Development of Barbiturate Tolerance and Dependence: A Systems Modeling Approach

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A system dynamics model is constructed to study the development of tolerance and dependence to phenobarbital in continuous use. Phenobarbital is a sedative drug targeting the brain. As a side effect, phenobarbital enhances its own metabolism rate. Also in regular use, the brain adapts to the presence of the drug and its sensitivity decreases with time. The resulting decrease in drug effectiveness urges the user to increase the dose. A feedback loop results as the increased dose affects metabolism and neuroadaptation dynamics. Because adaptive changes persist even after drug intake stops, upon abrupt discontinuation to the drug, the patient experiences unwanted rebound effects. Using the model, we monitor the drug user as he/she develops tolerance. Furthermore, we model the concurrent intake of a drug that causes enzyme inhibition. We also experiment with different dosing frequencies and dosing amounts. With these scenario analyses, we reveal the system's leverage points. We finally search for dosing regimens that facilitate gradual withdrawal from the drug so that rebound effects are avoided. Results show that a long period of withdrawal should be exercised to accomplish this.

Keywords: System dynamics, phenobarbital, enzyme induction, withdrawal syndrome

1. INTRODUCTION

Barbiturates are hypnotic/sedative drugs. Their target of action is the central nervous system (CNS). Because of having high abuse potential, they are being replaced by the safer benzodiazepines. However, they are still being used as anti-convulsants, intravenous anaesthetics, and death inducing agents (Hardman and Limbird 2001). Barbiturates are classified with respect to their onset and duration of action. For example, thiopental is classified as an ultra-short acting barbiturate because it takes only seconds for thiopental to reach the CNS and in a few minutes, its effect diminishes. On the other hand, phenobarbital is considered a long acting barbiturate. Both its onset and duration of action is much longer than thiopental.

A lot of people still use barbiturates for sedation or to fall asleep. The problems they create in prolonged use are similar to that of euphoric drugs such as cocaine or marijuana. Interestingly, a statistical study on twelfth grade high school students in the U.S. revealed that the frequency of barbiturate use has increased slightly over the last few years (Figure 1).

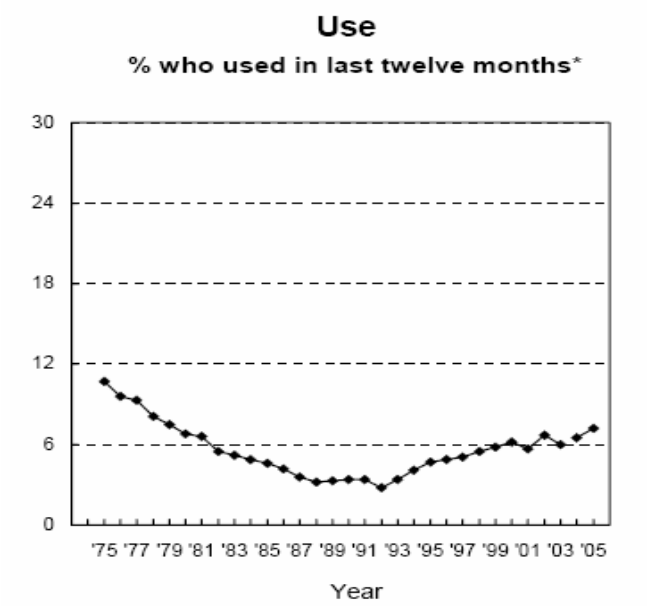


Figure 1. Frequency of barbiturate use among twelfth grade high school students in the U.S. (Monitoring the Future)

Although they have been used for several decades, mechanism of action of barbiturates is just recently being clarified. Before reviewing the mechanism, it would be useful to briefly overview the subject of neurotransmission.

1.1. Neurotransmission in the Central Nervous System

Neurotransmission means the communication of nerve cells (i.e. neurons). It is widely accepted that two opposing forces govern the activity of the CNS: Excitatory and inhibitory neurotransmission. Neurons communicate by means of neurotransmitters. Similar to hormones, these are synthesized inside neurons and are released outside. The neurotransmitter released by a neuron travels to the neighboring neuron and binds to a specific region on its membrane. After that, depending on the type of the neurotransmitter, it causes either excitation or inhibition. Excitation is also referred to as depolarization. An inhibitory input, on the other hand, causes hyperpolarization. These changes in electrical potential are accomplished by ions that flow through channels that are located on the neuronal membranes. Depolarization occurs with the help of positively charged sodium ions, whereas hyperpolarization occurs with the help of negatively charged chloride ions. States such as sedation, hypnosis, or sleep are consequences of inhibitory neurotransmission.

The main excitatory and inhibitory neurotransmitters in the CNS are glutamate and gamma amino butyric acid (GABA), respectively. The regions on neuronal membranes that bind neurotransmitters are called receptors. Each neurotransmitter binds to a specific type of receptor (Hardman and Limbird 2001). Of particular interest is the $GABA_A$ receptor which accepts the binding of the inhibitory neurotransmitter GABA. The receptor has a chloride channel on its center. Besides a binding site for GABA, it includes binding sites for numerous drugs. Binding of drugs modifies the function of the receptor and thus the chloride channel. A schematic of $GABA_A$ receptor is shown in Figure 2. The neuronal membrane is also shown on the figure.

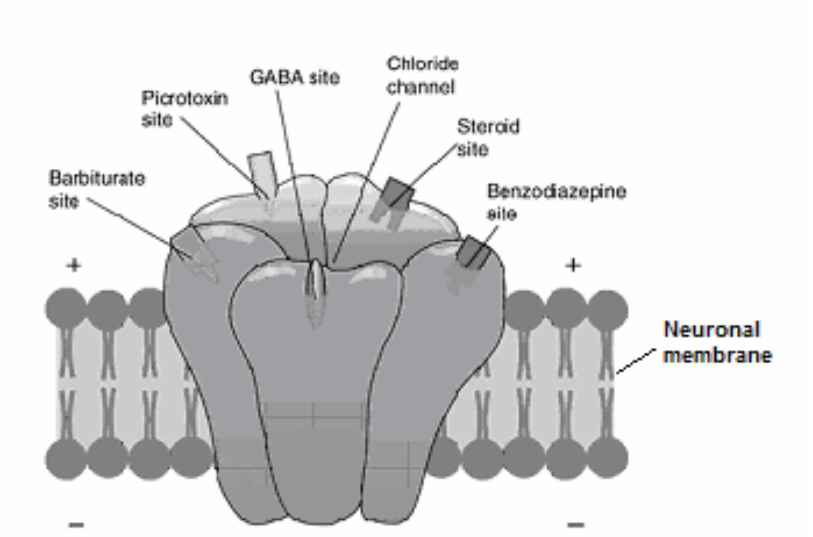


Figure 2. $GABA_A$ receptor-chloride channel complex. There are five binding sites on the complex (International Federation of Clinical Chemistry and Laboratory Medicine)

When GABA binds to its site, the channel opens and lets the inflow of chloride ions and results in hyperpolarization and thus excitation is inhibited.

1.2. Action Mechanism of Barbiturates

Most potent effect of barbiturates is promoting inhibitory neurotransmission mediated by GABA. They bind to the $GABA_A$ receptor and increase the chloride current through the channel. The increase in chloride flow results in sedation, and as the dose is increased, the sequence of events is sleep, and then anesthesia. Barbiturates were also shown to suppress excitatory transmission but this effect is seen in very high barbiturate concentrations, which are irrelevant to their sedative effects (Powis and Bunn 1995).

1.3. Development of Barbiturate Tolerance and Dependence

Barbiturates have been shown to cause the phenomenon of enzyme induction. In the liver, a system of enzymes is responsible for converting many substances into either active or inactive forms. In particular, the destructive enzymes in the liver are induced by barbiturates, especially PB. The inducing effect of PB causes more enzymes to be synthesized and thus a faster metabolism of PB and of other substrates of these enzymes (Magnusson 2007). In time, a tolerance to the barbiturate occurs and higher doses are required to exert the same effect.

It has been observed that enzyme induction is a saturable process. That is, the rate of metabolism increases at first, but as drug administration continues, rather than increasing indefinitely, it stagnates after a while. In case of barbiturates, at maximal induction, rate of metabolism doubles (Hardman and Limbird 2001). There are numerous inducing drugs each having its distinct induction mechanism and induction profile. For PB, the mechanism of induction is not fully understood (Handschin and

Meyer 2003). However, there are hypotheses. It is believed that inside liver cells, there exist several receptors that respond to different types of chemicals. These receptors are called nuclear receptors. It is believed that upon exposure to the chemical to which it is sensitive, these nuclear receptors travel to the nucleus of the liver cell and bind to specific regions on the DNA molecule and enhance enzyme synthesis. PB is believed to induce enzymes by this mechanism. The consequence of enzyme induction is a moderate tolerance of the individual to the drug.

As opposed to tolerance, which peaks in a few days to a week, dependence to barbiturates develops over a period of weeks to months. Contribution of enzyme induction to dependence is minor (Hardman and Limbird 2001). The major cause of dependence is brain's adaptation to the drug. This adaptation is called neuroadaptation.

In a research, although PB enhances inhibitory neurotransmission by increasing the rate of GABA binding, it was shown that after rats were treated with PB for a long time, they showed decreased GABA binding. It is believed that this is due to an adaptive response by the rats, which results in desensitized or down-regulated $GABA_A$ receptors (Ito et al. 1996). This down-regulation decreases chloride flow through the channel.

In another research where rats were chronically treated with PB, it was shown that upon abrupt cessation of PB treatment, rats experience rebound effects such as ear twitches, tremor, and tail erection. However, these withdrawal syndromes weakened as time elapsed (Gay et al. 1983).

In humans, such unwanted rebound effects are also observed upon abrupt discontinuation of PB (Liska 2001). It is generally suggested that PB dosage must be reduced gradually to avoid these unwanted effects.

The Himmelsbach hypothesis provides a good illustration by relating tolerance, dependence and withdrawal. In Figure 3, the Himmelsbach hypothesis is schematized for ethanol. Similar to barbiturates, ethanol also promotes inhibitory neurotransmission.

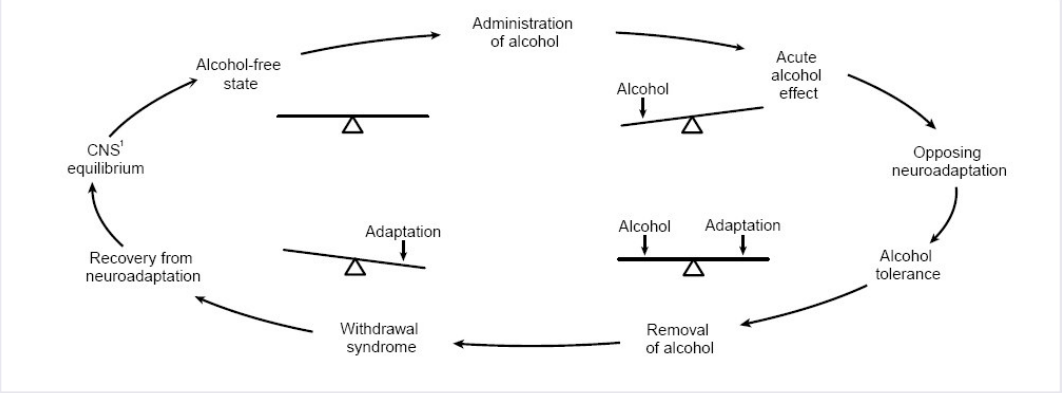


Figure 1 Pictorial representation of the Himmelsbach hypothesis as it applies to alcohol use. The balanced seesaw on the upper left side of the cycle represents brain neurochemistry in an alcohol-free state (i.e., before the brain has been exposed to alcohol). Consuming alcohol initially unbalances brain chemistry to produce the acute effects associated with alcohol use (e.g., sedation and incoordination). The brain then responds to this disruption by inducing an opposing chemical adaptation that tends to restore the neurochemical balance. At this stage, the effects of a given dose of alcohol are diminished (i.e., tolerance exists). If alcohol is removed, the adaptation is exposed, unbalancing the brain's neurochemistry in the opposite direction. The result is a withdrawal syndrome that includes signs and symptoms (e.g., agitation and seizures) that are opposite to alcohol's initial effects. These disturbances will continue until the adaptation can be removed from the brain (or until alcohol is consumed again), restoring equilibrium.

[1]CNS = central nevous system.

Figure 3. The Himmelsbach hypothesis (Littleton 1998)

1.4. Definition of Pharmacokinetics

There are several phases before an administered drug causes a response. After administration, the drug goes through many phases during which it may lose effectiveness. After oral administration, the drug must dissolve in stomach fluids, and it must be absorbed from the gastrointestinal tract. Once absorbed, it is directly transported to the liver via the hepatic portal vein. The metabolism in liver at this stage is referred to as first-pass metabolism. In drug development, it is aimed to design drugs that have little first-pass metabolism since it has a negative impact on drug efficacy. Furthermore, a drug may also undergo elimination in different regions such as the gastrointestinal wall, which too is an undesired property. After first-pass metabolism, the remaining drug enters blood circulation and reaches the target organ. There, it binds its receptor to exert its effect. While in blood circulation, the drug is transported to the liver once more and it undergoes further elimination. In addition, while in circulation, it may bind to blood plasma proteins or tissues of different organs. Once bound, a drug molecule is ineffective. This process of drug delivery in the body is referred to as pharmacokinetics.

2. SYSTEMIC PERSPECTIVE

2.1. Causal-Loop Diagram

Prolonged use of PB causes enzyme induction in a few days so that the rate of metabolism approximately doubles. As the drug is continued, the body tries to counteract the increase in inhibitory neurotransmission by down-regulating the $GABA_A$ receptors. Unlike enzyme induction, receptor down-regulation progresses over several weeks. Down-regulated receptors reduce the efficiency of inhibitory transmission and together with enzyme induction, it decreases the effectiveness of the drug. The decreased effectiveness urges the drug user to increase the doses. This is called tolerance. Tolerance always precedes dependence. Due to the increased dose, the down-regulation process speeds up. The major contribution to dependence development is by this down-regulation process. Upon abrupt withdrawal, the drug is cleared much rapidly but the reduced efficiency in inhibitory neurotransmission persists. This is manifested as a chloride current lower than normal. This disrupts the normal activity of the CNS since excitatory neurotransmission is not balanced by inhibitory neurotransmission. The result is a withdrawal syndrome. A withdrawal syndrome suggests that the drug user has become dependent to the drug. The causal loop structure is given in Figure 4.

