribute to a smaller area under the curve (AUC) during pregnancy.

1.9. Thematic Review

In the past decade, the predilected gumption of qualitative [133-137] & quantitative extant research [100, 139-148], albeit sparse, has emphasized buprenorphine utility in gestational women. Despite this, a dearth of information regarding the posological consideration, metabolic interaction as well as the dose optimization of buprenorphine therapy in this understudied populace exists.

La croix et al. reported a comparative prospective follow-up study in 90 women exposed to buprenorphine and 45 women exposed to methadone which highlighted an escalated propensity to the prevalence of buprenorphine influence in “threatening premature deliveries” in gestational women [135]. However, the crux of this study was weighted on neonatal outcomes confounded with a gender bias with the lack

of sufficient information to a speculative prose on escalated buprenorphine effects on pregnant women despite the mean reported dose utilized in the study at the beginning (6.3mg ± 5.3mg/day) and at the end (5.1mg/day ± 5.2mg/day) of gestation.

Additionally, Hytinantti et al., in their prospective study of buprenorphine median dose (5mg ± 4mg) related effect in 54 gestational women and 58 infants with emphasis on NAS, identified probable outcomes of maternal buprenorphine dose on neonates [136]. Despite this, a dearth of data regarding speculated buprenorphine utility in an increased fashion in gestation, as well as a lack of established control for the neonatal data comparison was not taken account of in the study. Again, the study conferred predilection to neonatal outcomes following maternal buprenorphine use.

Two double-blind, double-dummy, randomized control trials [100, 137] comprehensively evaluated buprenorphine utility as well as that of methadone in gestational women. The work reported by Fischer et al. in 18 pregnant women, initiated an induction dose for buprenorphine (8mg) and methadone (40mg) in a 'predefined titration algorithm,' and that published by Jones et al. in a MOTHER study comprising 175 pregnant women sensitized to buprenorphine in a flexible dosing range (2mg – 32mg), placed prominence on NAS assessment as well as neonatal outcomes. However, despite the robustness of these studies, there was no clear consensus about an optimal dosing regimen for buprenorphine to effectuate maternal safety during gestation.

A national cohort study conducted in 139 women by Welle-Strand et al. extensive assessed and established a clinical rational and clinical utility for buprenorphine (15.8mg ± 5.7mg range {2-26}) and methadone (101.6 ± 33.2 range [30 – 240]) over a 13-year period, proposed an increased efficaciousness to buprenorphine and methadone utility in opioid maintenance treatment [138]. Amidst the robust nature and theme of this study, as well as a weighted statistical analysis of resultant variables, there was no agreed consensus about a fatality threshold in buprenorphine administration as well as that of methadone.

The advent of quantitative modelling approaches in the field of pharmacokinetics enacted a trajectory which utilized the dynamic mathematical integration of physiological mechanisms & drug related parameters to predict the fate of administered molecules (Physiologically based pharmacokinetic modelling), specifically for buprenorphine, leveraging robust state-of-the-art modelling industrial software. This warrants provision of the mechanistic insights of the time course of buprenorphine kinetics. Several PBPK models developed and published in literature [143-150] as well as a pharmacometrics insight [142] have evaluated the fate of buprenorphine in adults, neonates, preterm & gestational women. However, the investigative standpoint heralding buprenorphine dose optimization in gestation, interaction influence as well as trimester specific impact on its kinetics exhibits a notable paucity of comprehensive arguments, indicating significant gaps that necessitate the criticality for further model-based exploration.

1.10. Study Objectives

This study attempts to utilize Physiologically Based Pharmacokinetics (PBPK) predictive approaches to optimize an appropriate dosing regimen for buprenorphine in pregnant women in a virtual clinical trial premise and further:-

1) To demonstrate the utility of the Simcyp derived pregnancy-Physiologically based pharmacokinetic model in assessment of sublingual buprenorphine pharmacokinetics in gestational women.
2) To quantitatively assess the influence of longitudinal gestational changes in CYP3A4 levels on plasma buprenorphine levels, as well as the interpatient discrepancies that may determine buprenorphine metabolism.
3) To evaluate the influence of pharmacokinetic drug-drug interactions on maternal sublingual buprenorphine concentrations in a specific gestational week in each trimester.
4) To investigate how various timepoints of gestation affect the achievement of safe and therapeutic exposure levels of sublingual buprenorphine for the therapy of opioid use disorder in gestational women.
5) Identify an optimal therapeutic range for sublingually dosed buprenorphine throughout gestation with a predilection on a proposed fatality threshold.

2. Methodology

2.1. Physiologically Based Pharmacokinetic Modelling in Simcyp

Physiologically based pharmacokinetic (PBPK) modeling is a mathematical modeling approach that mechanistically simulates the absorption, distribution, metabolism, and excretion (ADME) of drugs in the human body. This approach integrates physiological parameters—such as blood flow rates, tissue volumes, and organ functions—with drug-specific data to predict how a compound behaves within the body. PBPK modeling is especially valuable in drug development and regulatory science, as it allows researchers to forecast drug behavior in different populations, such as children, elderly patients, or those with specific health conditions, without extensive clinical testing.

Predicting xenobiotic exposure is made possible using PBPK modelling, which incorporates a drug's physicochemical characteristics, in vitro drug biotransformation estimates, physiological variables of humans, and population variability estimates [151]. The xenobiotic-specific metrics consist of physicochemical properties, the volume of distribution, affinity for plasma protein binding, tissue partitioning, and membrane permeability. The pregnancy physiologically

based pharmacokinetic model (p- PBPK) implemented in Simcyp® (Simcyp® Ltd., a Certara company, Sheffield, UK, Version 21) registers specific attributes of the gestational system through upheavals such as tissue blood flow, body weight, plasma volume, CYP450 enzymatic activity, transporter expression, renal function, and serum albumin levels [152].

For all predictions in this study, the p-PBPK model within Simcyp Simulator V21(Simcyp® Ltd., a Certara company, Sheffield, UK, Version 21) was utilized. Utilizing Caucasian population data, the model integrates the established physiological upheavals that occur during gestation and enables the creation of virtual pregnant populaces undergoing these upheavals in a time dependent manner between 0 and 40 gestational weeks. The p-PBPK model also considers the variation between individuals in the physiological parameters at a particular gestational week [153]. The model integrates increases and decreases of physiological metrics during gestation as continuous functions [154]. As pregnancy progresses, the Simcyp 'Pregnancy' population incorporates these changes, including variations in CYP enzyme expression, and modulates them (per weeks of gestation) [153].

The Simcyp "healthy volunteer" (HV) population group served as the baseline population for studies with females who were not pregnant and the Simcyp "pregnancy" population was utilized for the population groups that were pregnant. The simulator's built-in differential equations for describing compartment volumes/blood flows, enzyme kinetics, and population co-variate effects have previously been reported [155]. This population was created by Simcyp scientists and includes physiological changes, cardiac output, organ perfusion, blood volume, and biochemistry (such as the expression of enzymes and proteins) that are dependent on gestation [153; 156-158].

In the past, the Simcyp derived pregnancy-PBPK model has been harnessed to evaluate upheavals in plasma concentration of xenobiotics in expectant women [158, 159], and this study demonstrates its utility in relation to sublingually dosed buprenorphine.

2.1.1. Buprenorphine Drug Absorption in Simcyp

Simcyp does not incorporate a sublingual route of administration (V21, Simcyp Limited, Sheffield, UK). As a result, the inhalation module was used to simulate absorption through the oral mucosa, with the amount of buprenorphine inhaled serving as a proxy for the amount that is sublingually absorbed [144]. The remaining portion is assumed to be swallowed in the inhalation module, much like with sublingual drug administration, and can then be absorbed in the gastrointestinal tract. Because buprenorphine undergoes extensive first-pass metabolism, the amount of buprenorphine in Simcyp that is inhaled roughly equates to the amount that is absorbed orally.

2.1.2. Simcyp Virtual Population and Trial Design

In this context, the "virtual twin" of an individual is generated in order to achieve the delivery of individually tailored dosing to a population cohort, particularly pregnant women [152]. Adult Simcyp population files were used for pharmacokinetic (PK) simulations in the retrospective studies based on the study population's published demographics. According to the studies, PK parameters and plasma concentration-time points were predicted by creating a virtual cohort with a predetermined individual count and trial timepoint.

The dose and formulation of the buprenorphine that was administered, along with the cohort's age (or, preferably, age range), proportion of females, and other factors were matched to those in the clinical study. The last reported observable concentration was used to determine the virtual trial's duration.

A model workflow for this study is depicted in Figure 1.

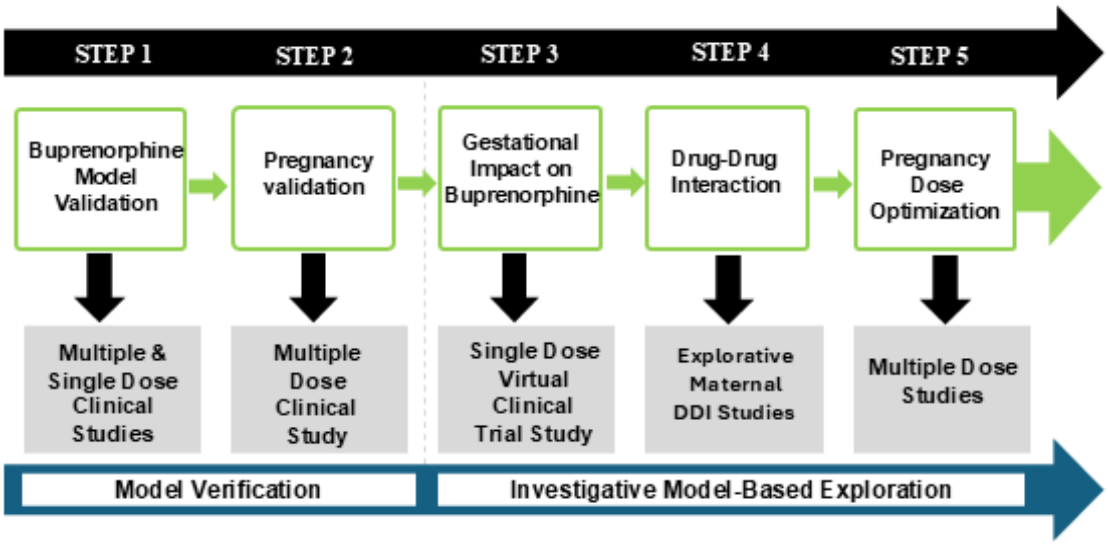


Figure 1. *A model workflow for buprenorphine.*

2.2. Step 1: Buprenorphine Model Validation

To validate the buprenorphine PBPK model within the context of this study, 10 retrospective clinical studies in which buprenorphine was administered intravenously were utilized [111, 160-167, 201]. For the sublingual route, two ascending dose studies and one single dose study was used: (i) 12 healthy adults (10 men and 2 women) aged between 22 and 34 years old dosed with single ascending doses of 4mg and 16mg of buprenorphine [169] (ii) 28 subjects (16 male and 7 women) aged between 21 and 45 years dosed with 8mg and 24mg of buprenorphine [170], (iii) 24 healthy volunteers (18 males and 6 women) aged between 21 and 55 years of age dosed with two 8mg sublingual tablets of buprenorphine [171]. In Simcyp, the trial design was based on these clinical studies.