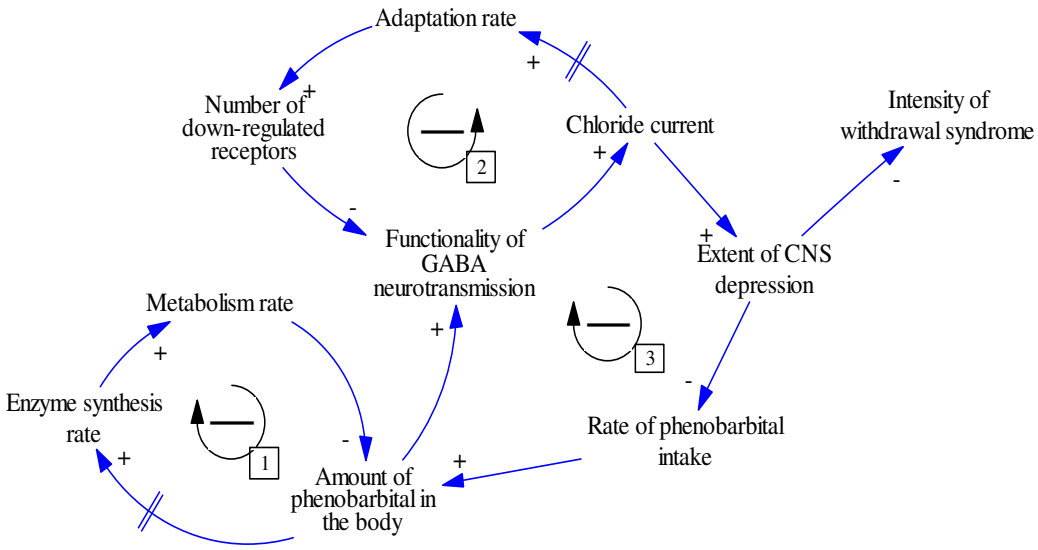


Figure 4.Causal loop diagram for tolerance and dependence development

There are three key feedback loops in the system. The first one, loop no. 1, is the negative feedback loop related to the development of pharmacokinetic tolerance as a result of enzyme induction. Sustained levels of PB in the body lead to a higher rate of enzyme synthesis. This leads to a faster PB metabolism and thus the amount of drug in the body decreases.

The second negative feedback loop, no. 2, is related to neuroadaptive changes in the brain. The primary effect of PB is to potentiate inhibitory transmission, which leads to depression of the CNS. If treatment is continued, continuous potentiation of inhibitory transmission is counteracted by desensitization (i.e. down-regulation) of $GABA_A$ receptors. This weakens the inhibitory neurotransmission system.

There is a third negative feedback loop, no. 3, which is a consequence of the two aforementioned loops. The decrease in inhibitory neurotransmission because of increased metabolism and desensitized receptors leads to less CNS depression. This urges the drug user to increase the administered dose, which leads to stronger inhibitory neurotransmission. This loop is operational only at later phases when the functionality of inhibitory neurotransmission is weakened.

2.2. Research Methodology and Objectives

We have defined a medical problem that involves several interdependent variables and feedback relationships. Indeed, we have defined a rather complex system: A human body exposed to an exogenous chemical. To capture the long-term dynamics, one has to study the system as a whole rather than focusing one at a time on individual elements of the system. By creating a mathematical model of the system and defining accurately the relationships, we can unfold the behavior of the system in the long term. System Dynamics (SD) methodology is most suitable for this task.

The aim of this research is build a SD model that imitates a regular PB user and to take into account the two related aspects: Enzyme induction and neuroadaptation.

Tolerance development will be followed by monitoring the dose increase decisions of the user. To provide insight on dependence development, the situation after withdrawal will also be studied and it will be investigated whether a feasible dosing scheme during withdrawal exists so that unwanted rebound effects are avoided.

3. THE MODEL

3.1. Model Perspective

The model assumes a hypothetical person that carries inducible genes so that he can experience enzyme induction. The person is assumed to take PB tablets every day for sedation. Pharmacokinetic data for the hypothetical person is taken from the paper by El-Masri and Portier (1998). The data is for an actual human being who had participated in their work.

3.2. Time Settings and Calculation Method

As simulation software, we used Vensim DSS Version 5.7a by Ventana Systems, Inc. Time unit used in the simulations is minutes because pharmacokinetic parameters related to rates are given in minutes. To study the development of dependence and the situation afterwards, we run the simulations for several months depending on PB treatment duration. We use Euler integration method with fixed time steps of 0.125 minutes.

3.3. Reference Modes

In their study, Gay et al. (1983) give PB to rats in a daily basis to obtain a fixed level of CNS depression. They give two doses daily: A morning dose, and an evening dose. In Figure 5, their dosing amounts are plotted as a function of days of treatment.

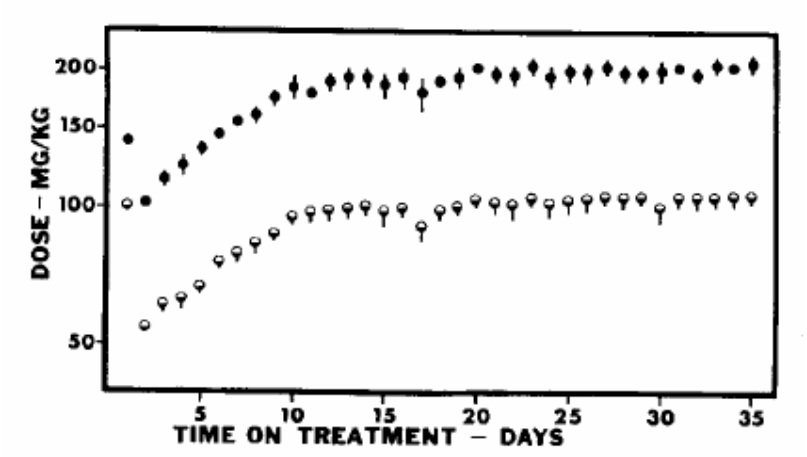


Figure 5. Administered doses of PB. Half-filled circles are morning doses, filled circles are total daily doses (sum of morning and evening doses). All doses result in the same level of CNS depression (Gay et al. 1983)

As can be seen, the dose required to cause the same level of sedation increase drastically in the first 10 days. This means that the rats became tolerant to the drug.

In the model, we focus on the chloride currents in the brain as an indicator of inhibitory neurotransmission. Inhibitory neurotransmission has direct relevance to behavioral outcomes such as sedation, and also to rebound hyperexcitability that is seen after abrupt withdrawal. In Figure 6, we see the extent of rebound effects experienced by rats after abrupt withdrawal from a 35 day PB treatment.

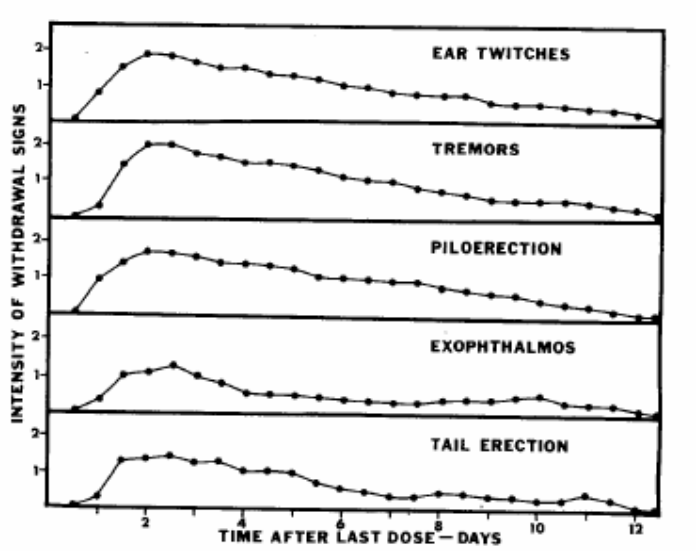


Figure 6. Change in the intensity of rebound behavior with time. Rats were observed twice daily for withdrawal signs following abrupt termination of 35 days of PB treatment (Gay et al. 1983)

The researchers also show that withdrawal signs are not as intense when drug treatment ends on the 10^{th} day, implying that dependence develops slower than tolerance.

3.4. Model Boundary

The model consists of three sectors: Pharmacokinetics sector, dose sector and central nervous system (CNS) sector. In the pharmacokinetics sector, absorption, distribution, metabolism, and excretion processes are modeled. We include only the organs and tissues that are large in volume and that receive high blood supply so that the amount of drug they accumulate is significant. These are brain, gastrointestinal tissue, kidney, liver, muscle tissue, and fat tissue. We also include enzyme induction dynamics in modeling the metabolism.

The dose sector represents the dose increase decisions of the PB user. We assume that when the level of sedation drops below a threshold because of tolerance, the user increases the dose so as to keep the level above the threshold.

In building the CNS sector, we assume that excitatory neurotransmission is not affected from PB. This assumption is justified since the effect on excitatory neurotransmission is realized only at very high concentrations, as mentioned previously.

3.5. Stock-Flow Structure

The complete stock-flow diagram of the model is shown in Figure 7. This stock-flow structure will be explained under three headings: Pharmacokinetics sector, dose sector, and CNS sector.

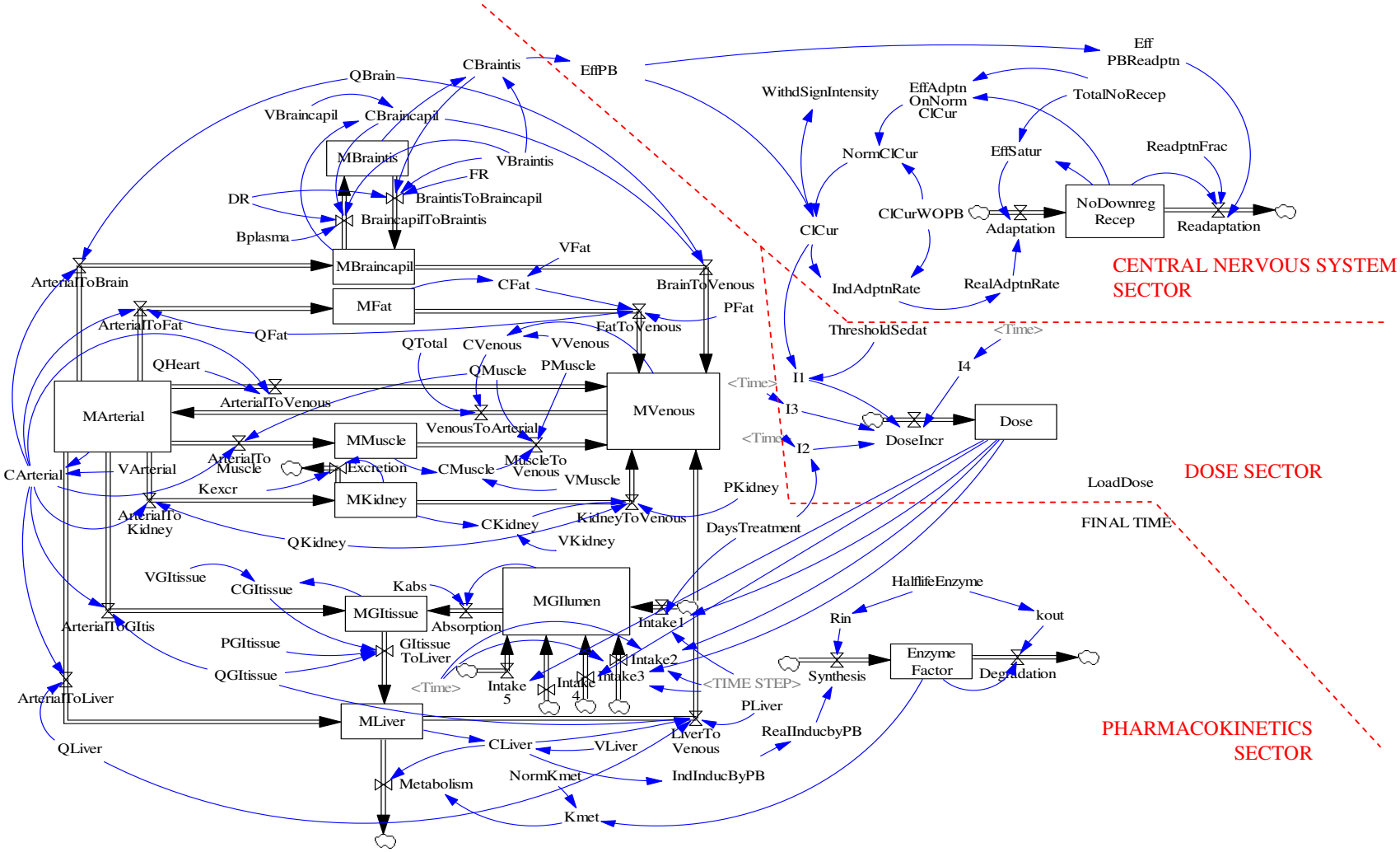


Figure 7. Stock-flow diagram of the model

3.5.1. Pharmacokinetic Sector

The stocks represent the amounts of drug in different organs. The flows represent the amounts flowing in blood. In modeling absorption and distribution, the assumptions used by El-Masri and Portier (1998) were utilized. Absorption is assumed to follow a first-order rate equation. Its equation is given below.

$$Absorption = Kabs * MGIlumen \quad (1)$$

where *Kabs* (min^{-1}) is the absorption constant, and *MGIlumen* (mg) is the amount of drug present in the gastrointestinal lumen.

To calculate concentrations, we divide the amounts to volumes. For example, the concentration of PB in brain tissue is given by Equation 2 below.

$$CBraintis = MBraintis / VBraintis \quad (2)$$

where *Mbraintis* (mg) is the amount of drug in brain tissue, and *VBraintis* (L) is the volume of brain tissue.

The amounts flowing via arterial blood into all organs are assumed to be flow-limited. To exemplify, the rate of PB transfer from arterial blood to brain is given in Equation 3 below.

$$ArterialtToBrain = CArterial * QBrain \quad (3)$$

where *CArterial* (mg/L) is the concentration of the drug in arterial blood and *QBrain* (L/min) is the rate of blood flow through the brain.

The outflows of all organs except liver and brain are formulated considering that only unbound drug can flow out of the organ into venous blood. For example, the rate of PB flow from kidney to venous blood is given by Equation 4.

$$KidneyToVenous = CKidney * QKidney / PKidney \quad (4)$$

where *QKidney* is the rate of blood flow through the kidney; *CKidney* is the concentration and *PKidney* is the tissue-blood partition coefficient in the kidney.

The liver is perfused by both the arterial blood and also by the blood coming from GI tissue via the hepatic portal vein. Therefore, its outflow towards venous blood is

$$LiverToVenous = CLiver * (QLiver + QGItissue) / PLiver \quad (5)$$

where *CLiver* (mg/L) is the concentration of drug in the liver, *QLiver* (L/min) is the blood flow rate through the liver, *PLiver* is the tissue-blood partition coefficient in the liver, and *Qgi* (L/min) is the blood flow rate through the GI tissue.

The brain is divided into two parts: Blood (in capillaries) and tissue. Blood in the brain is denoted by the stock “Brain capillary”. The amount of drug flowing from the brain into the venous blood is simply *QBrain*CBraincapil* where *QBraincapil* (L/min) is the blood flow rate through the brain and *CBraincapil* (mg/L) is the concentration of

the drug in brain capillaries. The diffusion of the drug into the brain tissue is modeled by assuming simple diffusion kinetics leading to the following equations.

$$BraincapilToBraintis = VBraintis * DR * Cbraincapil / (1+Bplasma) \quad (6)$$

$$BraintisToBraincapil = VBraintis * DR * CBraintis * FR \quad (7)$$

BraincapilToBraintis (mg/min) is the amount of drug diffusing from brain capillaries into brain tissue, *BraintisToBraincapil* (mg/min) is the amount of drug diffusing out of brain tissue to the capillaries, *VBraintis* is the volume of brain tissue (ml), *DR* is the diffusion rate constant (min^{-1}), *CBraincapil* (mg/L) is the concentration of drug in brain capillary, *CBraintis* is the concentration of the drug in brain tissue, *Bplasma* is the bound fraction of drug in red blood cells, and *FR* is the ratio of free to tissue concentrations of the drug. The values for blood flow rates, organ volumes used in calculating concentrations, partition coefficients, bound fractions and rate parameters are taken from the paper by El-Masri and Portier (1998) and are given together with all the equations of the model in the appendix.

Urinary excretion was assumed to be a first-order rate process. It is given in Equation 8.

$$Excretion = Kexcr * MKidney \quad (8)$$

In modeling metabolism rate (mg/min), we use the following equation.

$$Metabolism = CLiver * Kmet \quad (9)$$

As a matter of fact, *Kmet* is a function of *CLiver*. This functional relationship underlies the process of enzyme induction. To clarify, we start with the equation for *Kmet* given below.

$$Kmet = NormKmet * EnzymeFactor \quad (10)$$

NormKmet (L/min) is a constant and *EnzymeFactor* is modeled as a stock variable (See Figure 7). Initially, it equals 1, and its inflow and outflow are equal to each other. Its differential equation is given below.

$$d(EnzymeFactor) / dt = Synthesis - Degradation \quad (11)$$

As drug concentration in the liver increases, the inflow S*ynthesis* also increases. The following equation holds for *Synthesis.*

$$Synthesis = Rin *(1+RealInducByPB) \quad (12)$$

Rin is the synthesis rate of the enzyme when no drug is present. *RealInducByPB* is a smoothed version of *IndInducByPb,* the latter being a saturable function defined by Equation 13. We assume a smoothing time of 2 days. The reason for the delay is that enzyme induction is a process of protein synthesis involving several genetic processes such as transcription of genes, mRNA synthesis, etc. which take time.

$$IndInducByPb = \frac{E_{\max} * CLiver}{EC_{50} + CLiver} \quad (13)$$

E_{max} is the maximal induction effect and EC_{50} (mg/L) is the concentration of the drug that causes half the maximal effect.

The outflow *Degradation* is given by the following equation.

$$Degradation = kout * EnzymeFactor \quad (14)$$

where $kout = \frac{\ln(2)}{HalflifeEnzyme}$ which has units of min^{-1}.

To establish a baseline situation, initially (i.e. when no drug is present) we set *EnzymeFactor = 1*, and we also set *Rin = kout*. We assume an enzyme half-life of 2 days regarding the information in the literature that half-lives of CYP enzymes range between 1 to 6 days (Michalets 1998).

Other mathematical aspects of the model will be explained where relevant. For numerical values of model parameters, refer to Appendix.

3.5.2. CNS Sector

In formulating the effect of PB on chloride currents, we used the concentration-response data from literature (Ffrench-Mullen et al. 1993) which gives the per cent increase in GABA currents as a function of PB concentration in the brain. We use this function to model *EffPB* as in Equation 15.

$$EffPB = P_{max} * Cbraintis / (GABAEC50 + Cbraintis) \quad (15)$$

where P_{max} is the maximum chloride current increase percentage and $GABAEC_{50}$ is the concentration of PB that causes half the maximal response. The numerical values of these parameters are 600 per cent and 2.79 mg/L, respectively.

Eff of PB is used in the following equation.

$$ClCur = NormClCur*(1+EffPB/100) \quad (16)$$

It was not possible to find numerical data on chloride currents in the human brain. Thus, we modeled chloride current relative to its normal value which is assumed to equal 1 when no drug is present in the body.

$$ClCur = NormClCur = ClCurWOPB = 1 \quad (17)$$

We define the number of down-regulated $GABA_A$ receptors as a stock variable called *NoDownregRecep* having units of billions. It is an indicator of the extent of brain's adaptation to the drug. Its differential equation is given below.

$$d(NoDownregRecep) / dt = Adaptation - Readaptation \quad (18)$$

where

$$Adaptation = RealAdptnRate * EffSatur \quad (19)$$

Adaptation involves several steps at the cellular level which delay the desensitization of $GABA_A$ receptors. Therefore, we model *RealAdptnRate* as a third order smoothing of *IndAdptnRate*. The rate of adaptation is assumed to be proportional to the discrepancy between a base chloride current (without PB) and the actual chloride current. *IndAdptnRate* is therefore defined as a function of *ClCur / ClCurWOPB* and is given in Figure 8.

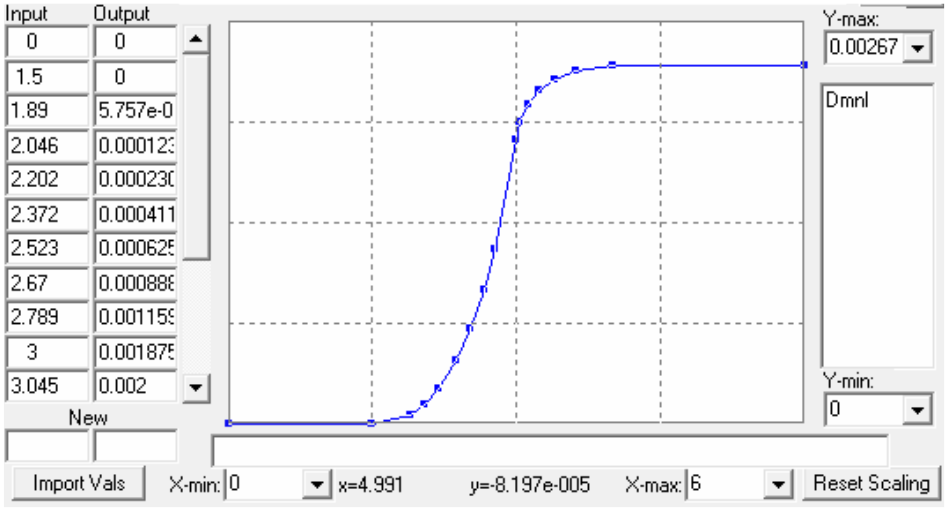


Figure 8. Graphical function for *IndAdptnRate*. Abscissa is *ClCur / ClCurWOPB*

EffSatur, as the name implies, slows down neuroadaptation as the number of desensitized receptors approach the total number of receptors. It is therefore defined as a function of *NoDownregRecep / TotalNoRecep* and is given in Figure 9.

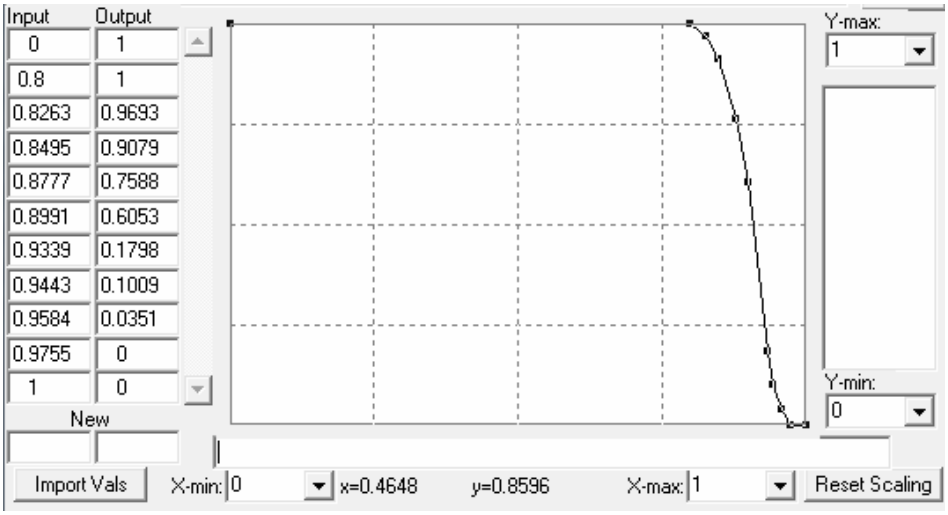


Figure 9. Graphical function for *EffSatur.* Abscissa is *NoDownregRecep / TotalNoRecep*

As can be seen, the saturation effect is operational after 80 per cent of the receptor population is down-regulated.

Since adaptation modifies brain physiology, normal chloride current is affected.

$$NormClCur = ClCurWOPB * EffAdptnOnNormClCur \quad (20)$$

where

$$EffAdptnOnNormClCur = F(NoDownregRecep/TotalNoRecep) \quad (21)$$

and *F* is assumed to be a decreasing function given in Figure 10.

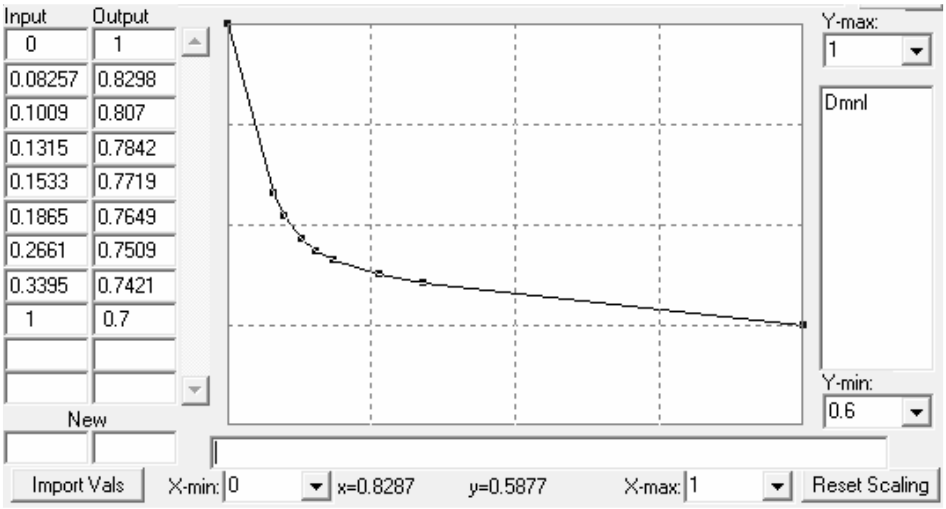


Figure 10. Graphical function for *EffAdptnOnNormClCur.* Abscissa is *NoDownregRecep / TotalNoRecep*

As can be seen, when all receptors are down-regulated, physiology becomes such that chloride current is 30 per cent less than that in a healthy person.

In modeling the re-adaptation process, we use the following equation.

$$Readaptation = EffPBReadptn * ReadptnFrac * NoDownregRecep \quad (22)$$

We assume that there is a critical concentration of the drug above which no re-adaptation can occur. This is captured by *EffPBReadptn* which is given in Figure 11.

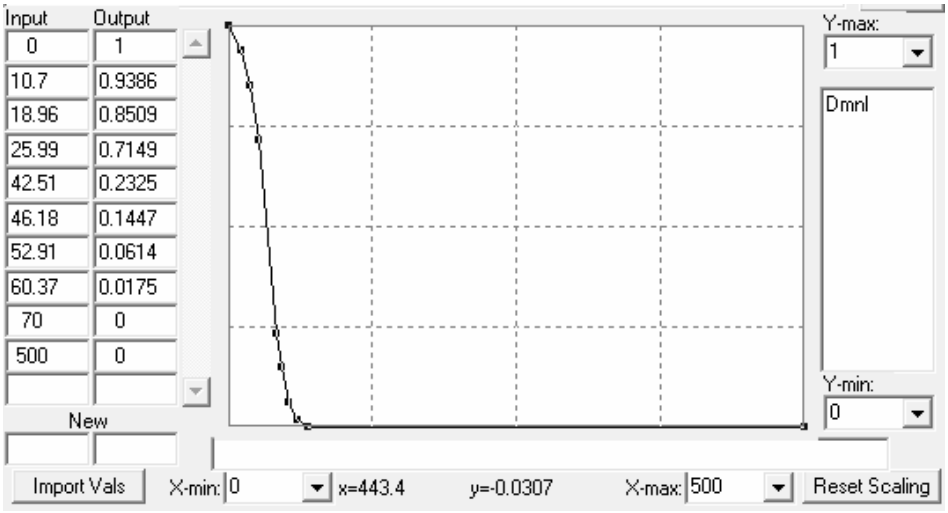


Figure 11. Graphical function for *EffPBReadptn.* Abscissa is *EffPB*

Figure 11 implies that when PB concentration in the brain is such that when the concentration-response function (i.e. *EffPB*) indicates less than a 70 per cent potentiation of the chloride current, re-adaptation can commence.

Finally, to see the intensity of withdrawal signs, we define a variable called *WithdSignIntensity* which is merely a shifted and inverted version of *ClCur* and is given below.

$$WithdSignIntensity = - (ClCur - 1) \tag{23}$$

The variable is only meaningful after drug treatment stops. We assume that when *ClCur* drops below its base value of 1, *WithdSignIntensity* becomes greater than 0 implying that inhibitory neurotransmission is compromised. Given that *WithdSignIntensity* is greater than 0, the larger it is, the less the inhibitory neurotransmission and the more likely the outburst of a withdrawal syndrome. To interpret this variable, we will first establish reference values that imply insignificant and significant withdrawal signs. This will be clarified in Section 4.

3.5.3. Dose Sector

The single differential equation in this sector is given below.

$$d(Dose)/dt = DoseIncr \tag{24}$$

where

$$DoseIncr=11*12*13*14*IncrRate \tag{25}$$

IncrRate is equal to 10 mg/min. The variables *I1*, *I2*, *I3* and *I4* are binary indicator variables. We want the dose dynamics to be operational only after the initial dose is effective. The variable *I3* serves this purpose and is given below.

$$I3 = IF\ THEN\ ELSE(Time>1440, 1, 0) \tag{26}$$

That is, if *Time* is later than 1440 minutes, *I3 = 1*, and *I3 = 0* otherwise.

The purpose of the variable *I2* is to stop dose increase decisions after the end of PB treatment. It is given in Equation 4.27.

$$I2 = IF\ THEN\ ELSE\ (Time<DaysTreatment,\ 1,\ 0) \quad (27)$$

During drug treatment, *I1* helps start the inflow when chloride current is below the sedation threshold and stop it when the threshold is exceeded.

$$I1 = IF\ THEN\ ELSE\ (ClCur<ThresholdSedat,\ 1,\ 0) \quad (28)$$

where *Sedation threshold* is 2.5 as explained and *dose incr rate* is calibrated to give 1/3 mg/min.

To model constant dose increments, we use *I4.* For example, in one-a-day dosing and for a constant increment of 30 mg, *I4* is as in Equation 4.29.

$$I4 = IF\ THEN\ ELSE\ (MODULO(Time,1440)>=1437,\ 1,\ 0) \quad (29)$$

Since the inflow *DoseIncr*, when it is open, equals 10 mg/min, after 3 minutes of inflow, 30 mg accumulate in the stock *Dose*. Additionally, since the inflow opens before a day is over, the dose increase decision can be implemented at the beginning of the next day.

4. MODEL ANALYSIS

In this section, we assume that the user employs one-a-day dosing. He/she is assumed to continue with 30 mg tablets after a loading dose of 180 mg (i.e. first dose). We use the initial conditions given in Table 1 for the stocks.