This model validation is buttressed by the standpoints of model judgment delineated by Resigno et al. [172], that is, prediction (extrapolation of present knowledge to future experiments), retrodiction (consistency with the original data from the primary retrospective studies) and understanding (increases insights into the primary system).

2.3. Step 2: Pregnancy Validation

In order to implement the in-built buprenorphine model during gestation, a further validation was conducted utilizing extracted data from a retrospective clinical study [173] that assessed buprenorphine levels in the second (T2) and third (T3) trimesters of gestation, as well as in the postpartum period. This study included 17 expectant mothers and 3 dose adjusted buprenorphine plasma concentrations. However, the model validation for this study only considered buprenorphine levels for the second and third trimesters.

A mean of the reported pharmacokinetic parameters in gestational trimesters (second and third) and the delineated number of participants in each trimester [(n =7, T2) (n=11, T3)] study design with buprenorphine doses administered over a 12-hour period were used to replicate the Bastian et al. study. In 2017, Kalluri et al. reported a novel perfusion limited buprenorphine sublingual full PBPK model incorporating gestational upheavals in physiological parameters and a fetoplacental compartment as a fused component which was validated in healthy subjects as well as in pregnant subjects virtually [174]. The Simcyp pregnancy PBPK model permits the model to operate dynamically, updating the prediction of the volume of distribution at steady-state (V_{ss}) throughout the study based on revised estimates of the tissue-partition coefficient (K_p), in contrast to using stationary estimates of K_p and V_{ss} with a time vector [175]. The model effects changes to the mother's physiology (e.g., tissue volumes, cardiac output, enzyme abundances) throughout the duration of the study. Although it was initially attempted to calibrate the in vitro values of the enzymes involved in the metabolism of buprenorphine to decreased levels within Simcyp to evaluate the impact of gestation on the levels of the different enzymes, the Simcyp pregnancy-PBPK model does not implicitly account for longitudinal upheavals in CYP2C8, UGT1A1, UGT1A3, and UGT2B7, and these were not included in this study. However, an intersystem extrapolation factor (ISEF) for the CYP3A4 isoform is integrated by default to account for the metabolic breakdown of buprenorphine in this study.

2.4. Step 3: Impact of Gestation on Buprenorphine Levels

The research utilized a 10 x 10 trial design with 18 – 45-year-old women a daily dose of 16 mg sublingually once daily throughout gestation and sampling (of plasma concentration) conducted every 5 weeks and presented as the last 24 hours of that period. The study gathered plasma concentration data for the last 24 hours of every fifth week. The trial was replicated for baseline (healthy nonpregnant females) using the same dosing method.

The Simcyp pregnancy-PBPK model simulates longitudinal upheavals in gestation from the first week of gestation to term. Therefore, the study was conducted from two weeks to the final 24 hours for stipulated gestational weeks (5, 10, 15, 20, 25, 30, 35, 40), allowing for steady state buprenorphine levels to be attained. The rationale for the model validation in gestation is to account for upheavals that occur at the maternal level during gestation, that affect the metabolic breakdown of buprenorphine as well as the pharmacokinetic metrics that are subject to upheavals.

2.5. Step 4: Impact of Drug-Drug Interaction (DDI) On Buprenorphine Levels during Gestation

To investigate the impact of drug-drug interactions on buprenorphine levels during gestation, perpetrators of drug-drug interactions (an inducer and an inhibitor) designated to influence induction and inhibition was dosed at select weeks in gestational trimesters.

2.5.1. Step 4a: DDI Induction Study

The inducer used in the study to assess DDI on buprenorphine levels is Rifampicin. The choice of inducer is due to its potential to elicit a reported 4 – 31-fold induction on CYP3A4 levels [176]. Simcyp® Simulator was used to induce CYP3A4 in a virtual pregnant population (Version 21; Certara, Sheffield UK). Simulations were run using a PBPK model with built-in buprenorphine and rifampicin substrate and inducer profiles. 600mg rifampicin was orally dosed in a once daily regime in the pregnant subjects at the week 5, week 20 and week 35 of gestation and the results were compared before and after the interaction simulation output.

2.5.2. Step 4b: DDI Inhibition Study

Clarithromycin was utilized as an inhibitor to assess the impact of DDI on buprenorphine levels in gestation. The choice of the inhibitor is due to its potential to increase the AUC of the substrate (buprenorphine) through inhibition of CYP3A4 by equal or more than 5-fold [176].

A virtual 'pregnant population' was subjected to clarithromycin mediated CYP3A4 inhibition using the Simcyp® Simulator (Version 21; Certara, Sheffield UK). Using a comprehensive physiologically based pharmacokinetic (PBPK) model and built-in substrate and inhibitor profiles for buprenorphine and clarithromycin, simulations were conducted. Previously, the simulator's built-in differential equations for describing compartment volumes/blood flows, enzyme kinetics, and population covariate effects have been reported in literature [154]. The simulations were conducted using the built-in pregnant population profile ('Sim-Pregnant'). For each simulation scenario, simulations of 10 trials, each involving 10 subjects (total = 100), were conducted. The virtual study cohort included an equal number of 18-to-45-year-old women. 500mg of Clarithromycin was orally dosed twice daily in the pregnant subject at week 5, week 20 and week 35 of gestation.

2.6. Step 5: Buprenorphine Dose Optimization during Gestation

To investigate the effects of buprenorphine dose titration during parturition on plasma concentrations, dosing was initiated sublingually at 4 mg once daily and escalated in 4 mg increments to a maximum of 32 mg once daily across selected gestational weeks (GW) in each trimester (GW 10, 25, 35). The study considered a proposed target concentration of 1ng/ml reported as the threshold for withdrawal suppression [177] and a mean fatality limit of 22.4ng/ml (range 1.8ng/ml – 43ng/ml) reported as the mean from a post- mortem analysis of demise involving concomitant buprenorphine utility with other psychotropic agents [178].

2.7. Predictive Performance

For simulations in steps 1 and 2, an "optimal" predictive performance has been defined as a prediction of pharmacokinetic metrics within twofold (0.5–2.0 fold) of those reported in clinical studies [179, 180]. This was applied in the context of the study carried out. Furthermore, utilizing a visual predictive checking (VPC) strategy [176], this performance parameter was further clarified by comparing the predicted mean and 5^{th} and 95^{th} percentiles of the concentration-time profiles (generated within Simcyp) against the observed data for any validation datasets. Validity of the prediction was determined when the model predicted and observed data points overlapped [159, 175].

2.8. Data and Statistical Analysis

Utilizing WebPlotDigitizer v. 3.10 (http://arohatgi.info/WebPlotDigitizer/), the retrospective (observed) clinical data were extracted from published studies according to best practices [168]. As reported in studies, tabulated (observed) clinical data were utilized, specifically the mean and standard deviation (Steps 1 & 2). Unless otherwise specified, the exploratory investigations (Steps 3, 4, and 5) were reported as mean and standard deviation. Where a DDI simulation was performed, the AUC ratio or C_{max} ratio comparison largely determined the performance of the model (ratio of the AUC or C_{max} in the absence and presence of the inhibitor or inducer). AUC ratios or C_{max} ratios greater than 1.25 indicate an inhibition reaction, ratios less than 0.8 indicate an induction reaction, and ratios between 0.8 and 1.25 indicate no interaction. The model predicted pharmacokinetic parameters were visualized using the LabPlot version 2.11. For the statistical analysis, the nonparametric Students *t*-test and Dunn's multiple comparison post-hoc test were conducted. $P < 0.05$ indicated statistical significance.

3. Results

3.1. Step 1: Buprenorphine Model Validation

The default Simcyp-derived model was utilized, incorporating a full PBPK model to accurately model physiological upheavals in the time course of xenobiotic (buprenorphine) movement and the impact on pharmacokinetic parameters. The sublingual buprenorphine model was verified against 10 retrospective studies (dosing IV intravenously), two dose escalation studies and a single - dose study (dosing buprenorphine sublingually). The resultant predicted plasma concentration time profiles successfully predicted the outcomes of the 10 retrospective clinical studies (IV administration) (Figure 2[A-L]), the two dose escalation studies and the single-dose study (Table 1) utilized for the model validation step. The predicted versus the observed ratios for each study (Table 1) were within the two-fold range (0.5 – 2.0). In addition, the predicted pharmacokinetic parameters [t_{max}, C_{max}, and area under the curve (AUC)] from Simcyp were within twofold of the reported values. The accuracies of the predicted means of C_{max} were within 89 – 120% of the observed means, as well as that of the AUC which was within 93 - 98% for all the studies validated. Likewise, the accuracy of the t_{max} ranged from 68 – 174% which appears to be over predicted by the model considering the accuracy limit the study implemented as an arbitrary standard for the pharmacokinetic metrics (85 – 130%).

3.2. Step 2: Pregnancy Validation

This step compared the model predicted buprenorphine plasma concentration-time profiles to that of the report by Bastian et al., [173] providing a buprenorphine concentration time profile, following single dosing of sublingual buprenorphine in the second (8mg) and third trimester (10mg). This

was done in order to implement the Simcyp-derived p-PBPK model within the context of gestation.

The model predicted mean buprenorphine plasma concentration profiles were within the reported range of buprenorphine (mean ± SD), and the predicted pharmacokinetics parameters (C_{max}, AUC, and t_{max}) were also within two-fold of the reported values [173] (Table 2). The predicted mean dose converted concentration time profiles fell between the fifth and ninety-fifth percentiles of the observed data (Figure 3).