Table 1. Initial values for the stocks

STOCK	INITIAL VALUE
All (except M*GIlumen* and *Dose*)	0
MGIlumen	180
Dose	30
EnzymeFactor	1
NoDownregRecep	0

4.1. Single Dose

To observe the initial pharmacokinetic processes such as absorption from the gastrointestinal lumen, distribution to organs and tissues, and elimination, we give the results for the first 300 minutes (5 hours) after the loading dose of 180 mg. We display only the most informative stocks for this run.

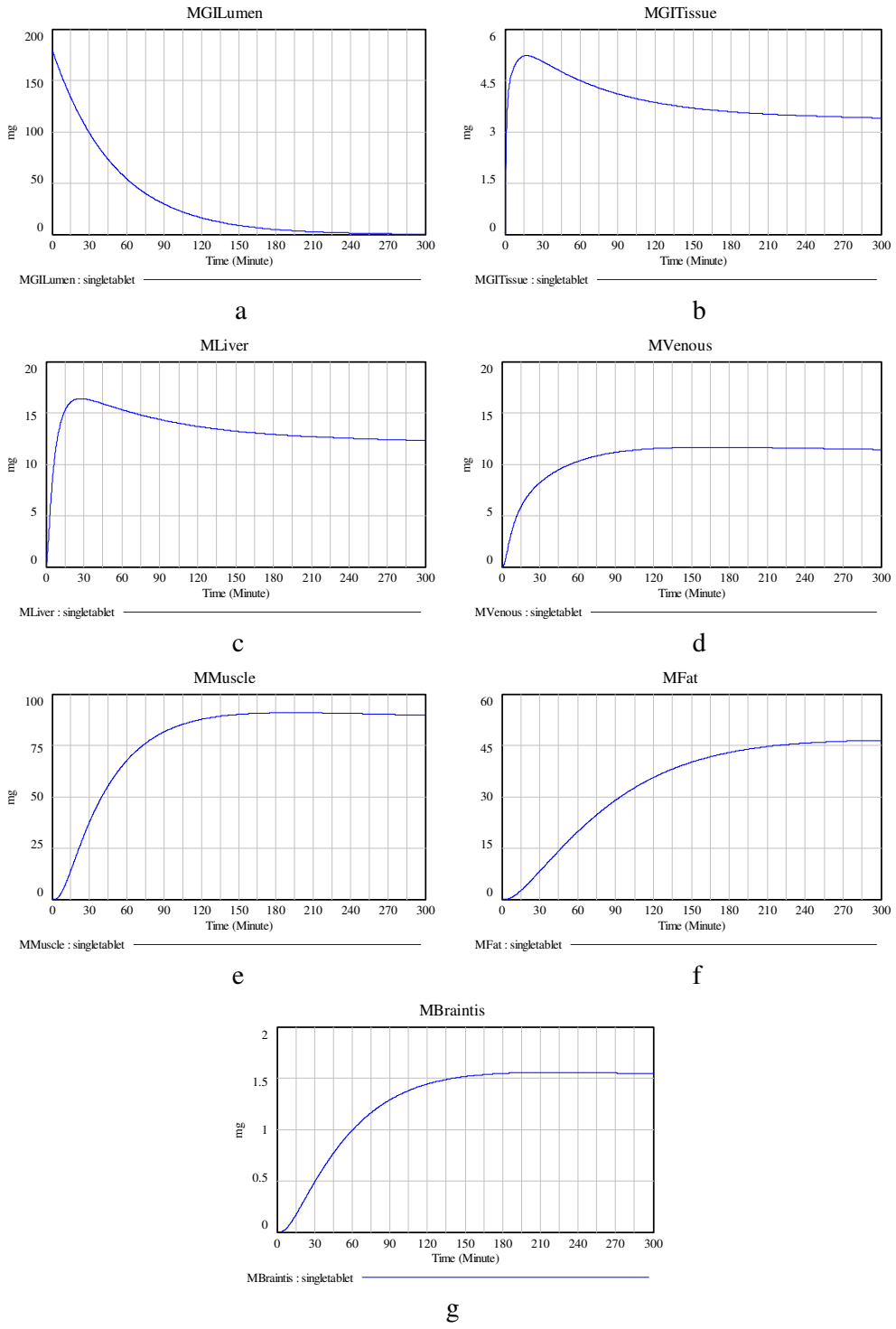


Figure 12. Absorption and distribution of a single 60 mg tablet

After diffusing from the gastrointestinal lumen into the gastrointestinal tissue, the drug does not stay here and it is immediately distributed to various organs, its first

destination being the liver. The sharp increase in liver PB content during the first 15 minutes confirms this (Figure 12c). From Figure 12e, we note that about half the amount administered is distributed to muscle tissue. This is expected since muscle tissue constitutes 40 per cent of total body volume and receives approximately 35 per cent of total blood supply. The amount of PB accumulated in fat is also large (Figure 12f). Similar to muscle tissue, fat constitutes a large percentage of total body volume. As can be seen from Figure 12g, the amount of drug in the target site (i.e. brain tissue) reaches a plateau in 3 hours. Although, it is only a small fraction of the amount administered, its effect is not insignificant. This can be seen in the following figure.

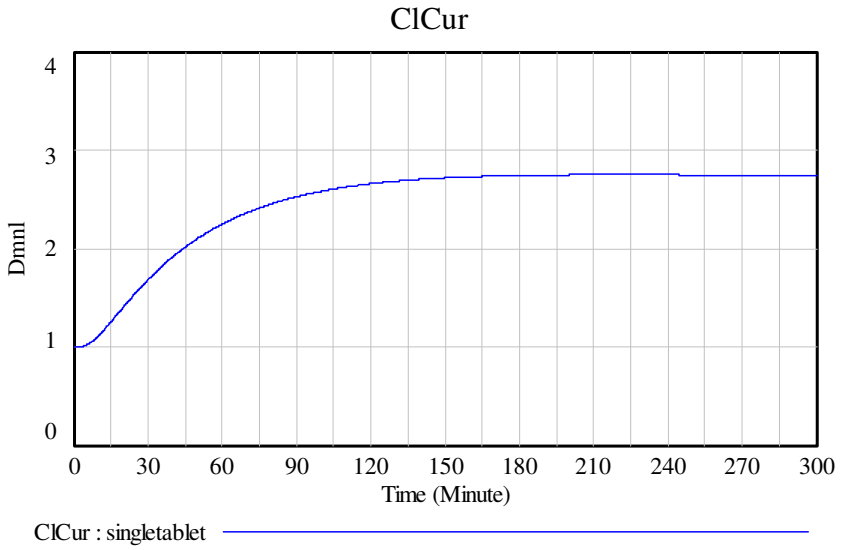


Figure 13. Increasing chloride current in the brain after a single 30 mg tablet

It can be seen that chloride current (i.e. inhibitory neurotransmission) has more than doubled. As expected, no enzyme induction or neuroadaptation took place in such a short time. Enzyme amount stays at the undrugged level (Figure 14a). The number of down-regulated receptors is an insignificant fraction of the total receptor population of 60 billion (Figure 14b).

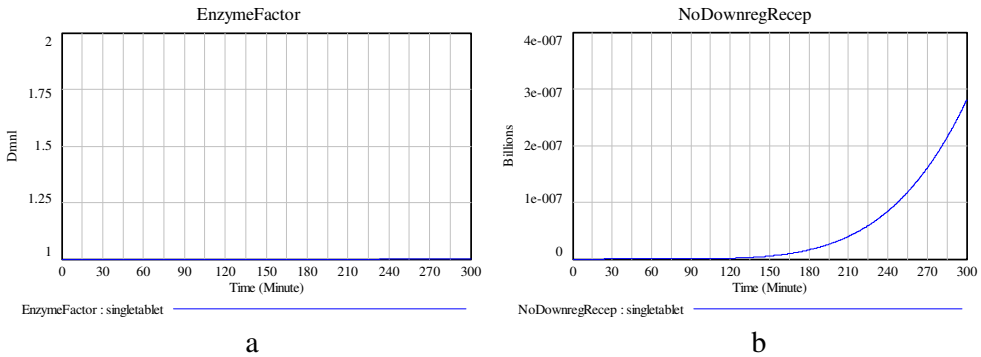
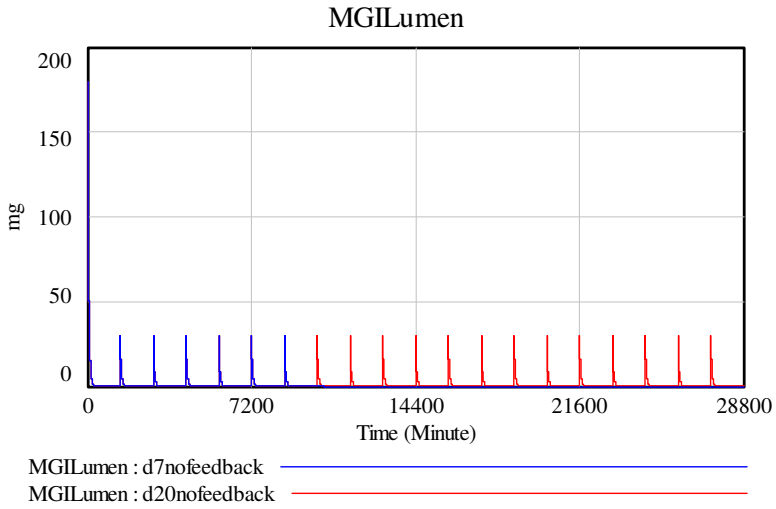


Figure 14. Dynamics of enzyme induction and neuroadaptation for a single 30 mg tablet

4.2. Continuous Drug Intake without Dose Increase

In this section, we give the results of simulation experiments in which we assume a regular user of PB. We use the term “treatment” in place of “use” or “intake”. Recall that our dynamic hypothesis defends that the user would be urged to increase the doses as tolerance develops to the effects of the drug. In this section, however, we assume that the user is not urged and takes constant doses after the loading dose. We therefore show the failure of constant doses to maintain a constant level of sedation. We comparatively study two scenarios to show different extents of tolerance and dependence development: A seven day treatment and a 20 day treatment. The results are as follows.



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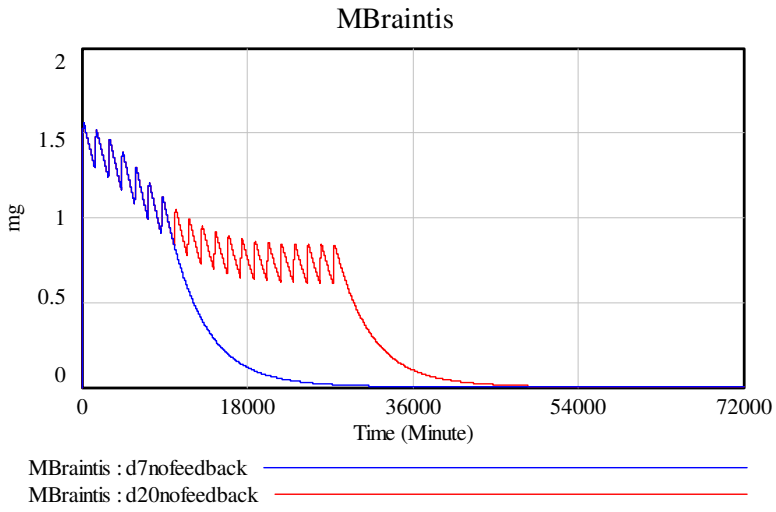


b

Figure 15. Drug profiles in different organs. The user takes constant doses.

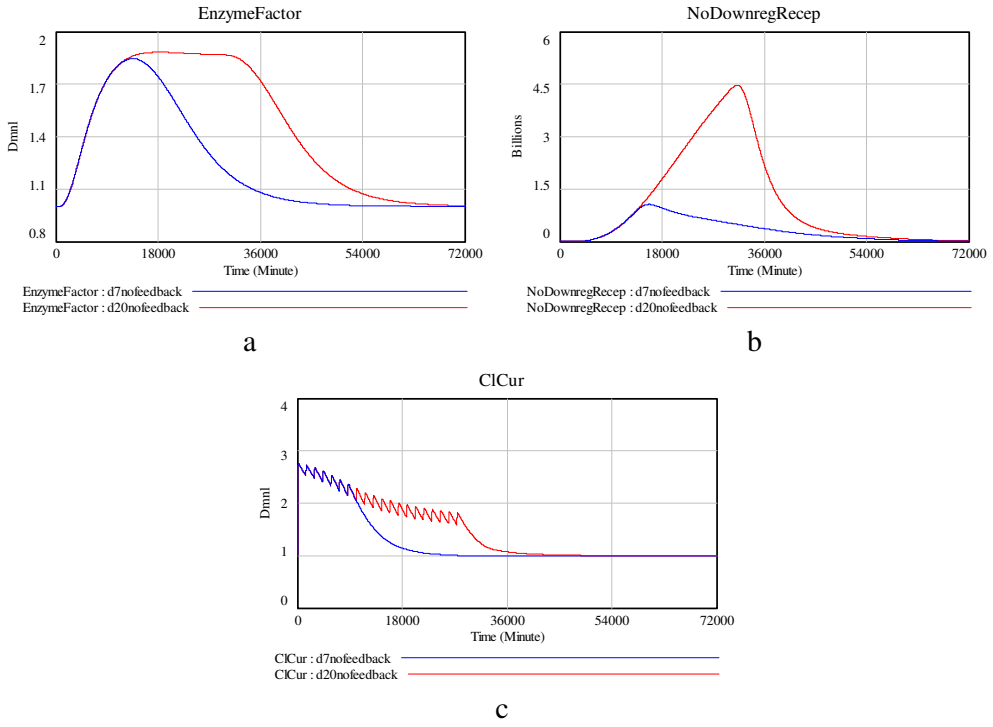


Figure 16. Enzyme induction and neuroadaptation and the resulting chloride current profile when the user takes constant doses.

The constant 30 mg doses can be seen in Figure 15a. Although the extent of enzyme induction is the same in seven days and 20 days (Figure 16a), neuroadaptation progresses much slower (Figure 16b). As a result of enhanced metabolism, the amount of PB in the brain decreases constantly (Figure 15b). Although in the 20 day treatment the amount in the brain approaches a steady state, chloride current continues to fall as can be seen in Figure 16c. These results demonstrate that to maintain sedation, the doses must be increased. Starting from the following section, we incorporate this feedback loop into our analyses.