Except for the converted C_{max} in the second and third trimesters of pregnancy (-56 percent and 58 percent) respectively, the difference between the predicted and observed means of dose converted AUC_{0-12} and t_{max} were within ± 50 percent throughout all trimesters of pregnancy.

3.3. Step 3: Impact of Gestation on Buprenorphine Levels

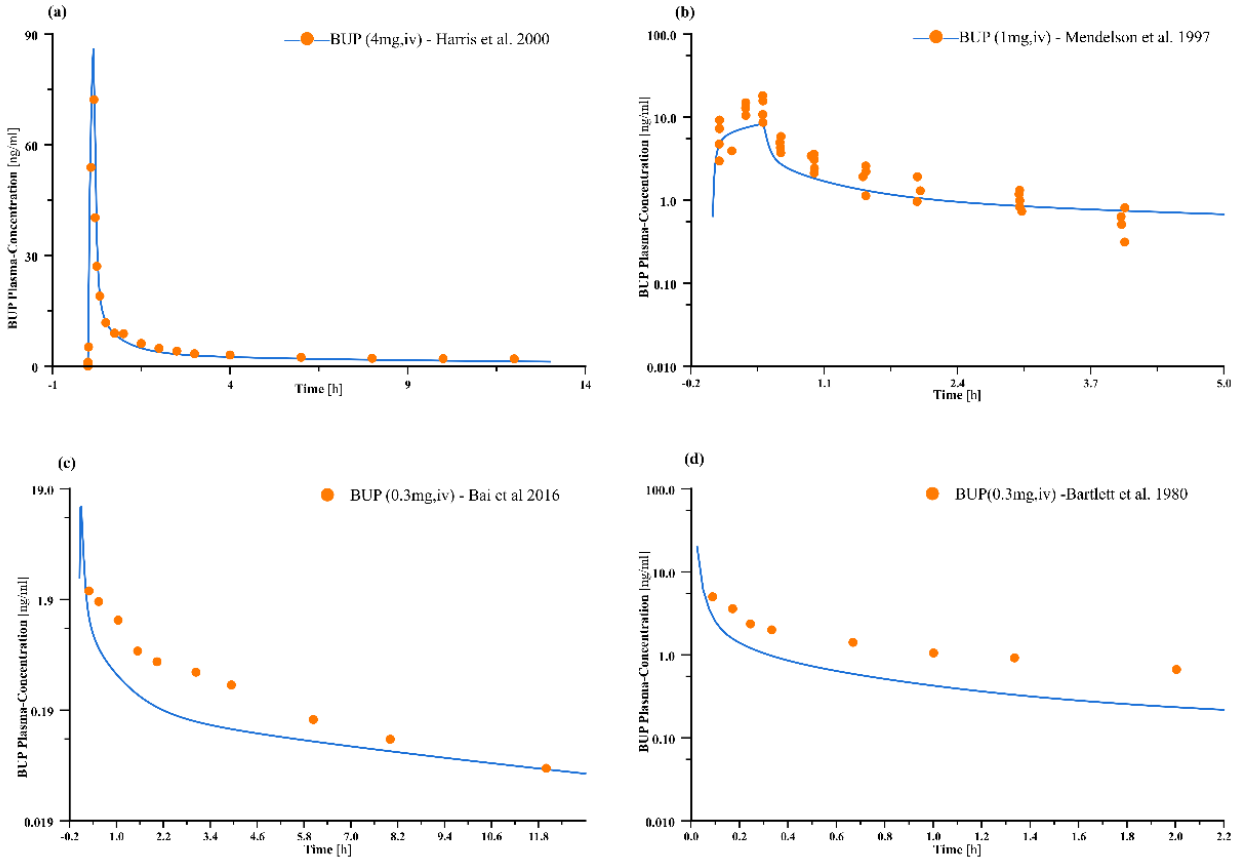
To investigate the impact of pregnancy on buprenorphine levels, the study administered buprenorphine sublingually in once daily doses of 16mg across 40 weeks of pregnancy, with plasma levels reported on the last day of each 5th week and was compared to baseline. A trend across the depicted buprenorphine plasma concentration-time profiles (Table 3) showed statistically significant decreases in the mean peak (C_{max}) levels from the week 15 (7.09ng/ml ± 1.63ng/ml) of gestation to week 40 (5.6ng/ml ± 1.24ng/ml) as well as insignificant changes in the trough (C_{min}) levels throughout the assessment time periods (Table 3).

From baseline (306.72 L/h ±88.25 L/h) to week 40 (402.70 L/h ± 89.90 L/h), the decrease in plasma levels of buprenorphine was accompanied with a 31% increase in clearance (Table 3). In addition, by week 40, the CYP3A4-induced metabolic breakdown of buprenorphine in the liver increased to 49.1 % from 34.39 % (baseline).

The dynamically increasing enzyme abundance levels across the sampled gestational weeks (Table 3) contributed to the decreased plasma concentration profiles thus leading to statistically significant decreases in the mean area under the curve (AUC) from week 15 (51.85ng/mL.h ±12.41 (ng/mL.h) to week 40 (41.56 ng/mL.h ± 8.64 ng/mL.h) when compared to baseline. Likewise, 1.31, 1.64, 2.32-fold increases of the CYP3A4 enzyme abundance were observed in week 15, week 25 and week 40 upon further analysis with Simcyp Simulator V21's default equation (1), which characterizes the longitudinal changes in CYP3A4 activity during gestation:

$$CYP3A4_{\text{Pregnancy fold change}} = 1 + 0{:}0129\ GW + 0.0005\ GW2 \quad (1)$$

This equation uses the dextromethorphan/3-hydroxymorphinan metabolic ratio and midazolam clearance [185, 186, 238] after binding protein correction.



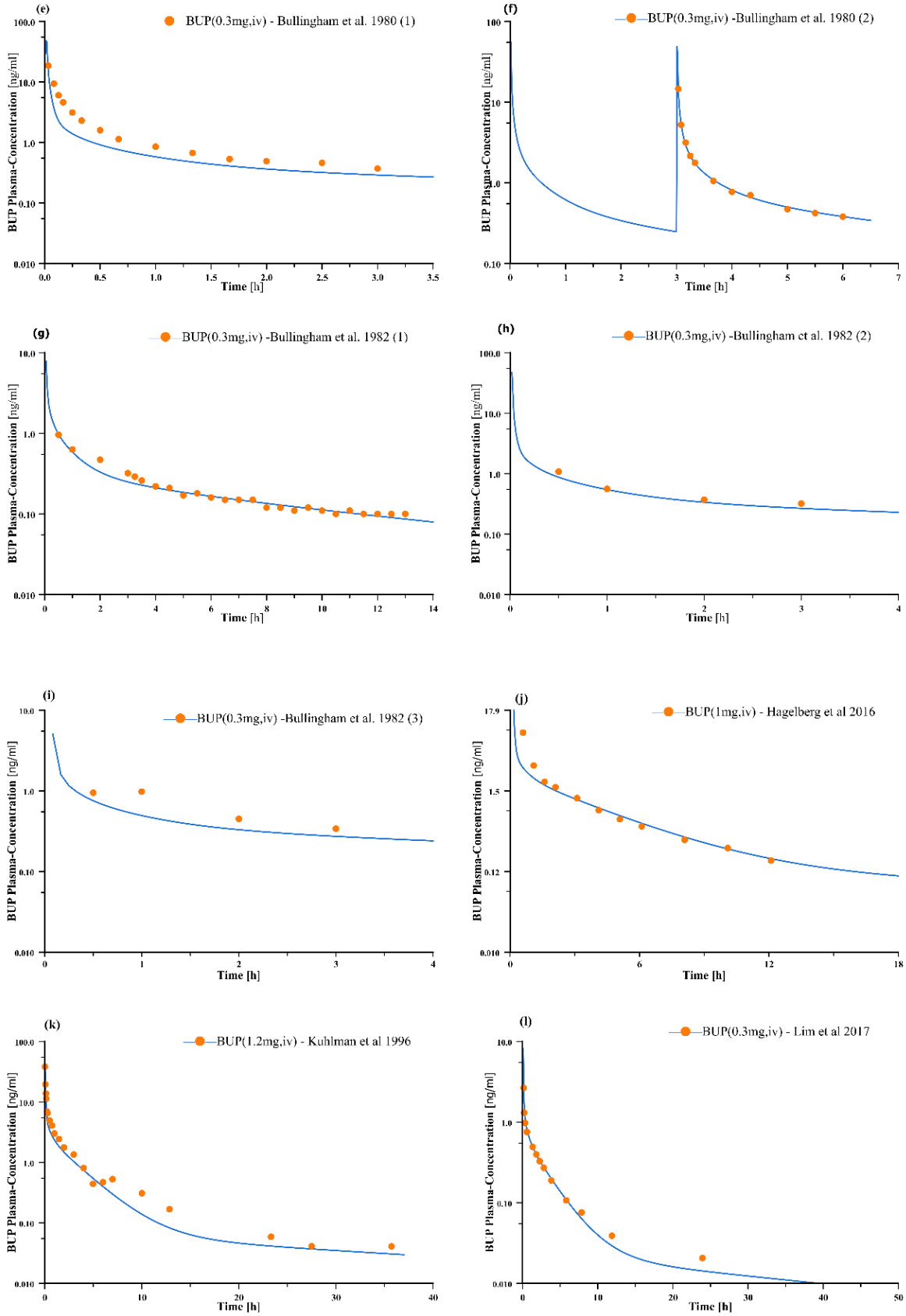


Figure 2. *Simulated buprenorphine plasma concentrations compared to clinical plasma concentrations derived from retrospective studies.*

Solid blue lines depict mean model predicted concentration-time profile; BUP - Buprenorphine; Orange circles represents observed data at different timepoints.

Table 1. *Predicted and observed buprenorphine pharmacokinetic parameters following sublingual administration in healthy volunteers.*

	N	Mean age (range)	Dose (mg)	AUC	C_{max}	Tmax (h)
Harris et al., [169]	8	33 (22 – 42)	4mg	12.52 ±4.37 a	1.84 ±0.72 c	1.06 ±0.42
Predicted	8	30.2 (23 – 43)	4mg	12.03 ±2.91a	1.65 ±0.38 c	1.48 ±0.33
P/O ratio				0.96	0.90	1.39
Harris et al., [169]	8	33 (22 – 42)	16mg	35.25 ±9.89 a	4.54 ±1.01 c	1.51 ±0.32
Predicted	8	30.2 (23 – 43)	16mg	32.63 ±8.23 a	5.47 ±1.27 c	1.04 ±0.65
P/O ratio				0.93	1.20	0.68
Ciraulo et al., [170]	28	33 (21 – 45)	8mg	19.92 ±12.67 b	2.65 ±1.05 d	1.15 ±0.49
Predicted	28	29.6 (22 – 45)	8mg	19.61 ±7.66 b	2.5 ±0.83 d	1.58 ±0.35
P/O ratio				0.98	0.94	1.37
Ciraulo et al., [170]	28	33 (21 – 45)	24mg	48.81 ±31.07 b	5.41 ±3.42 d	0.92 ±0.45
Predicted		30 (22 – 45)	24mg	48.15 ±22.09 b	5.87 ±2.40 d	1.60 ±0.37
P/O ratio				0.98	1.08	1.74
Compton et al., [171]	24	48.5 (18 – 65)	16mg	70.32 ±22.64 b	10.38 ±3.45 d	1.24 ±0.36
CV (%)		NR		33.3	29.4	32.2
Minimum		NR		4.12	0.5	43.16
Maximum		NR		19.51	2	19.51
Predicted	24	33.2 (27 – 41)	16mg	66.24 ±20.46 b	9.27 ±2.27 d	1.5 ±0.41
CV (%)		NR		24	28	31
Minimum		NR		5.96	0.9	37.91
Maximum		NR		13.82	2.25	109.73
P/O ratio				0.94	0.89	1.20

[a] - units expressed as (µg/L.h); [b] - units expressed as (ng/ml.hr); [c] - units expressed as (µg/L); [d] - units expressed as (ng/ml) CV = Coefficient of variation; P/O ratio, fold difference between mean predicted vs observed values, N.R, not reported; C_{max}, peak concentration; $AUC_{0-\infty}$, area under the curve from zero to infinity, N – Number of study participants. Pharmacokinetic metrics are expressed as mean ±standard deviation.

Table 2. *Predicted and observed buprenorphine pharmacokinetics parameter following sublingual administration in pregnant women.*

Reported Data	N	Trimester	Dose (mg)	AUC 0-12 ng/ml.hr	Difference %	Cmax ng/ml	Difference %	Tmax (h)	Difference %
Bastian et al., [173]	8	2	8	15.2 ±1.4a		4.0 ±0.1b		1.6 ±2.8	
Predicted	8	2	8	11.06 ±2.04	-27	1.75 ±0.28	-56	1.22 ±0.30	-24
P/O ratio				0.72		0.40		0.76	
Bastian et al., [173]	13	3	10	22 ±1.2a		5 ±0.19b		1.0 ±1.1	
Predicted	13	3	10	13.31 ±2.75	-40	2.10 ±0.44	58	1.29 ±0.26	29
P/O ratio				0.61		0.42		1.29	

[a]- converted area under the plasma concentration time curve*8mg from published report; [b]- Converted peak concentration *8mg from published report; Difference (%) = (predicted - observed mean value)/observed mean value*100; AUC_{0-12}, area under plasma concentration–time curve from time 0 to 12 h; t_{max}, time to maximum concentration; N – number of study participants

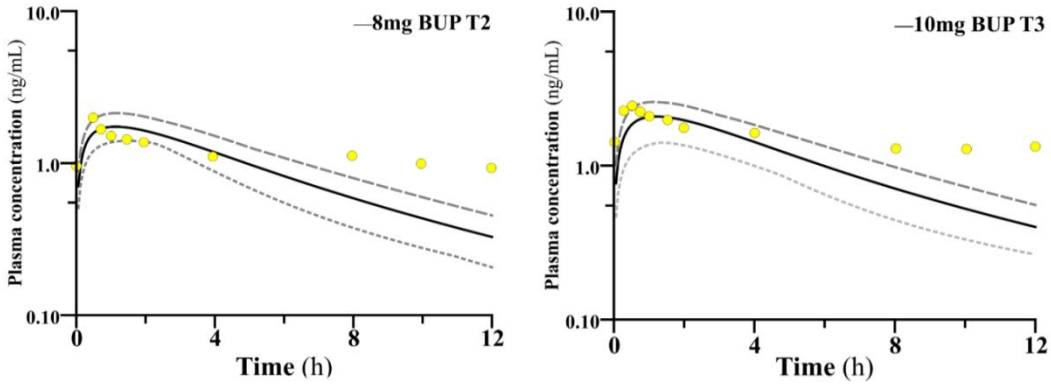


Figure 3. *Predicted Log of buprenorphine plasma concentration-time profiles in gestational trimesters. Second (T2) and third (T3) compared to clinical plasma concentrations derived from a retrospective study [173]. Solid black line depicts logged mean predicted concentration-time profile. Dotted lines (orange and ash) represent the 95th and 5th percentiles; T: Trimester.*

Table 3. *Impact of gestation on buprenorphine pharmacokinetic parameters.*

	AUC (ng/mL.h)	Tmax (h)	Cmax (ng/mL)	Cmin (ng/mL)	CL (L/h)	CYP3A4 Enzyme Abundancea (pmol P450)	BUP fm CYP3A4 Liver (%)
Baseline	56.66 (17.40)	1.29(0.31)	7.69 (2.23)	0.31(0.18)	306.72 (88.25)	6587897.996 (4084787.61)	34.39
GW 5	57.18 (14.83)	1.26 (0.31)	7.85(1.87)	0.30 (0.16)	297.52 (73.87)	7120473.37 (3769062.41)	35.30
GW 10	54.49 (13.57)	1.24 (0.32)	7.46 (1.75)	0.29 (0.15)	311.09 (75.51)	7748429.23 (4101456.71)	36.77
GW 15	51.85 (12.41)**	1.21 (0.32)	7.09 (1.63)**	0.29 (0.15)	325.86 (77.50)	8547025.26 (4524175.56)	38.54
GW 20	49.37 (11.39)**	1.20 (0.31)	6.74 (1.53)**	0.29 (0.14)	341.34 (79.73)**	9516261.47 (5037218.95)	40.51
GW 25	47.09 (10.52)**	1.19 (0.31)	6.43 (1.44)**	0.29 (0.14)	357.06 (82.14)**	10656137.87 (5640586.88)	42.61
GW 30	45.03 (9.77)**	1.20 (0.30)	6.15 (1.37)**	0.29 (0.13)	372.68 (84.66)**	11966654.44 (6334279.35)	44.78
GW 35	43.19 (9.15)**	1.22 (0.30)	5.90 (1.30)**	0.29 (0.13)	387.94 (87.25)**	13447811.19 (7118296.35)	46.96
GW 40	41.56 (8.64)**	1.27 (0.30)	5.66 (1.24)**	0.28 (0.12)	402.70 (89.90)**	15099608.11 (7992637.90)	49.10

AUC - area under the curve; t_{max} - time to maximum concentration; C_{max} maximum concentration (peak); C_{min} - minimum (trough) concentrations; CL - total clearance; CYP3A4 - Cytochrome P450 isoform 3A4; BUP – buprenorphine; f_m - fraction metabolised; ** indicates statistical significance denoted by $P < 0.05$. [a] enzyme abundance data expressed as geometric mean (standard deviation). Pharmacokinetic parameters expressed as mean (standard deviation)

3.4. Step 4: Impact of DDI on Buprenorphine Levels During Gestation

The simulation data for the impact of drug-drug interaction on buprenorphine levels during gestation depicts significant upheavals on the level of administered buprenorphine levels on the last day of week 5 (first trimester), week 25 (second trimester) and week 35 (third trimester) of gestation.

3.4.1. Step 4a: DDI Induction Study

The simulated drug interaction perpetrated by Rifampicin is depicted in Figure 4(A-C). A trend across the concentration time profiles of buprenorphine in the selected gestational weeks showed over a twofold decrease in buprenorphine levels in about 24 hours after Rifampicin treatment.

Comparison of the mean (standard deviation) pharmacokinetic metrics (AUC, C_{max}, t_{max}, CL) before (Table 1- ESM) and after (Table 2 - ESM) rifampicin mediated interaction, showed statistically significant decreases ($P < 0.05$). In addition, the mean AUC ratio as well as mean C_{max} ratio reflects induction potential perpetrated by rifampicin exposure. Across the selected gestational weeks in each trimester (Table 2 - ESM), profound increases in clearance following Rifampicin treatment were observed when compared to baseline (Table 1 - ESM); that is, 75% (gestational week 5), 58% (gestational week 20). However, a subtly reduced clearance metric was observed at gestational week 35 (44%).

Furthermore, statistically significant decreases ($P < 0.05$) in

AUC values (55%, 62%, 68%) were observed for gestational week 5, gestational week 20 and gestational week 35 respectively. The influence of rifampicin mediated induction on the total hepatic intrinsic clearance of buprenorphine with time was further evaluated to predict a mean steady-state induction on the total hepatic intrinsic clearance over time was evident at about 173 hours in week 5 [13005 L/h (44681 – 4063 L/h)], 252 hours in week 20 [17396 L/h (60975 – 5635 L/h)]; and 242 hours in week 35 [20010 L/h (670301 – 6993 L/h)] following rifampicin 600mg once daily administration (data not reported).

3.4.2. Step 4b: DDI Inhibition Study

Figure 5(A-C) depicts the simulated drug-drug interaction between clarithromycin and buprenorphine. A trend across the concentration time profiles of buprenorphine in the selected gestational weeks revealed a more than two-fold increase in buprenorphine levels in approximately 24 hours after treatment with clarithromycin. Slight percentage increases in the mean peak levels (C_{max}) of buprenorphine in each week in the gestational trimester were observed, that is, 33% for week 5, 28% in week 20 and 25% in week 35. Furthermore, statistically significant increase in the mean trough (C_{min}) levels as well as percentage increases in week 5 (82%), week 20 (69%) and week 35 (64%) respectively. Comparing the pharmacokinetic metrics (AUC, C_{max}, C_{min}, t_{max}) prior to (Table 3 - ESM) and after (Table 4 - ESM) the clarithromycin-mediated interaction revealed statistically significant increases ($P < 0.05$) in all cases. Conversely, the predicted clearance metric demonstrated statistically significant decreases compared to its initial value (before interaction). In addition, the mean AUC ratio and the mean C_{max} ratio indicate that clarithromycin elicited a potent inhibition potential.