4.3. Continuous Drug Intake with Dose Increase

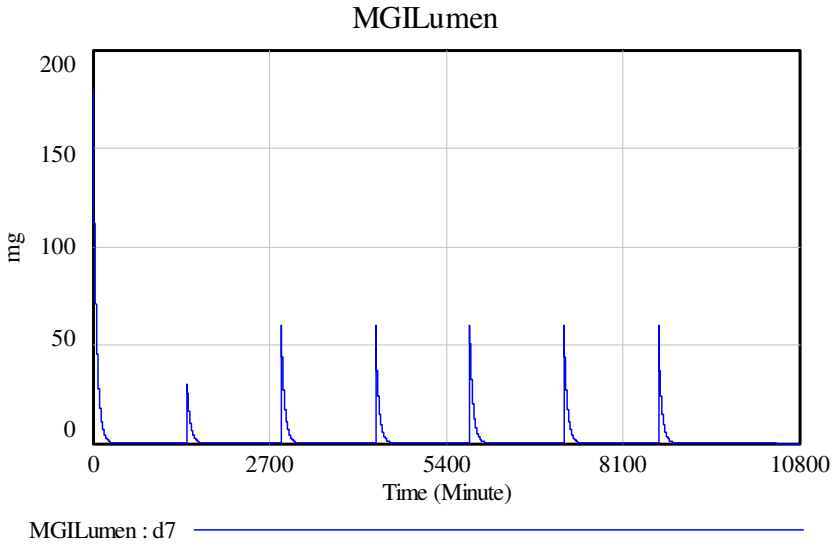
We consider the following drug treatment durations all of which end with abrupt withdrawal: 7 days, 20 days, and 60 days. In all drug treatments, the user is assumed to start with 30 mg tablets after the loading dose of 180 mg. As time elapses, the user would increase the dose in constant increments to compensate the reduced effectiveness. To model the daily drug administration process, we use a pulse function. The inflow named *Intake1* of the stock M*GIlumen* is given in Equation 30.

*Intake1 = (Dose/TIME STEP)*PULSE TRAIN(1440, TIME STEP, 1440, DaysTreatment*1440+TIME STEP)* (30)

Dose is a stock variable previously explained in detail in Section 3.5.3, and *DaysTreatment* is simply the number of days of PB administration. The first term in parentheses is the pulse amplitude. The function *PULSE TRAIN* is a built-in function in Vensim whose arguments are start time of pulse, pulse duration, pulse repeat time, and final time of pulse, respectively.

4.3.1. Drug Treatment for Seven Days

To see the situation after withdrawal as well, we set the final time to 27 days (38,880 minutes), and *DaysTreatment* to 6. Recall that at time zero, the stock M*GIlumen* contains the loading dose. The tablets are administered starting from the second day (i.e. Time=1440) and for four days. The sum is seven days of drug treatment. We obtain the following dynamics for the key variables. We first present drug profiles in key organs.



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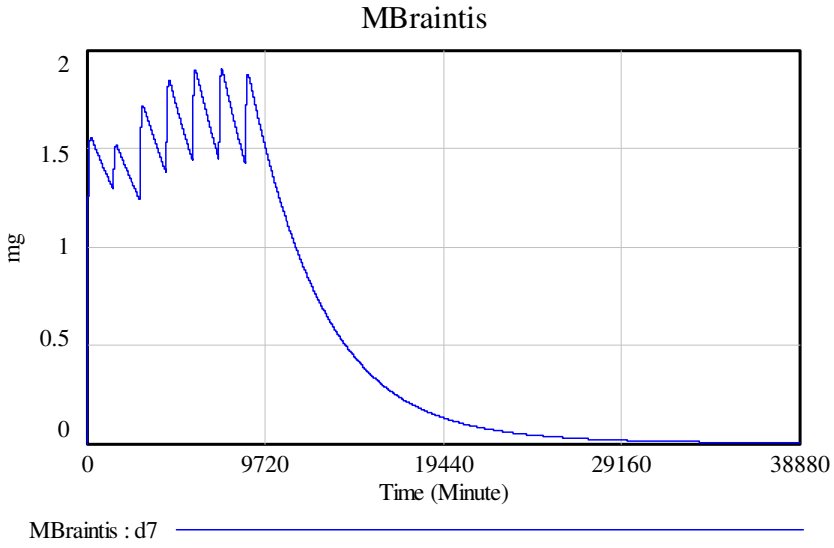


b

Figure 17. Drug profiles in different organs in the seven day drug treatment followed by abrupt withdrawal

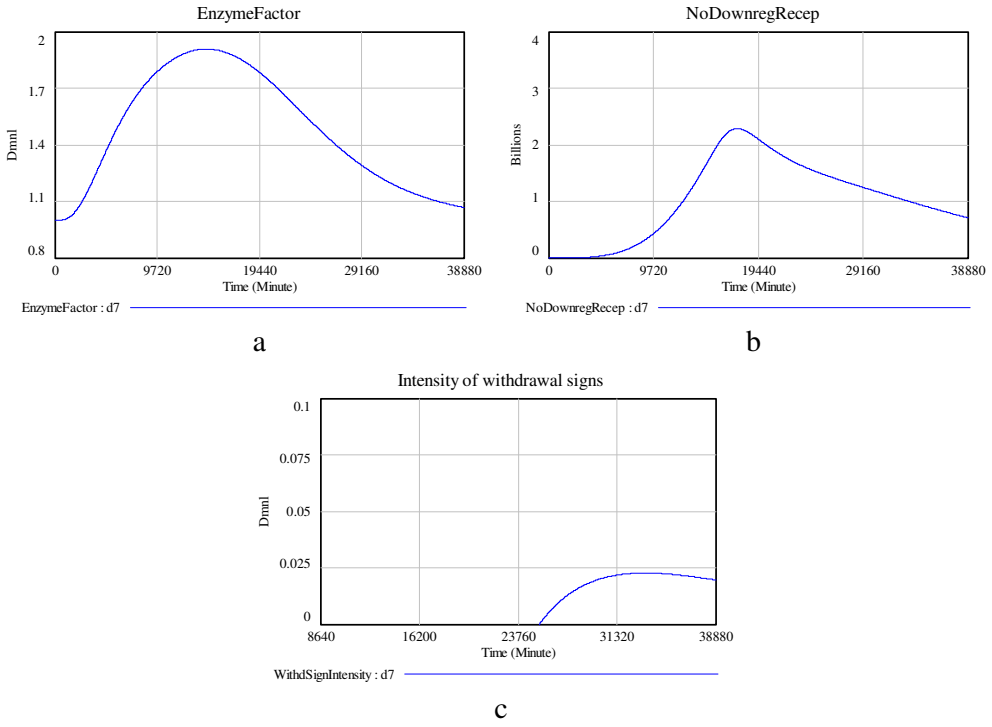


Figure 18. Enzyme and neuroadaptation dynamics in the 5 day drug treatment followed by abrupt withdrawal

Looking at figure 17a we see that the user increases the third dose. This is because chloride current drops below the threshold as can be seen in Figure 19. By doubling the dose, the user allows only a very slight decrease below the threshold.

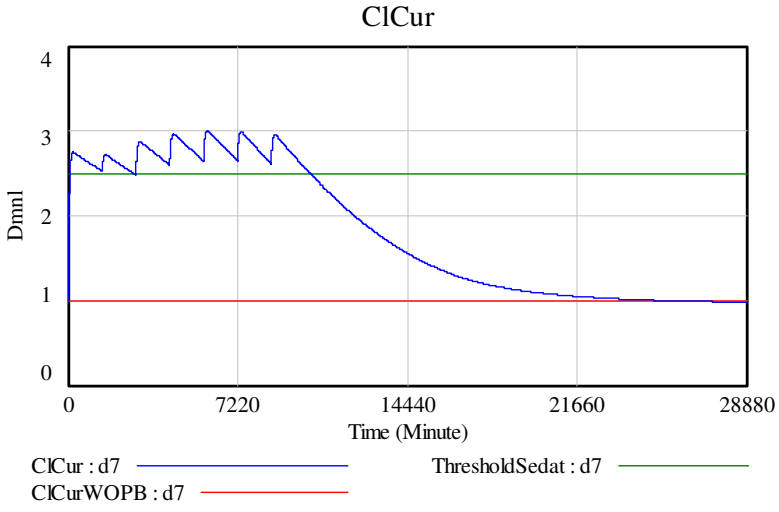


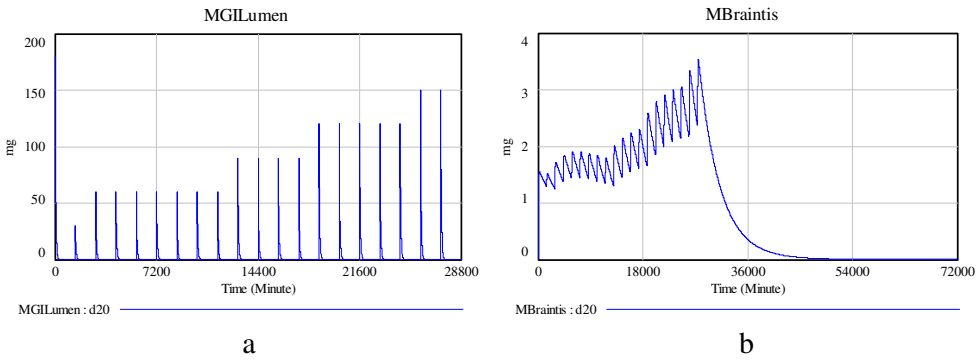
Figure 19. Behavior of chloride current in the seven day drug treatment

In Figure 18a, it is interesting to note that although drug treatment stops on the seventh day (8640 minutes), enzyme induction continues its progress until around the ninth day (12,000 minutes). Furthermore, there is an onset of enzyme induction. This inertia is due to genetic processes related to enhanced synthesis of enzymes such as gene transcription, mRNA synthesis, etc. which take time. Nevertheless during drug treatment, *Enzyme factor* approaches 2, implying that induction is almost complete (Recall that at maximal induction, rate of metabolism doubles).

The inertia in neuroadaptation is more significant. Observe from Figure 18b that although drug intake stops, similar to enzyme induction, down-regulation continues its progress six more days (i.e. the curve peaks around the 13th day). However, only a very small fraction of total receptor population is down-regulated implying that dependence has not yet developed. We therefore assume that the peak intensity in Figure 18c is insignificant and thus establish a reference. Hereafter, we regard any peak intensity below 0.025 as insignificant. The reports in literature stating that dependence to barbiturates develops in several weeks also support the validity of our assumption.

4.3.2. Drug Treatment for 20 Days

Following are the results for 20 days of 30 mg one-a-day doses ending with abrupt withdrawal.



a b

Figure 20. Drug profiles in different organs in the 20 day drug treatment followed by abrupt withdrawal

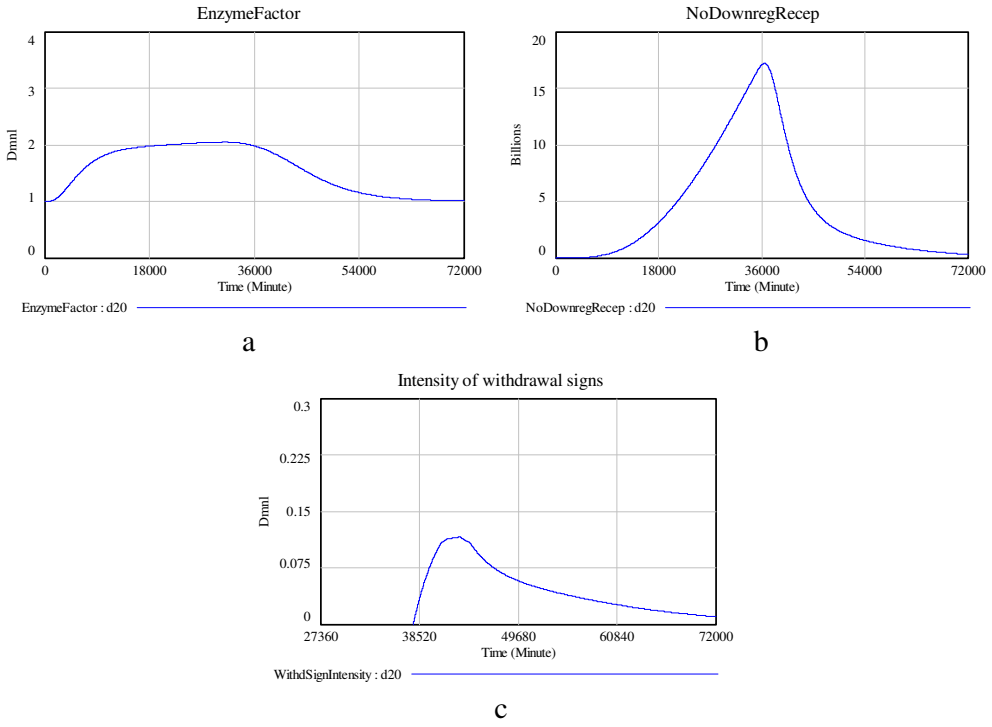


Figure 21. Enzyme and neuroadaptation dynamics in the 20 day drug treatment followed by abrupt withdrawal

The inertia in enzyme and neuroadaptation dynamics is again evident. The onset of enzyme induction is shorter than that of receptor down-regulation. Figure 21a shows that in a few days, enzyme induction peaks and although intake stops on the 20th day, fast metabolism persists six more days (until the 36,000th minute).

As can be seen in Figure 21b, more than a quarter of the receptor population is down-regulated. This weakens inhibitory neurotransmission by decreasing normal chloride current (See the variable named *Normal Cl current* in Section 4.2.2). Together with fast metabolism this reduces the effectiveness of the drug, urging the user to increase the dose several times (Figure 20a). The decrease in drug effectiveness is so severe that the final dose is five times the initial dose. Looking at Figure 22 below, we conclude that the dose increase decisions are justified since chloride current is maintained above the threshold with a few insignificant undershoots throughout 20 days.

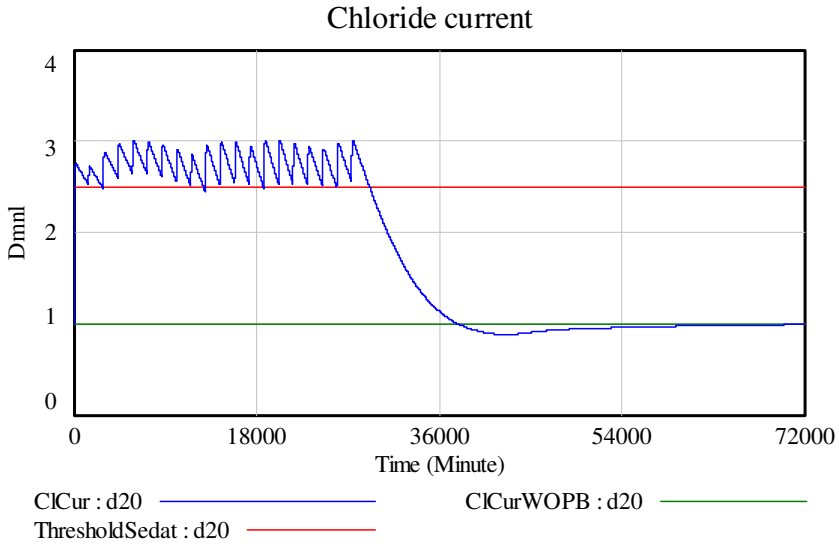
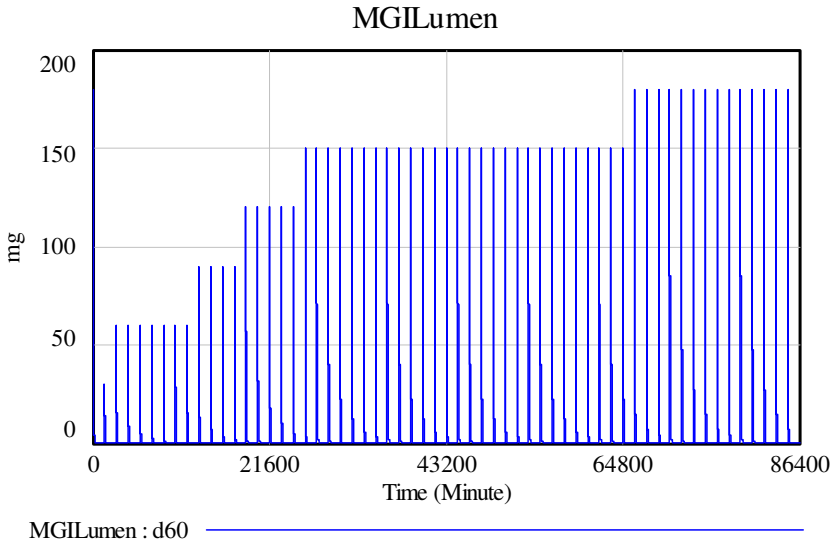


Figure 22. Behavior of chloride current in the 15 day drug treatment

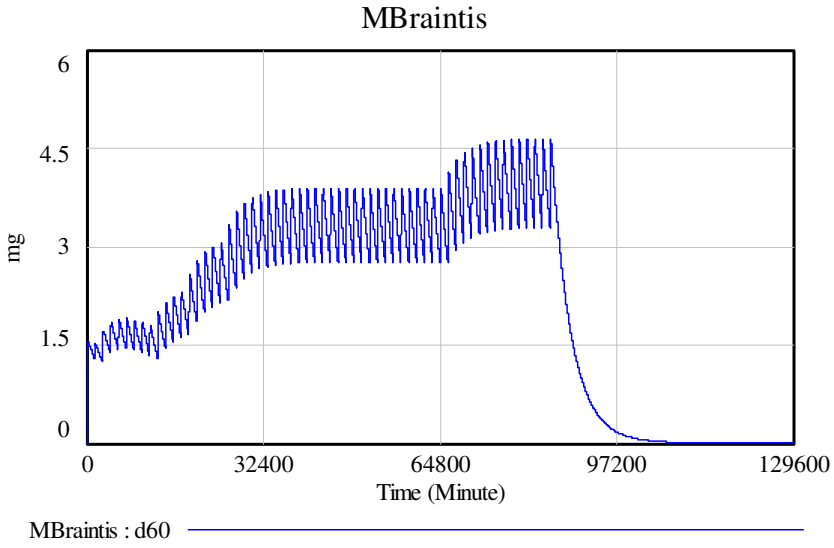
The peak intensity of withdrawal signs is around 0.1 as can be seen in Figure 21c. As mentioned in Section 1.5, clinical research suggests that dependence to barbiturates develops in a few weeks. This suggestion and our ourputs showing that more than a quarter of total receptors are desensitized leads to the conclusion that the user has become dependent-at least partially-to PB and thus upon abrupt discontinuation, he/she would experience a significant withdrawal syndrome. In Figure 21c, the peak intensity of withdrawal signs is around 0.1. Accordingly, hereafter we shall regard any withdrawal sign intensity above 0.1 as severe. We now have two reference points to help us assess the significance of withdrawal signs in further simulation experiments. Finally, the delay in the outburst of the withdrawal syndrome is due to the long half-life (despite enhanced metabolism) of PB.

4.3.3. Drug Treatment for 60 Days

We set the final time to 90 days (129,600 minutes) and *DaysTreatment* to 59 days. We obtain the following results.



a



b

Figure 23. Drug profiles in different organs in the 60 day drug treatment followed by abrupt withdrawal

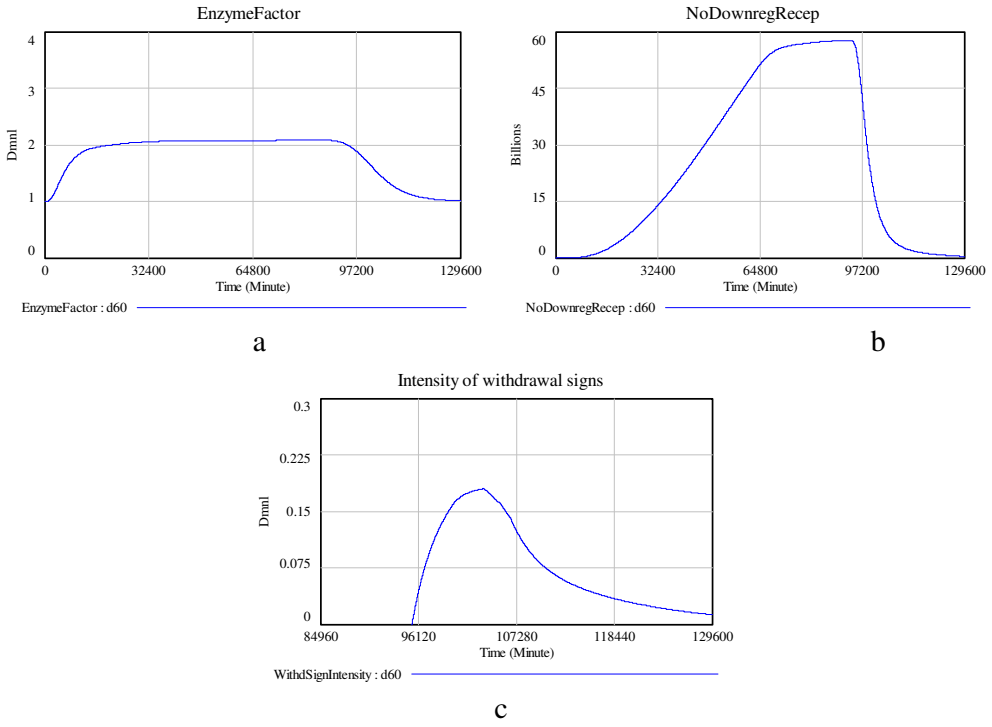


Figure 24. Enzyme and neuroadaptation dynamics in the 30 day drug treatment followed by abrupt withdrawal

Elevated enzyme levels persist even after drug administration stops as was the case in the shorter treatment durations studied previously. We see from Figure 24b that in 60 days, practically all receptor population is desensitized implying that the user has been rendered completely dependent. Around the 45th day, desensitization saturates. Tolerance, on the other hand, is almost complete after the user increases the dose to 150 mg at the 19th dose. Further dose increase is a month later (45th day).

Abrupt withdrawal causes a severe withdrawal syndrome as can be verified from Figure 24c. The peak intensity is nearly twice our reference of significance. In Figure 25 below, we present the chloride current profile. The elevated dosages are efficient in maintaining the desired sedation level.

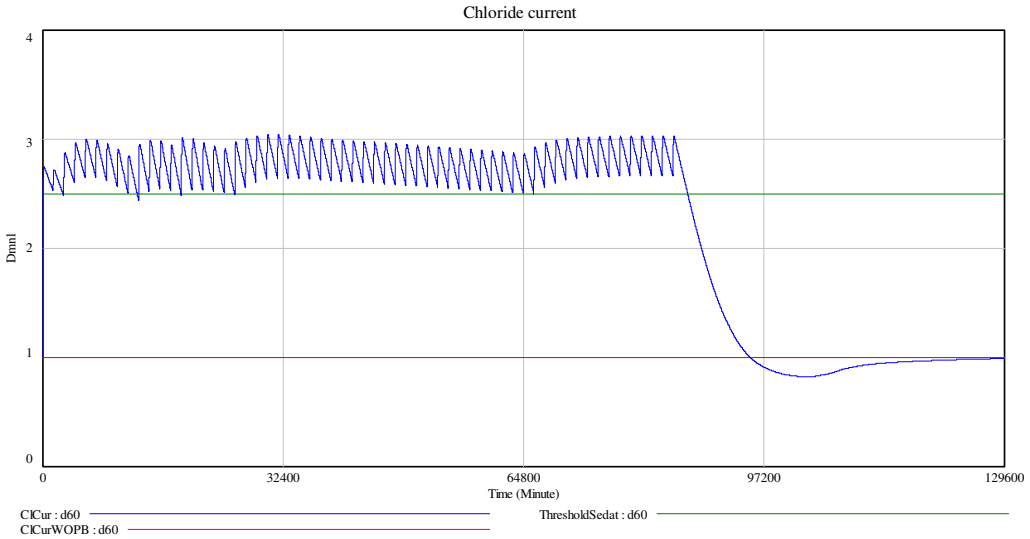


Figure 25. Behavior of chloride current in the 60 day drug treatment

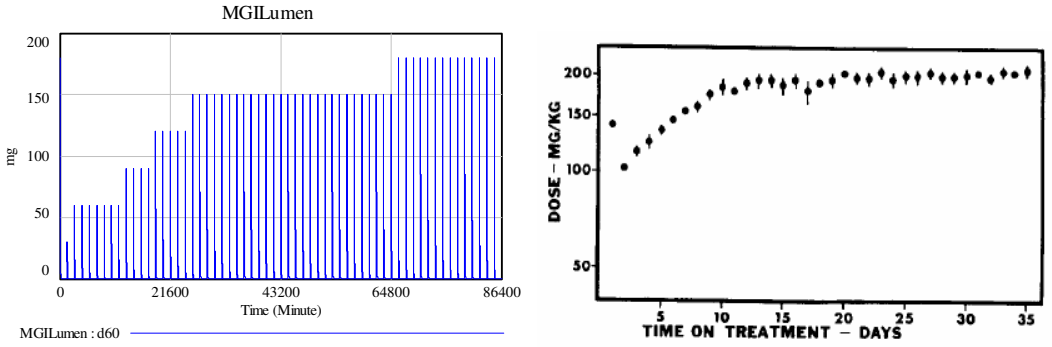
4.4. Model Validity Discussion

A point-by-point match is not a major concern in SD models. The crucial thing is to capture the behavior pattern. We thus draw our comparisons according to this approach.

The validity of the pharmacokinetic sector is established since the same assumptions were used in a previous study and a good fit with real data has been shown (El-Masri and Portier, 1998). Urinary excretion was also included in this model and it is assumed to follow first-order kinetics. In the literature, it is reported that 24 per cent of administered PB is excreted unchanged. It was a straightforward issue to calibrate the rate constant using this information (Engasser et al. 1981).

Regarding enzyme induction, it is reported in the literature that the rate of metabolism doubles at maximal induction and this peak occurs in days to weeks. Parameter calibrations were done using this information. Revisiting the model outputs related to enzyme dynamics of the 20 day treatment case given by Figure 21a, we conclude that our findings conform well to literature reports.

Since no quantitative human data regarding tolerance and dependence development are available in the literature, we use data from studies on animal models such as the one by Gay *et al.* (1983). Our assumptions are fairly similar to theirs. Similar to our model, they target a constant sedation level in rats while adjusting doses. They administer PB orally to rats for 35 days and observe that tolerance development is complete after the first 10 days. To compare, in Figure 26 we display their daily dosing history together with our model outputs for the 60 day drug treatment case.

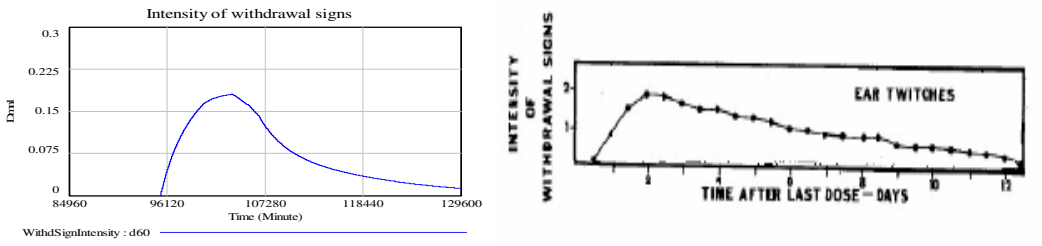


a b

Figure 26. Validation of tolerance dynamics generated by the model.

Similar to the findings by Gay *et al.*, our drug user increases the doses most aggressively in the first few weeks. Afterwards, the doses are relatively constant. A good pattern match is thus observed.

Gay *et al.* also monitor rats for withdrawal signs after abrupt discontinuation to the drug. They quantify the intensity of withdrawal signs which occur a few days after discontinuation. They also observe that the signs attenuate as time elapses. Although their proxy for the intensity of withdrawal signs is different from ours (i.e. their proxy is behavioral outcomes; ours is chloride currents), it indicates the same: The more intense the behavioral sign (the lower the chloride current), the more severe is the withdrawal syndrome. We compare our results in Figure 27 below. As can be seen, the sudden-boom-gradual-bust behaviour is well captured by the model.



a b

Figure 27. Tolerance and dependence indicators for 60 days of continuous PB intake

Gay *et al.* also observe that although tolerance development is almost complete in the 10 day group, the rats withdrawn from PB after 35 days of continuous administration experience more intense withdrawal signs. Our 20 day case is analogous to their 10 day group. In Figure 28 below, we show that the difference in withdrawal signs of the 20 day drug user and the 60 day user is captured by our model.

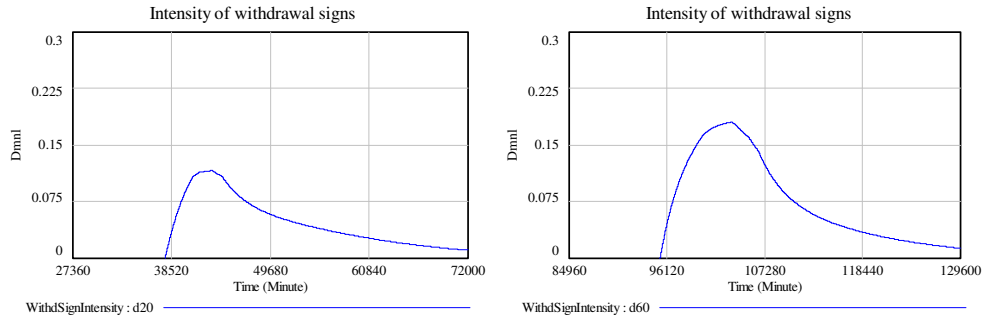


Figure 28. The difference in withdrawal signs between a partially dependent and a completely dependent PB user.

5. SCENARIO ANALYSIS

5.1. Co-administration of a Drug That Causes Enzyme Inhibition

In this scenario, we study a possible drug-drug interaction. Most drug-drug interactions are due to the effects of drugs on liver enzymes (i.e. CYP enzymes). The CYP enzymes are either inhibited or induced by drugs leading to altered metabolism of the substrates of (chemicals that are metabolised by) these enzymes. Usually, the drugs themselves are also substrates of these enzymes and thus pharmacokinetics of a drug may vary considerably if administered together with another drug. To illustrate, suppose that drug A is taken together with drug B which is an inhibitor of a CYP enzyme. Suppose also that drug A is a substrate of this CYP enzyme. This would lead to a slower metabolism of drug A and a normal dose of drug A might actually be fatal. Therefore, in multi-drug treatment, levels of drugs must be carefully monitored to avoid unwanted results.

There may be infinitely many forms of drug-drug interactions. In this scenario, we assume that our hypothetical person has been taking fluconazole, an anti-fungal drug, before starting PB treatment. Fluconazole has been shown to be an inhibitor of PB metabolizing enzymes (Venkatakrishnan, 2000).