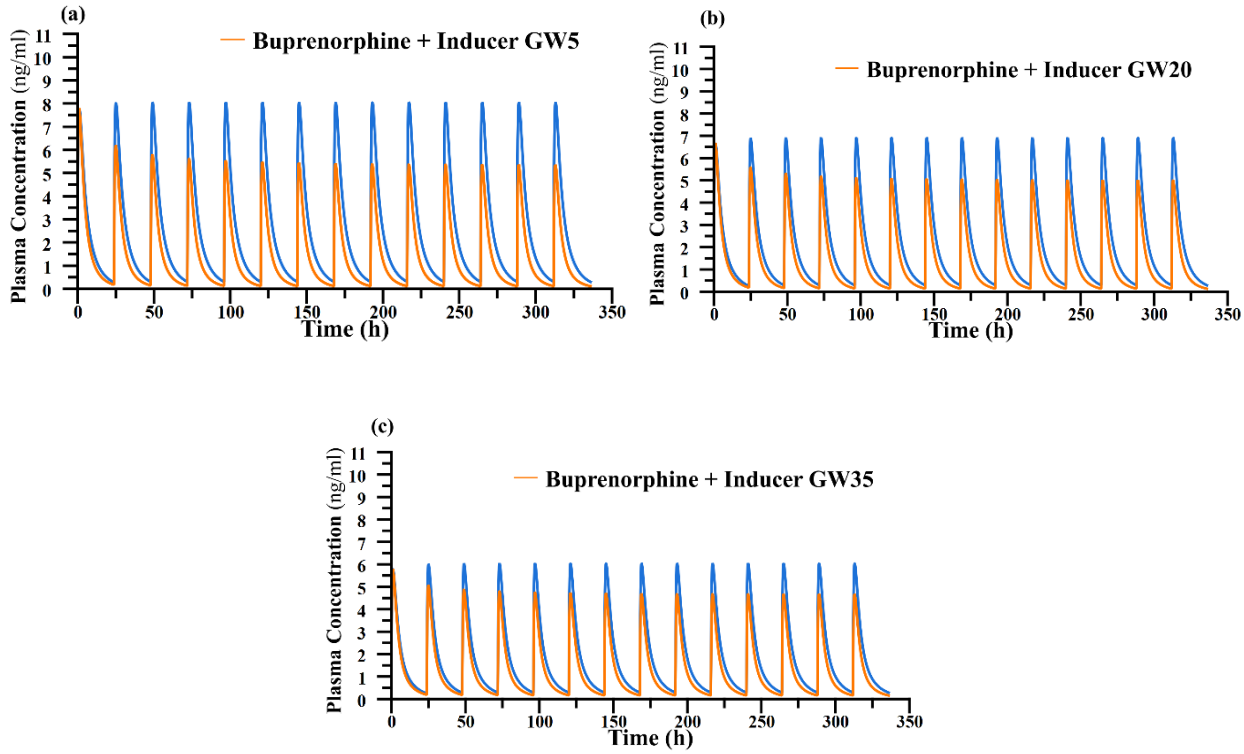


Figure 4. *(A - C). Simulated mean concentration-time profiles of buprenorphine daily doses (16mg) in presence and absence of Rifampicin (600). GW – gestational week; b.d – twice daily dosing; Orange line displayed as 'DDI'; Blue Line depicted as 'No DDI'.*

Across the selected gestational weeks in each trimester (Table 4 - ESM), significant decreases in clearance were observed following clarithromycin treatment when compared to baseline (Table 3 - ESM); 72% (gestational week 5), 74% (gestational week 20), and 77% (gestational week 35). In addition, significant increases in AUC values (47 percent, 41 percent, and 36 percent) were observed for gestational weeks 5, 20, and 35, respectively (Table 4 - ESM).

Furthermore, the impact of clarithromycin-mediated inhibition on the total intrinsic hepatic clearance of buprenorphine over the time course of the concurrent administration of both xenobiotics was investigated. Within the first 72 hours of twice-daily administration of 500 mg of clarithromycin, a mean steady-state inhibition of the total hepatic intrinsic clearance over time, was observed in week 5 [3446 L/h, range (7432 – 758)], week 20 [3876 L/h range (9072 – 802 L/h)], week 35 [4558 L/h range (11682 – 857 L/h)]. Further, a percentage steady-state inhibition of active CYP3A4 levels (22%) was evident at about 122 hours (data not reported).

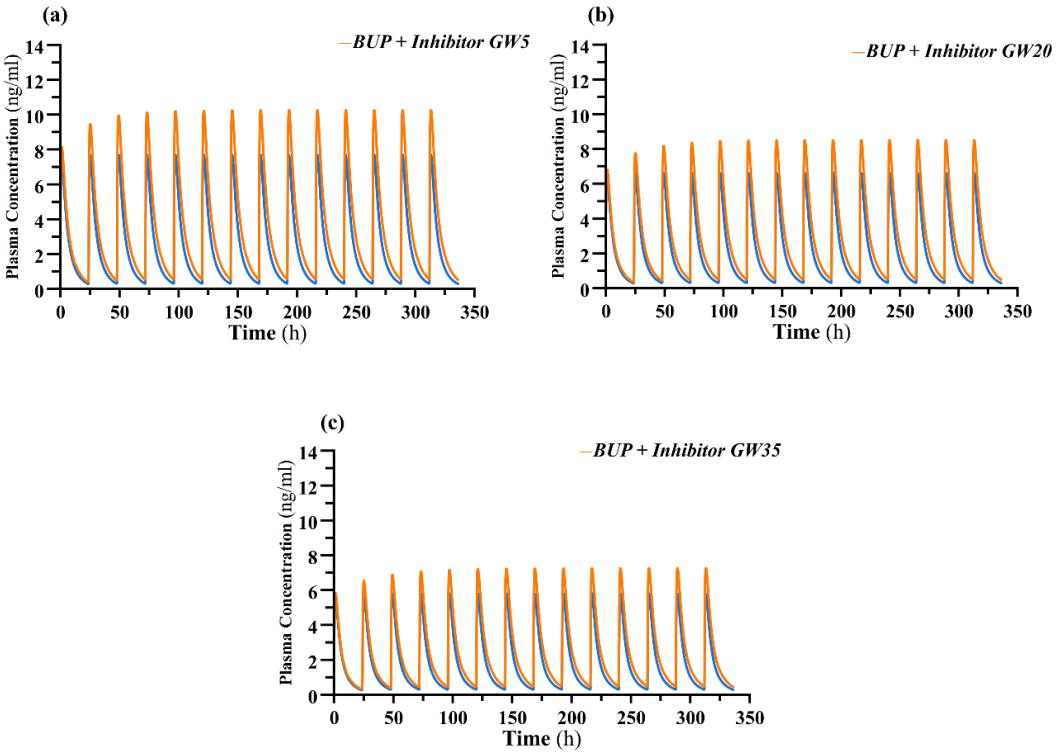


Figure 5. *(A - C). Simulated mean concentration-time profiles of buprenorphine daily doses (16mg) in presence and absence of Clarithromycin. GW – gestational week; b.d – twice daily dosing; Orange line displayed as 'DDI'; Blue Line depicted as 'No DDI'.*

3.5. Step 5: Buprenorphine Dose Optimization in Gestation

This step considered methods for quantitative dose escalation to make sure the study maintained plasma peak levels below the lower limit of the proposed fatality threshold given the decrease in buprenorphine plasma concentration throughout gestation. The study measured the proportion of the subjects with peak levels at the upper target concentration and above the fatality limit, respectively, to further address changes in sublingual buprenorphine levels during gestation. Furthermore, due to CYP3A4 allelic absence in buprenorphine metabolism, phenotypic characterization of subjects was not taken into consideration during the dose optimization step, thus leading to the assumption that all subjects had an extensive metabolizer (EM) phenotype (Table 4).

To determine the optimal dose, the study design made sure that a high percentage of subjects had concentrations that were both above the suggested target concentration level (1 ng/ml) and below the fatality limit (22.2 ng/ml). An ideal dose was defined as one in which more than 50% of the subjects had concentrations within the therapeutic window. A dose of 8 to 24 mg once daily is recommended as being ideal throughout gestation for the subjects across the chosen gestational week in each trimester (week 10, 25, 35). More than 90% of the subjects had peak levels above 1ng/mL after the initial dose of 4mg once daily. However, a dose of 28 mg and 32 mg administered once daily led to 1% and 3% of subjects in trimester 1(GW 10), having peak levels above 22.2 ng/ml. The subjects maintained their therapeutic peak levels below the fatality limit in trimesters two and three at these doses (28mg & 32mg), respectively.

The doses were titrated over a range of 4mg - 32mg once daily throughout gestation, with increments of 4mg in each trimester-specific gestational week. Peak levels were recorded for the virtual Caucasian population group on the last day of dosing in the selected gestational week of each trimester. The percentage of subjects whose plasma concentration (peak) exceeded both the fatality limit (22ng/ml) and the target concentration (1ng/ml) was reported (Table 4).

4. Discussion

Gestation is associated with an escalated impact on buprenorphine pharmacokinetics, and results to subtherapeutic levels of buprenorphine administered in pregnant women, thus necessitating the need for dose adjustments.