To investigate the extent of enzyme inhibition by fluconazole, Kumar *et al.* (2008) use flurbiprofen as a substrate of the inhibited enzyme. They study three groups of subjects. To the first group, they administer flurbiprofen only. To the second group, they administer flurbiprofen after pre-treatment with 200 mg fluconazole for 7 days. Finally to the third group, they administer flurbiprofen after pre-treatment with 400 mg of fluconazole for 7 days. They monitor flurbiprofen clearance in all groups. Their averages are plotted in Figure 29.

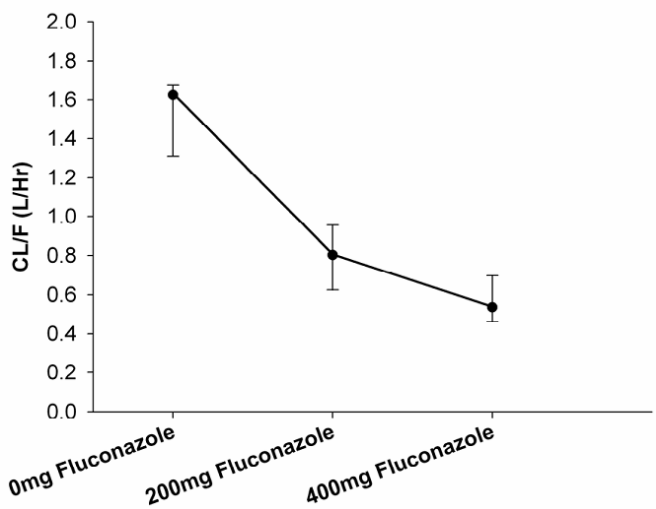
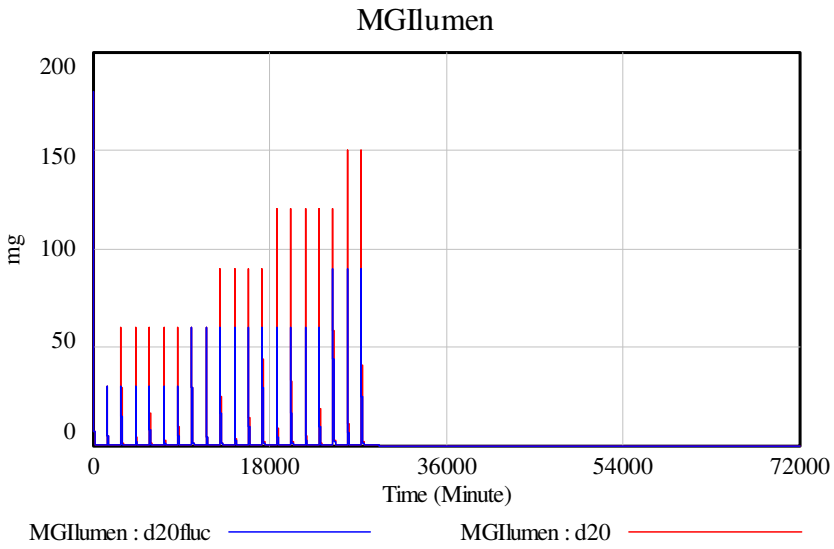


Figure 29. Flurbiprofen average clearance as influenced by fluconazole pre-treatment. Values are given as median $\pm$ 25th percentile (Kumar *et al*., 2008).

Observe from the figure that a 7 day pre-treatment with 200 mg fluconazole halves the rate of metabolism of flurbiprofen. Clearing rate drops from 1.6 L/hr to 0.8 L/hr.

Although there is no comprehensive clinical study on PB-fluconazole interaction, it is reported in the literature that when co-administered with PB, fluconazole leads to increased PB levels via inhibition of enzymes similar to the flurbiprofen case. Since both PB and flurbiprofen are substrates of the same enyzme, we may argue that extent of inhibition will be similar for both drugs. Here we assume that before starting PB treatment, the user has been taking 200 mg doses of fluconazole for the past 7 days. Therefore, by the start of treatment, metabolism rate of PB is assumed to be half the normal rate (i.e. initially the model variable *Enzyme factor* is equal to 0.5). However, enzyme induction still occurs and in a few days the metabolism rate is doubled (i.e. *Enzyme factor* becomes approximately 1). We assume that fluconazole has no effect on any other part of the system. Assuming that PB treatment duration is 20 days, we get the following results.



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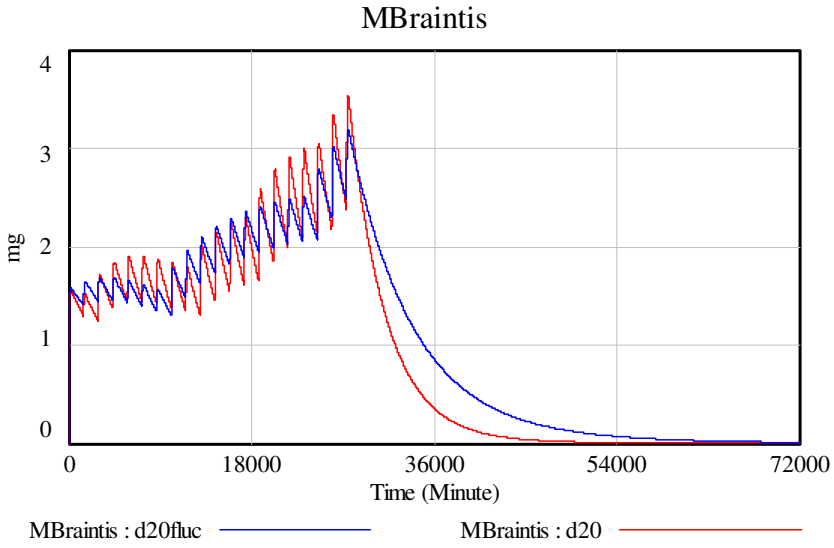

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Figure 30. Drug profiles in different organs with and without fluconazole pre-treatment. PB treatment duration is 20 days ending with abrupt discontinuation.

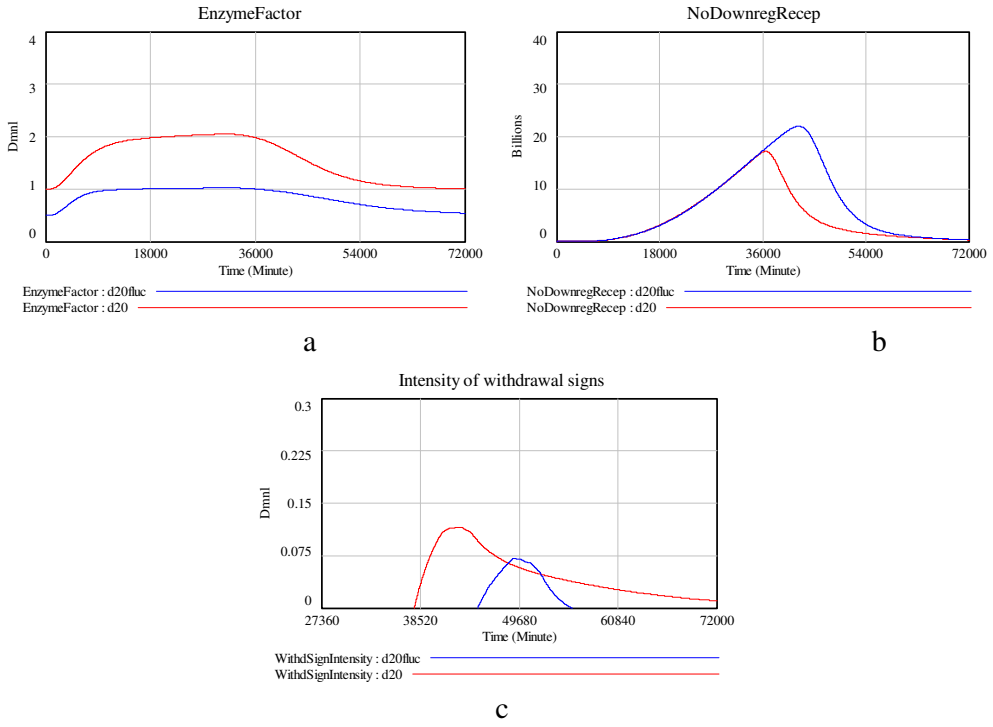

Figure 31. Enzyme and neuroadaptation dynamics with and without fluconazole pre-treatment. PB treatment duration is 60 days ending with abrupt discontinuation.

Figure 30a shows that inhibition of metabolism has slowed down the progression of tolerance. Since PB is cleared much slower, a milder increase in dose is enough to yield the same level of sedation. Compared to a final PB dose of 180 mg, pre-treatment with fluconazole necessitates half that dose. In Figure 30b, we see that the PB amount in the brain is not increased significantly and thus there is no toxicity concern.

Neuroadaptation and withdrawal dynamics are rather interesting. Observing Figure 31b, we see that neuroadaptation has progressed more severely after fluconazole pre-treatment. Interestingly, upon withdrawal, the intensity of rebound effects is much lower. This can be explained as follows: Although the number of down-regulated receptors is larger when fluconazole is administered prior to PB, the reduced rate of metabolism (and thus increased amount of PB in the body) permits more time for re-adaptive mechanisms to restore brain physiology. This can be verified by observing Figure 31c and noting that the withdrawal syndrome is not only lighter, but also the outburst of the syndrome is later in the fluconazole pre-treatment case. Recall that chloride current is a function of both the extent of neuroadaptation (proxied by the number of downregulated receptors) and the concentration of PB in brain tissue. Although more extensive neuroadaptation lowers chloride current in the brain, elevated levels of PB more than compensates this.

5.2. Different Dosing Frequencies

In all preceding simulation runs, we assume the drug user employs one-a-day dosing. One may reasonably suspect that in terms of tolerance and dependence, employing different dosing schemes could yield different results. Therefore in this section we compare four different dosing schemes in which we vary the initial doses and dosing frequencies. The initial average daily dose is 30 mg in all schemes. In the first scheme, the user starts with 60 mg tablets taken every two days. Second scheme is our base assumption in which the user takes a single tablet every day and starts from 30 mg. Third scheme assumes 15 mg tablets taken two-a-day, and finally the fourth scheme assumes 10 mg tablets taken three-a-day. We comparatively show tolerance and dependence dynamics together with the behavior of chloride current. Treatment duration is assumed to be 20 days followed by abrupt discontinuation.

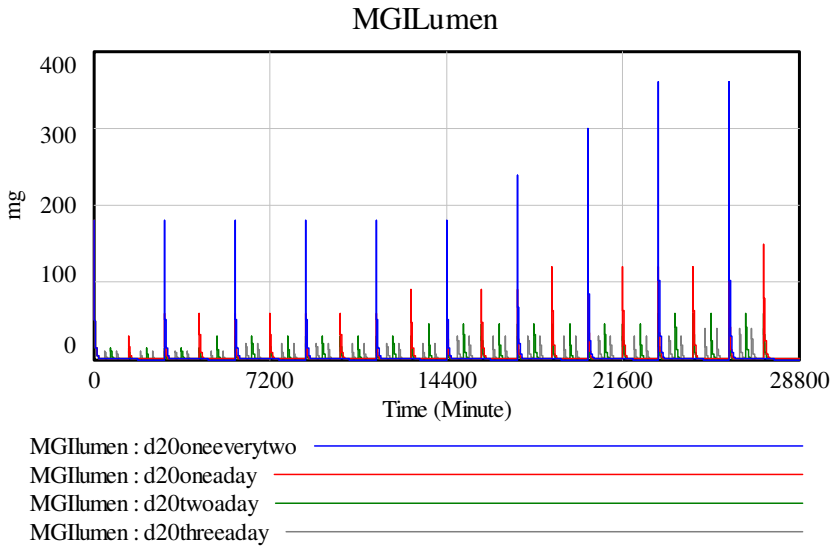

Figure 32. Difference in the extent of tolerance development w.r.t dosing schemes

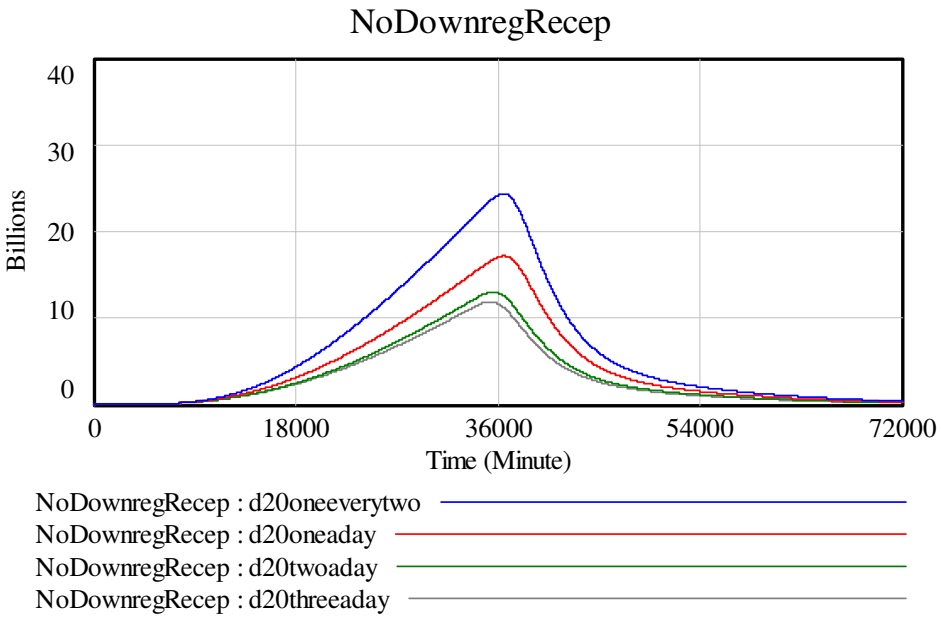

Figure 33. Neuroadaptation dynamics for different dosing schemes

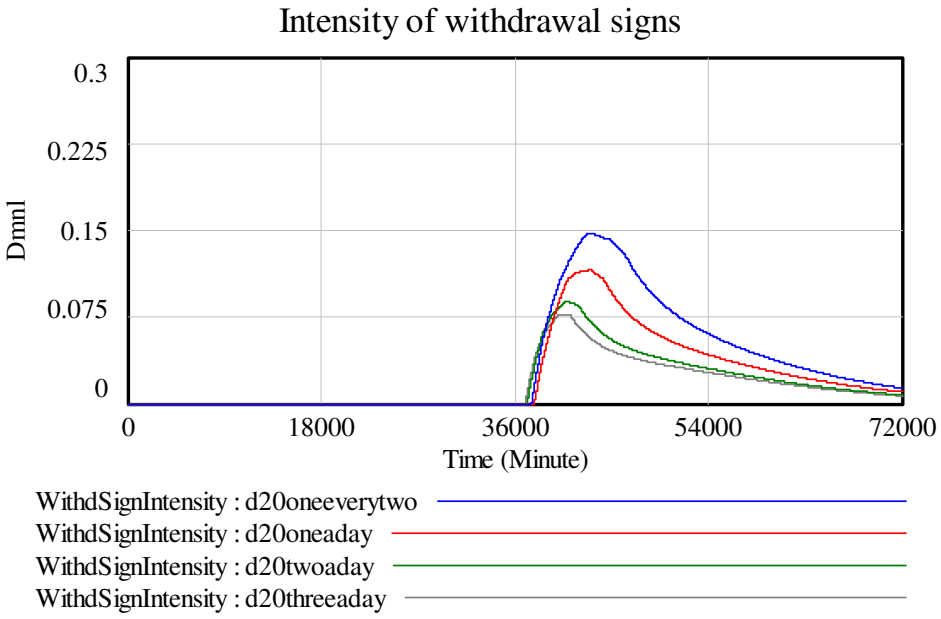

Figure 34. Dependence dynamics for different dosing schemes

It turns out that both tolerance and dependence development is less when frequency of doses is increased. In three-a-day dosing, the total amount of drug administered in 20 days is 1560 mg. As the frequency is decreased, this total amount increases. In the extreme case where the user takes one tablet every two days, the total amount administered is 2340 mg which is approximately 50 per cent more than the

three-a-day case. Additionally, in one-every-two-days dosing, the peak number of down-regulated receptors is 24 billion whereas in three-a-day dosing, the peak is 12 billion. As anticipated from this, the severity of rebound effects is most potent in one-every-two-days dosing. Finally, the amplitude of oscillations in chloride current is less in frequent dosing. This outcome is in favor of homeostasis: The body prefers stability. The comparative behavior of chloride current is given in Figure 35 below. Also note the wideness of the band spanned by the blue curve (one-every-two-days dosing).