4.1. Step 1 & 2: Buprenorphine and Pregnancy Model Validation

Table 4. *Buprenorphine dose optimization during gestation.*

		T1 (Gestational Week 10)			T2 (Gestational Week 25)			T3 (Gestational Week 35)		
Dose	**Pheno-type**	**Cmax (ng/ml)**	**% > 1 ng/mL**	**% > 2 ng/mL**	**Cmax (ng/ml)**	**% >1 ng/mL**	**%>22 ng/mL**	**Cmax (ng/ml)**	**% > 1 ng/mL**	**% > 2 ng/mL**
4mg	EM	1.86 (0.44)	99	0	1.61(0.36)	97	0	1.47 (0.33)	92	0
8mg	EM	3.73 (0.87)	100	0	3.22 (0.72)	100	0	2.95 (0.65)	10	0
12mg	EM	5.59 (1.31)	100	0	4.82 (1.08)	100	0	4.42 (0.98)	100	0
16mg	EM	7.46 (1.75)	100	0	6.43 (1.44)	100	0	5.90 (1.30)	100	0
20mg	EM	9.32 (2.18)	100	0	8.04 (1.80)	100	0	7.37 (1.63)	100	0
24 mg	EM	11.19 (2.62)	100	0	9.65 (2.16)	100	0	8.84 (1.96)	100	0
28mg	EM	13.19 (3.06)	100	1	11.26 (2.52)	100	0	10.32 (2.28)	100	0
32mg	EM	14.52 (3.49)	100	3	12.86 (2.89)	100	0	11.79 (2.61)	100	0

EM – Extensive metabolizer; C_{max} – maximum concentration: data expresed as mean (standard deviation)

In this study, the Simcyp simulator was utilized to predict the systemic sensitization during gestation for sublingually dosed buprenorphine. In a stepwise workflow (Figure 1), the p-PBPK model was first validated by comparing simulated systemic buprenorphine exposure against published data from retrospective (two dose escalation and a single dose) studies in healthy subjects (Figure 2 [A-L]). Additionally, the predictive performance of the p-PBPK was assessed by comparing it to the observed plasma concentration of buprenorphine in second and trimester pregnant women from the study in Step 2 (Figure 3, Table 2). There are currently no recommendations regarding the validation standards for model predictions. However, utilizing a visual predictive checking (VPC) strategy [176], the mean observed data were consistent with the predicted mean concentration-time profiles, 95th and 5th percentiles in the pregnant populations as well as the healthy volunteers in the retrospective studies, authenticating the validation. Given the variation in the metrics and buprenorphine biotransformation in this population, a 50 percent discrepancy was deemed to be plausible. In general, the Simcyp-derived model successfully predicted buprenorphine exposures that were within ± 50 percent of the observed reported mean values.

A further analysis of the pharmacokinetic metric ratios (mean predicted/mean observed) of the model validation steps (1 & 2) as depicted (using select studies) in the forest plot (Figure 1 - ESM), illustrated an overall model predictive performance consistency within a twofold range in affirmation with that reported in numerous studies [179, 180]. However, a slight deviation of the peak concentration (C_{max}) in the trimester specific (T2 & T3) dose validation study (Figure 3) could be thought to be due to reasons that the sublingual route of administration utilized in the clinical study probably did not consider an absolute absorption of buprenorphine since some of the drug is swallowed and the rest is absorbed into systemic circulation. One of the limitations of the sublingual model is that it cannot make up for every circumstance that could affect sublingual mucosal absorption and since the significant proportion swallowed could be accounted for, the non-mechanistic inhalation model functioned as a suitable proxy for the Simcyp Simulator's absence of a sublingual model. Furthermore, the C_{max} variability from the proscribed two-fold range assessment criteria in the forest plot (Figure 1 - ESM) and the difference (%) in the second trimester (Table 2) could be explained from viewpoint of epistemic and aleatoric model uncertainty [183]. The epistemic model uncertainty may emanate from an incomplete knowledge of the system under scrutiny (gestation), and the aleatoric model uncertainty connotes a deep-rooted characteristic of a system, thus effecting a variability in the assessed metric (C_{max}). The deviation depicted in the C_{max} may also be substantiated with claims by Clewell III et al. that, “the level of detail incorporated into a model is necessarily a compromise between biological accuracy and parsimony” [184].

Natural variability may also account for the model over prediction of the t_{max} metric in the validation steps (1 & 2) due to the explanation that, after sublingual buprenorphine administration in the reported clinical studies, there may be variations in the amount of the formulation that is swallowed versus absorbed; some patients may disregard instructions and pulverize the formulation prior to swallowing; others

may keep the sublingual formulation in their mouths for varying periods and some patients may take the tablets whole while others may cut or crush the product before use. This consequently impacts the time taken for buprenorphine to attain plasma concentrations.

4.2. Step 3: Impact of Gestation on Buprenorphine Levels

The impact of gestation on the model-predicted buprenorphine plasma concentration time profiles (Table 3) reflects a 1.3-fold reduction in buprenorphine levels at term compared to baseline and statistically significant changes ($P < 0.05$) were observed in the peak levels (C_{max}) as well as in the AUC from week 15 of gestation up till term (week 40). However, a statistically significant increase for the model predicted clearance metric (Table 3) was evident from week 20 up to week 40 contrary to expectations. This variability in the clearance metric decline across gestational weeks corroborates with the report by Coker et al., [185].

Gestation is associated with a decrease in plasma protein concentration, which could result in escalated unbound buprenorphine fraction in the blood [186]. Additionally, increased cardiac output, hepatic perfusion, and expression in activity of the enzymes CYP3A4, UGT2B7, UGT1A1, and UGT1A3 [187, 238], could theoretically be thought to be a plausible account for the decreased buprenorphine plasma concentration profiles across gestational weeks.

Several published reports [188, 189] have highlighted the utility of xenobiotic trough (C_{min}) concentrations as a proxy marker for xenobiotic exposure. However, this was not the case for the Simcyp-derived model predicted buprenorphine trough levels in this study (Table 3), as there were insignificant changes across the gestational weeks in comparison to baseline. This could probably be explained by buprenorphine's escalated lipophilicity and extensive protein binding that are not subject to the physiological upheavals in gestation such as the expansion of the fluid compartment of the maternal body as well as a decrease in plasma protein levels. This finding corroborates with the study reported by Johnson et al. highlighting the insignificant changes of the mean buprenorphine trough levels (0.36ng/ml, range 0.12 - 0.79ng/ml) in several (three) opioid-dependent gestational women exposed to buprenorphine in doses of 8mg/day – 12mg/day in the third trimester of gestation [190]. Likewise, there were insignificant changes in the model-predicted t_{max} metric (Table 3). Clinically, the t_{max} metric is not linked to any established effects. However, the suppression of withdrawal symptoms; characterized as "the substance-specific problematic behavioural change, with physiologic and cognitive components, that is due to the cessation of, or reduction in, heavy and prolonged substance use," [191] manifesting through a constellation of signs, is pivoted above a threshold of 1ng/ml as reported by Greenwald et al. [177].

During gestation, physiological upheavals in cardiac output skyrockets from 35% to 50%, and CYP3A4 activity increases from 35% to 38%. Therefore, the increased model-predicted clearance metric of buprenorphine during gestation (Table 3) is likely attributable to an increase in intrinsic clearance and hepatic perfusion. This could be as a result of the reported intermediate to high hepatic extraction ratio of buprenorphine [150] which is circa 0.67 and both intrinsic hepatic clearance and hepatic perfusion affect drug disposition for intermediate to high-clearance drugs.

Furthermore, reported physiological escalations in oestradiol levels, which is mediated by an increased mRNA expression level of CYP3A4 through activation of constitutive androstane receptor (CAR) and pregnane X receptor (PXR) [192], impacts the biotransformation of substrates (such as buprenorphine) for this enzyme and could theoretically lend a support to account for the model predicted quantitative increase in CYP3A4 enzyme abundance levels (Table 3) that impacts the metabolic breakdown of buprenorphine across gestational weeks assessed in this study, leading to decreased AUC exposures.

4.3. Step 4a: DDI Induction Study

The impact of the model predicted pharmacokinetic drug-drug interaction on sublingual buprenorphine in gestational women was assessed in this study utilizing an inducer and an inhibitor. Across selected gestational weeks (Figure 4 A – C), a trend towards a decrease in the plasma concentration time profile of buprenorphine was evident in each gestational week following concomitant 600mg Rifampicin once daily administration for a duration of two weeks. From Figure 4 (A – C), an apparent decrease in the peak levels of buprenorphine was evident in twenty-four hours following Rifampicin administration. This induction could be thought to be due to the short half-life of rifampicin as well as the propensity to cause an induction magnitude (Ind_{max}) of 16 times the actual value of CYP3A4 enzyme responsible for the majority of buprenorphine metabolism. Likewise, activation of the nuclear PXR receptor by rifampicin induces CYP3A4. This was evident in the quantitative changes in the CYP3A4 enzyme abundance levels across each assessed gestational week in the Simcyp output data file (not reported). Additionally, in concert with physiological upheavals occurring throughout gestation, rifampicin mediated induction of buprenorphine metabolism may precipitate withdrawal symptoms and result to low drug levels or to increased adverse effects if rifampicin treatment is unexpectedly discontinued without a dose adjustment of buprenorphine.

It has been reported that rifampicin is one of the most potent inducers of CYP3A4 [193] and is also an inducer of glucuronidation [194, 195]. The reported inhibition constant (K_i) value denoted 15 within Simcyp, which is reflective of the binding affinity of Rifampicin as well as the resulting escalation of the zero-order synthesis rate of CYP3A4 in vivo [196], may most likely contribute to its potency. Addi-

tionally, the rates of messenger ribonucleic acid (mRNA) turnover determine the lag time that corresponds to the peak rate of enzyme synthesis [197]. The integration of these effects in synergism with pregnancy-linked physiological upheavals may significantly reduce buprenorphine exposure, making predisposed gestational women more susceptible to developing opiate withdrawal symptoms.

Further statistical analysis (paired t-test) of buprenorphine metrics in the absence (Table 1 - ESM) and presence of a two-week 600mg Rifampicin once daily treatment (Table 2 - ESM) across the gestational weeks (5, 25, 40) revealed statistically significant decreases ($P < 0.05$) in the mean peak (C_{max}) (67%, 72%, 77%), mean trough (C_{min}) (40%, 45%, 57%), mean AUC (56%, 62%, 68%) and mean t_{max} (88%, 89%, 92%) levels. This could probably be accounted for as a result of the escalated total hepatic intrinsic clearance occurring across the gestational weeks. The expediency of the sublingual route of administration of buprenorphine increases its bioavailability to 30 – 55% [110, 161] as it undergoes transmucosal absorption from the oral cavity [198]. However, buprenorphine is subject to extensive first-pass metabolism [150], with circa hepatic extraction ration of 0.67, therefore this consequently impacts its blood levels when administered through this route. In addition, a statistically significant increase in the clearance metric (75%, 58%, 44%) was documented and is most likely as a result of the physiological upheavals (for instance, increased cardiac output and hepatic perfusion) occurring throughout gestation in synergy with Rifampicin-perpetrated DDI induction.

The reported AUC ratios (0.57 [week 5], 0.63 [week 25], 0.69 [week 35]) and C_{max} ratios (0.67 [week 5], 0.72 [week 25], 0.77 [week 35]) (Table 2 - ESM) in the DDI assessment in each gestational week reflected the likelihood of a clinically significant drug interaction perpetrated by Rifampicin. Again, this could be accounted for due to the long duration of rifampicin administration. The report by Niemi et al., highlighting a full induction period of CYP3A4 enzyme to be approximately one week ($\approx$ 168hrs), could lend a support to the increasing percentage multiplier of active CYP3A4 (data not reported) in the liver following the once daily 14-day rifampicin treatment [199]. Clinically, the repercussions of this Rifampicin-mediated induction scenario in tandem with the myriad physiological upheavals occurring throughout gestation may synergistically culminate in the precipitation of opioid withdrawal symptoms manifested by opioid craving and an increased propensity to relapse toward illicit opioid utility hence, necessitating a dose adjustment in buprenorphine administration. The findings of this DDI induction study are consistent with the published studies by McCance-Katz et al., and Hagelberg et al., albeit with a small cohort of healthy subjects (varying proportion of males and females) and a shortened study period [200, 201]. However, claims regarding the precipitation of opiate withdrawal symptoms following established induction of metabolic enzymes may be further assessed and reported in this group (gestational women).

4.4. Step 4b: DDI Inhibition Study

Figure 5 presents the model-predicted simulation impact of clarithromycin mediated drug interaction on sublingually dosed buprenorphine levels across selected gestational weeks (5, 20, 35) in each trimester. The displayed profiles (Figure 5 A – C) depict a trend portraying significant increases in the plasma concentration time profiles of buprenorphine after a two week twice daily administration of 500mg of Clarithromycin. Clarithromycin is a macrolide anti- infective that irreversibly and time-dependently inhibits CYP3A4 and is N-demethylated by CYP3A4 to generate a nitrosoalkene, which covalently forms a complex with CYP3A4 to render it deactivated [202]. This escalation in the model-predicted buprenorphine levels (Figure 5 A – C) is probably attributable to hepatocyte CYP3A4 irreversible inhibition in a mechanism-based conduit perpetrated by Clarithromycin, consequently necessitating *de novo* synthesis of the inactivated enzyme and the elimination of the mechanism-based inhibitor (Clarithromycin) over time to restore baseline activity of the enzyme. The maximal inactivation rate constant (K_{inact}) and half-maximal inhibitor concentration characterizing time-dependent inhibition (K_i) are reported within Simcyp (2.13 & 12) respectively and are consistent with the report by Rowland Yeo et al. [203] and these metrics could most likely account for the time- dependent inhibition mechanism perpetrated by Clarithromycin administration in this study.

Comparison (paired t-test) of the reported buprenorphine metrics before (Table 3 - ESM) and after the 500mg Clarithromycin twice daily mediated DDI (Table 4 - ESM) revealed statistically significant increases across the gestational weeks (5, 20, 35) in the mean AUC (47%, 41%, 36%), C_{max} (33%, 28%, 25%), C_{min} (82%, 68%, 64%,) t_{max} (8%, 7%, 6%) and a decrease in the clearance metric (72%, 74%, 77%) respectively. CYP3A4 is highly expressed in the liver and small intestine [204] and is responsible for the disposition of over 30% of small molecule drugs [205]. In terms of inhibitor attributes, the magnitude of inhibition increases in accordance with increasing inhibitor concentration in parallel to its potency [196], and the duration of Clarithromycin administration in this study most likely attained concentrations sufficient to potently inhibit CYP3A4 expression, consequently influencing the increased pharmacokinetic metrics of buprenorphine, as well as a culminating decrease in the clearance metric (Table 4 - ESM) in parallel with the shortened time taken to effect steady-state inhibition of the total hepatic intrinsic clearance across the gestational weeks (data not reported). Additionally, the probability that the drug's pharmacokinetics will be altered increases as the victim's dependence on the inhibited route of elimination increases. The model predicted reported mean AUC ratios (1.44 [week 5], 1.39 [week 25], 1.34 [week 35]) and mean C_{max} ratios (1.32 [week 5], 1.28 [week 25], 1.24 [week 35]) (Table 4 - ESM) in the DDI assessment across each gestational week, reflected a likelihood of clinically significant drug interac-

tion perpetrated by Clarithromycin. These may be supported by theoretical recapitulation that, inhibition due to high first pass extraction for a high-clearance victim drug can result in a significant increase in AUC in the presence of an inhibitor, making it more susceptible to DDI than a drug with low clearance [196]. Conversely, the rate of escalated CYP3A4 expression and synthesis across gestation despite the extended dosing regimen of Clarithromycin may contribute to the model-predicted inhibition DDI scenario. Although the systematic reproducibility and robustness of clinical trial data is critical, conduction of trials necessitates implementation of principal discretions in line with stated principles in the Declaration of Helsinki, requiring that subjects are not sensitized to wanton risks. Clinical consideration for clarithromycin utility is linked with a commonplace adverse event identified as "Torsades de Pointes" (TdP) [206]. Torsades de pointes is a potentially fatal ventricular arrhythmia that results from a prolonged QT interval on the electrocardiogram. Clarithromycin-induced QT interval prolongation is associated with a greater risk and magnitude at higher doses and lengthier durations [207, 208]. Affirmative to expectations, the simulated results presented in this inhibition study suggests incidence of a potent DDI following concomitant Clarithromycin 500mg twice daily doses over a 2-week period in gestational women due to the CYP3A4 inactivation magnitude and fold AUC increments (> 5) in the selected gestational weeks (Table 4 - ESM). It has been demonstrated that the administration of clarithromycin (500 mg twice daily) to healthy subjects over a 10-day duration is safe and increases the risk of QT interval lengthening only minimally [209]. However, the findings of this study warrant the necessity for future qualitative research in pregnant women.

4.5. Step 5: Buprenorphine Dose Optimization in Gestation

The dose optimization approach implemented in this study considered the reported threshold above which suppression of withdrawal symptoms is evident [177] and a reported mean fatality limit [178] with a propensity of precipitating adverse events associated with buprenorphine utility in a dose escalation conduct. The study allocated the dose range to clinically reported doses [148, 173, 185, 210-212]. The superintending principle in this method was to maintain peak levels in abundance of 1ng/ml and below 22.2 ng/ml (fatality limit). The percentage of subject above the threshold for withdrawal was > 90% (Table 4) across the selected gestational weeks in each trimester for the 4mg dose of buprenorphine. The titrated dose ranges 8mg – 24 mg in the virtual subjects demonstrated a model-predicted optimal dosing within the proposed pivot of therapeutic levels (above 1ng/ml, below 22.2ng/ml) in this study. Further dose titrations at 28mg and 32mg yielded subjects (1% and 3%) above the fatality limit in the first trimester, respectively. Hence the study identified that steady state dosing range between 8mg and 24mg daily maybe be optimal prenatally. The proportion of subjects that tend to be subtherapeutic at the onset of dose titration (4mg) may be due to possible reasons: the extensive first pass metabolism profile and resulting low bioavailability in buprenorphine sublingual absorption may influence the peak levels. Likewise, the argument reported by Selvi et al. that a decline in salivary pH during gestation may elicit an impact on the dissolution of oral xenobiotics [134] could contribute to explanations for the subtherapeutic levels seen across the trimester specific gestational weeks (Table 4). Additionally, a constitutive increase in the enzyme abundance of CYP3A4 in concert with physiological factors (for instance, increased cardiac output) as well as the clearance across the gestational weeks in each trimester may be implicated. Furthermore, an oral mucosal "reservoir" architecture has been identified to influence buprenorphine systemic absorption [111], and this could lend a support to the model predicted variability in the subtherapeutic levels for the subjects.

The model predicted doses (28mg & 32mg) above the fatality limit in the first trimester (GW 10) may be attributable to discrepancies in elimination half-life of buprenorphine. The elimination half-life estimate tends to be prolonged for sublingual buprenorphine than for intravenous administration [110]. Clinically, incidences of unpleasant side effects such as nausea and vomiting, as well as adverse effects specifically, respiratory depression and altered cognition may occur. The disparity in the apparent clearance of buprenorphine as well as its rapid accumulation into physiological tissues (fat, muscle) in gestation may likely be attributable for the model predicted concentrations above the proposed fatality limit considering the 28mg and 32mg doses in the first trimester (GW 10, Table 4). The model predicted mean plasma concentration time profiles are consistent with those reported by Walsh et al. [148], albeit with a small cohort and a tailored gender inclusion (males). Introspective analysis of the model generated demographics of the affected percentage of virtual subjects in the 28mg (1%) and 32mg (3%) dose titration scenarios revealed an increased physiologic human serum albumin (HSA) concentration despite a decrease in other virtual subjects. The extensive protein binding profile of buprenorphine may be a reason for the exposure at these doses. Additionally, the biotransformation pathways involved in buprenorphine disposition may be subject to individual variability and may be responsible for the toxicity profiles for the model predicted concentrations in the first trimester at the afore mentioned doses (28mg & 32mg) respectively. CYP3A4 is implicated for the major metabolism of buprenorphine [213], followed by CYP2C8 and well as UGT1A1, UGT1A3 UGT2B7. However, there may be individuals with low constitutive levels of this enzyme (CYP3A4) and could cause saturation in the metabolic capacity despite the increased enzyme levels occurring in gestation. Furthermore, polymorphisms exist for CYP2C8 [214, 215] and UGT enzymes [216] and this may impact the biotransformation of buprenorphine.

Theoretically, the development of tolerance to escalated

doses of buprenorphine have been reported [217] and published studies in animal experiments [218, 219] could lend support to plausibly account for the retarded dissociation kinetics of buprenorphine from *miu*-opioid receptors hence consequently eliciting prolonged pharmacodynamic effects. Additionally, reports to account for the propensity for fatality associated with buprenorphine mono-utility in escalated doses are sparse. However, several reports have identified fatal occurrences to be associated with concomitant usage of illegal psychotropics and neuroleptics [220-223]. Thus, this study may suggest that the quantitative model predicted concentration profiles above the proposed fatality limit may not likely precipitate adverse events. The case report by Ross [224] may likely substantiate this claim. Clinically, the incidence of NAS in neonate has been documented albeit with an abridged likelihood of occurrence. Buprenorphine traverses the placenta. However, its confinement in a "depot" architecture could be thought to be a reason for the low incidence of the development of NAS in neonates. Additionally, postpartum associated instantaneous decline in intravascular volume could influence buprenorphine volume of distribution and may constitute a necessity for tapering. In spite of this, several reports [225, 226] may lend a support for the successful tapering regarding buprenorphine utility as well as of methadone [227]. The dose tapering strategies reported for methadone utility by Badhan et al., may be adopted to successfully tailor pharmacotherapy to buprenorphine-sensitized gestational women [227]. However, ambiguity exists warranting the need for dose reduction of both medications postpartum [173, 228-230], thus, a gauntlet of further qualitative and quantitative investigations may be instigated to further usher streamlined evidence for adoption in cadres of therapeutic approaches for pregnant women.

4.6. Study Strengths, Limitations & Future Research

There were strengths and limitations associated during this investigation. The Simcyp-derived model successfully predicted pharmacokinetic metrics in validation against retrospective studies (healthy subjects and pregnant women). Although some metrics were within the twofold range in the validation studies (Steps 1 and 2), some metrics (e.g., t_{max}) were overpredicted by the model and this may warrant further studies to propagate robust model refinement in concert with deft sensitivity analysis to accurately predict these metrics.

The impact of pregnancy on sublingual buprenorphine doses investigated in this study contributes to the field of research in regarding pregnant women and the necessity for dose adjustments. However, the Simcyp-derived model utilized in this study, did not take in to account the detailed biotransformation pathways for buprenorphine contrary to reported literature evidence highlighting several routes as well as metabolite influence on the pharmacokinetics of buprenorphine [149, 150]. Additionally, the comprehensive p-PBPK model for buprenorphine has been reported by Kalluri et al. [174], albeit with subtle discrepancies in allelic polymorphic characterization of enzymes involved in buprenorphine biotransformation, may guide further research in optimizing the model within Simcyp. Therefore, a robust mass balance approach ought to be integrated in the model to account for these biotransformation pathways most likely through in vitro – in vivo extrapolation techniques (IVIVET), as well as ISEFs for the various enzymes responsible for buprenorphine metabolism.

The model predicted DDI study with Rifampicin (induction) and Clarithromycin (inhibition) on buprenorphine dosing in gestation assessed in this study yielded C_{max} ratios and AUC ratios that are consistent with reported values to account for DDI magnitude and fold inference [176]. The former (induction) DDI model predictions corroborate with published reports [227] and the later (inhibition) may be the first model informed DDI study with Clarithromycin in pregnant women. Rifampicin has recently been demonstrated to elicit pleiotropic attributes in a PBPK study [231], that is, it induces both hepatic CYP3A4 and p-glycoprotein (P-gp) in the colon simultaneously. Likewise, several authors have identified norbuprenorphine (NBP) [232, 233]; an active metabolite of buprenorphine as a substrate of P-gp to effect profound influence on maternal and foetal buprenorphine metrics clinically [234]. Likewise, the discrepancy in sensitivity to clarithromycin-induced inhibition between the intestine and liver is proposed to be a consequence of customary CYP3A4 enzyme degradation and expulsion of the inhibitor xenobiotic from the small intestine [235]. These provenances may contribute to the knowledge base to establish novel scientific arguments. However, this study lacked an integrative implementation of the advanced dissolution, absorption and metabolism (ADAM) model to account for the P-gp-mediated efflux occurring across compartments of the intestine. Future DDI research may implement these to account for a robust output of data in concert with mass balance studies within the Simcyp derived model. Furthermore, those who utilize opiates could have ancillary comorbid conditions that necessitate adjusting the buprenorphine doses, adherence may be inconsistent, or people may use additional xenobiotics (such as illegal opioids, tranquilizers, and neuroleptics) that could cause situations of an overdose where the buprenorphine dose is not changed appropriately to reduce risk occurrence. This constitutes a setback of the research, and thus it may need to be investigated further to consider clinical applications. Furthermore, the investigations by Lindelmam et al., [236] and Ilett et al., [237], propose qualitative arguments regarding the consequence of buprenorphine traversal in breastmilk, albeit with a conclusive predilection on mitigated risks of adverse effects to the neonate. The version of the Simcyp-derived model utilized in this study lacked a quantitative prediction of buprenorphine concentration in milk postpartum as foetal buprenorphine transfer. Though a future version may be developed to deftly integrate a bridge of models to accommodate the mater-

nal-foetal dyad comprehensively, this is a limitation of this study and may likely warrant future research.

The dearth of available information, backed with rigid ethical impediments to trial conduct in pregnant women, could adversely limit data generation for robust p-PBPK model development. Despite this, the propensity for DDI occurrence in tandem with dose adjustments in gestation, underscores the criticality for clinician indulgence in sublingual buprenorphine utility for maintenance treatment of opioid use disorder as well as in dosing regimen optimization.

5. Conclusions

This study has demonstrated in a pragmatic and translational conduit, through a first-time prediction, that the PBPK modelling technique is a robust and developing procedure that could be utilized to comprehend SL buprenorphine pharmacokinetics and address dose optimization challenges in pregnant women.

The Simcyp derived PBPK model was utilized to investigate the stipulated aim and objectives. Following the initial validation of the model against the retrospective clinical studies, the model performed optimally in the DDI predictions with a CYP inducer (Rifampicin) and a time-dependent mechanism-based inhibitor (Clarithromycin) as well as in the mechanistic prediction of the pharmacokinetics of sublingually administered buprenorphine in pregnant women across selected weeks of gestation. The dose optimization investigation of the model derived virtually pregnant subjects was proportionally predicted with likely concatenations to the myriad physiological processes occurring in gestation.

Abbreviations

ADAM	Advanced Dissolution, Absorption and Metabolism
AUC	Area Under the Curve
BMT	Buprenorphine Maintenance Therapy
BUP	Buprenorphine
BTDS	Buprenorphine Transdermal System
B3G	Buprenorphine-3-glucuronide
CAM	Complementary/Alternative Medicine
CBT	Cognitive Behavioral Therapy
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 Isoform 3A4
CYP2C8	Cytochrome P450 Isoform 2C8
C_{max}	Peak Concentration
C_{min}	Trough Concentration
CAR	Constitutive Androstane Receptor
CL	Total Clearance
CL_{int}	Intrinsic Clearance
CM	Contingency Management
DDI	Drug-Drug Interaction
EM	Extensive Metabolizer
ESM	Electronic Supplementary Material
F	Bioavailability
f_m	Fraction metabolised
GABA	Gamma Amino-Butyric Acid
GW	Gestational Weeks
HSA	Human Serum Albumin
HV	Healthy Volunteer
Ind_{max}	Induction magnitude
IVIVET	In vitro in Vitro Extrapolation Technique
ISEF	Intersystem Extrapolation Factor
K_i	Inhibition Constant
K_{inact}	Maximal Inactivation Rate Constant
KOR	Kappa Opioid Receptor
K_p	Tissue-partition Coefficient
MOTHER	Maternal Opioid Treatment Human Experimental Research Study
MMT	Methadone Maintenance Therapy
MOR	Mu Opioid Receptor
NAS	Neonatal Abstinence Syndrome
N3G	Norbuprenorphine-3-glucuronide
OUD	Opioid Use Disorder
OST	Opioid Substitution Therapy
p-PBPK	pregnancy Physiologically Based Pharmacokinetic Model.
PBPK	Physiologically Based Pharmacokinetic Modelling
PK	Pharmacokinetic
PXR	Pregnane X Receptor
QT interval	Time Interval Between Onset of Ventricular Depolarization and End of Ventricular Repolarization
SL	Sublingual
SIDS	Sudden Infant Death Syndrome
SPC	Summary of Product Characteristics
$t_{1/2}$	Half-life
t_{max}	Time to Maximum Concentration
T2	Second Trimester
T3	Third Trimester
TdP	Torsades de Pointes
UGT	Uridine 5'-diphospho-glucuronosyltransferase Enzymes
UGT1A1	Uridine 5'-diphospho-glucuronosyltransferase Enzyme Isoform 1A1
UGT1A3	Uridine 5'-diphospho-glucuronosyltransferase Enzyme Isoform 1A3
UGT2B7	Uridine 5'-diphospho-glucuronosyltransferase Enzyme Isoform 2B7
VPC	Visual Predictive Checking
V_{ss}	Volume of Distribution at Steady-State
V_d	Volume of Distribution

Supplementary Material

The supplementary material can be accessed at https://doi.org/10.11648/j.ijpc.20241004.11

Author Contributions

Tobechi Brendan Nnanna is the sole author. The author read and approved the final manuscript.

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The data is available from the corresponding author upon reasonable request

Conflicts of Interest

The author declares no conflicts of interest.

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Biography

Tobechi Brendan Nnanna is a pharmacist professional with over two years of expertise in pharmacokinetic (PK) and pharmacodynamic (PD) modelling, PBPK simulation, and statistical data analysis. Holding a Master of Science in Pharmacokinetics (Distinction) from Aston University, United Kingdom, and a Bachelor of Pharmacy from Madonna University, Nigeria, he demonstrates a strong academic foundation enhanced by the prestigious Ferguson Scholarship Award. Professionally, Tobechi is currently engaged as a Clinical Pharmacology Researcher(freelance), leveraging advanced PK modelling tools such as SimCYP, PK-Sim, Mobi, nlMixR for drug distribution studies and clinical outcome predictions as well as other novel published open-source state-of-the art software. His work emphasizes translational modelling, population PK, clinical pharmacology to improve therapeutic efficacy. Previously, he contributed to pharmaceutical projects as a Consultant Pharmacist, guiding clinical insights and mentoring junior professionals. With a passion for data-driven & lab-based research, Tobechi strives to optimize therapeutic strategies through innovative pharmacometrics approaches and collaborative multidisciplinary efforts.

Research Field

Tobechi Brendan Nnanna: Pharmacokinetics in Special Population, Drug-Drug Interaction Mechanism, Personalized Medicine & Pharmacogenomics, Toxicokinetics & Safety Evaluation Studies, Drug Metabolism & Enzyme Kinetics, Population Pharmacokinetics, Pharmacometrics, Preclinical Pharmacokinetic & Pharmacodynamic Correlation, Physiologically based Pharmacokinetic Modeling, Pharmacokinetic Modelling & Simulation