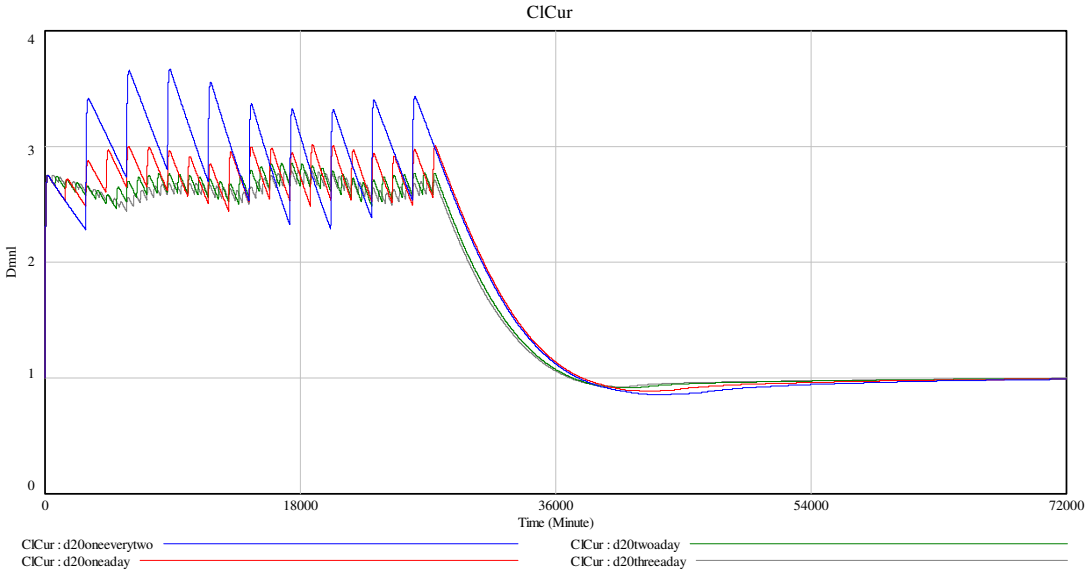

Figure 35. Behavior of chloride current in different dosing schemes

We may confidently argue that the most appropriate dosing scheme is three-a-day dosing. Although further increases in dosing frequency could prove better, such high frequencies would not be practical since the user would have to remember too often taking a tablet.

6. ANALYSIS OF WITHDRAWAL POLICIES

It is shown in the preceding sections that abrupt withdrawal results in an unwanted withdrawal syndrome. This suggests that the dose should be reduced gradually. During the withdrawal period, the decision variables are dosing times, dosing amounts and duration of the withdrawal regimen. The best policy would be the one that causes very few or no withdrawal signs with a minimum total amount of administered PB. In this section, we demonstrate both unsuccessful and successful withdrawal dosing regimens after one-a-day dosing for both 20 and 60 days. We assume a healthy user taking PB one-a-day for sedation as in Section 4. It is anticipated that withdrawal would be easier after the 20 day treatment since the drug user would not be totally dependent on the drug as was shown in section 4.3.2. On the other hand, we have shown in section 4.3.3 that the user is maximally tolerant to and dependent on PB after the 60 day treatment and this would complicate withdrawal.

In hypothesizing effective withdrawal regimens, we use intuition and therefore start with relatively good regimens. Simulation experiments were conducted as follows: We start with an initial guess and we check, at the end of the regimen, whether the user experiences rebound effects. If this is the case, we prolong the regimen and/or modify the doses until we observe no withdrawal syndrome. In summary, by improving upon our previous postulations, we try to come up with regimens that help avoid a withdrawal syndrome. For each case of drug treatment duration, we present first an unsuccessful postulation. Then we discuss necessary modifications that lead to a successful regimen.

6.1. Withdrawal after 20 days of treatment

6.1.1. An unsuccessful regimen

Since the half-life of PB is long, when drug intake is stopped on the 20^{th} day, the drug stays in the body and is still effective. Trials show that the chloride current stays above the base value (i.e. 1) for at least seven days after the last dose. Thus, we wait for seven days before starting the withdrawal regimen. This regimen lasts for 10 days: After taking no tablet in the first seven days, the user is supposed to take one-tenth of the last dose (dose on the 20^{th} day) for the following three days and then discontinue. The dynamics that result are given in Figure 36.

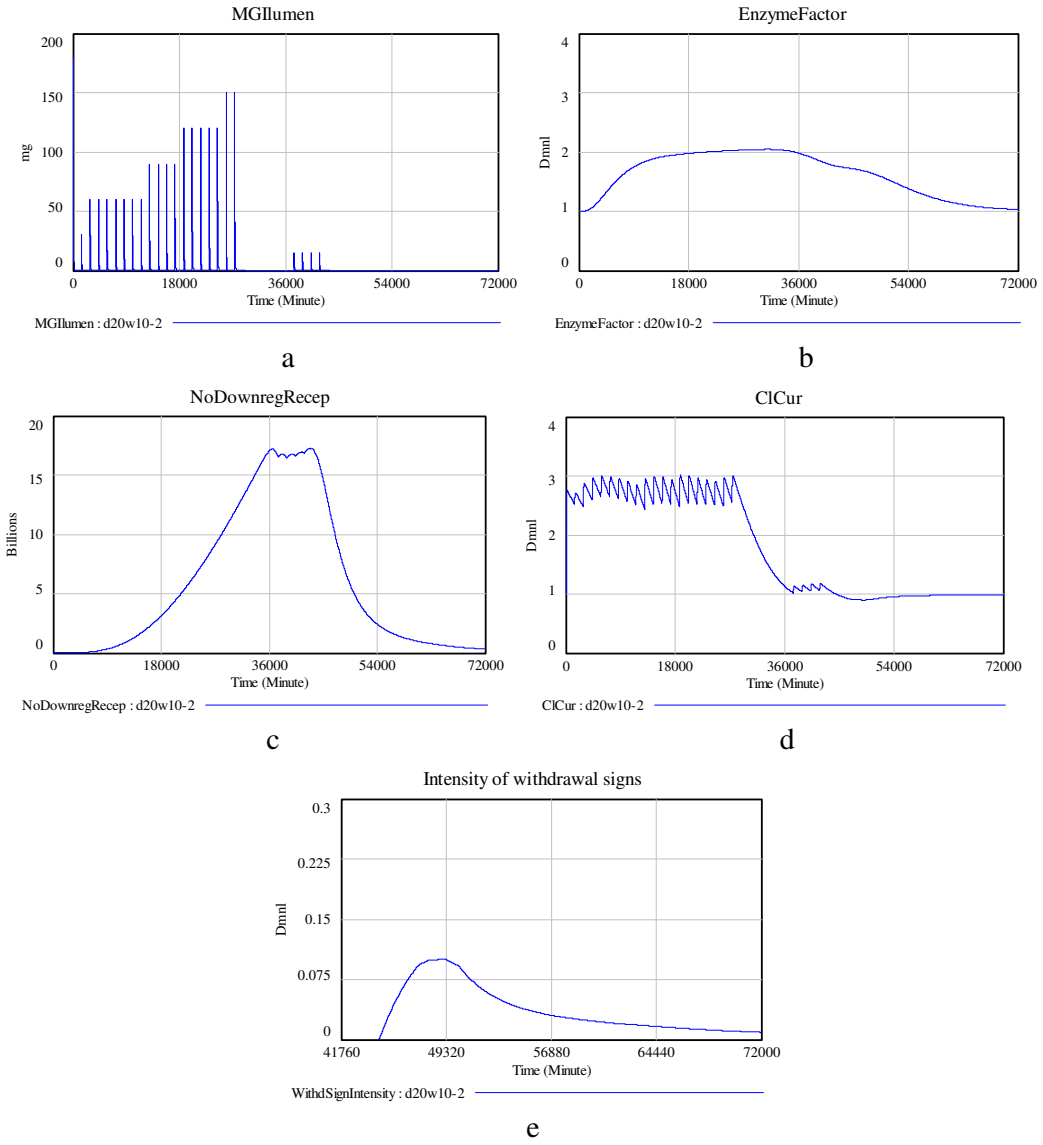

Figure 36. Dynamics of an unsuccessful withdrawal regimen after partial dependence

Looking at Figure 36b, we see that although enzyme levels are being restored during withdrawal doses, the duration of the withdrawal regimen is not long enough to complete this restoration. Enzyme factor is more than 1.5 at the time of complete withdrawal. Furthermore, Figure 36c shows that the dose amounts are too high that down-regulated receptors merely stop increasing and re-adaptive mechanisms are not operational at all. The result is a severe withdrawal syndrome as can be seen in Figure 36d (chloride current undershoots 1) and more clearly in Figure 36e.

6.1.2. A successful regimen

The failure of the 10 day withdrawal period suggests a longer withdrawal period with decreased dosages. After tedious trial-and-error, we come up with the following 15 day regimen: We administer one-fifteenth of the final dose between days 27 and 31; and we administer one-twentieth of the final dose between days 32 and 35. The following dynamics result.

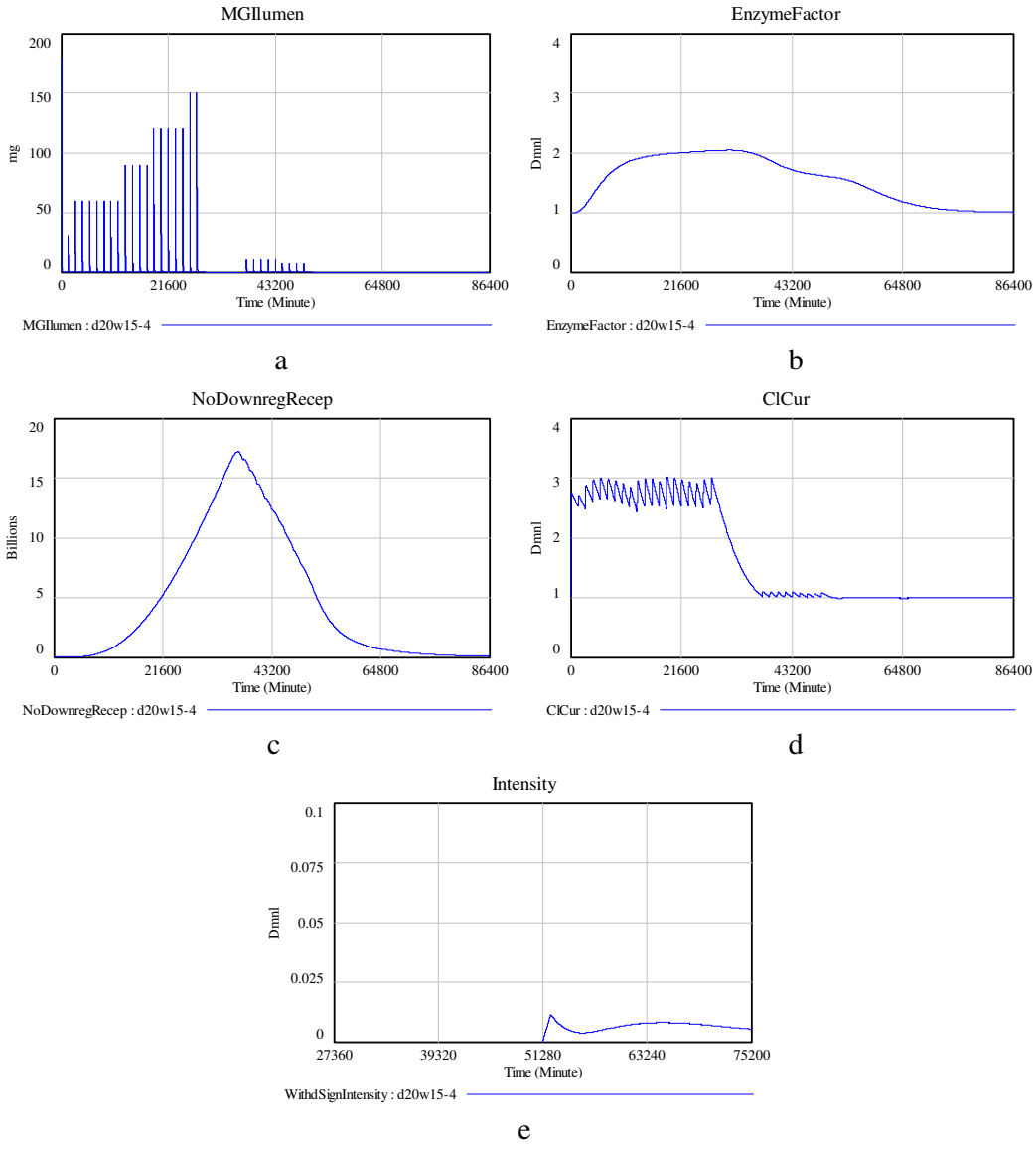

Figure 37. Dynamics in a successful withdrawal regimen after partial dependence

Our anticipation turned out correct. The duration of withdrawal is now long enough so as to facilitate complete recovery of down-regulated receptors (Figure 37c). Although the metabolism is still 50 per cent higher than normal (Figure 37b, around the 35th day), complete withdrawal does not lead to a significant withdrawal syndrome as

can be seen from Figure 37e. Observe that the peak intensity of withdrawal signs is well below the 0.025 reference. This suggests that the contribution of enzyme induction to development of dependence is minor. In fact, this is reported in the literature as well. This result is thus an additional clue of our model's validity.

6.2. Withdrawal after 60 days of treatment

6.2.1 An unsuccessful regimen

We now experiment with withdrawal regimens after 60 days of continuous PB use after which the user becomes completely dependent on the drug. As a first trial, we propose a 20 day regimen as follows: We wait 7 days before administering reduced doses and after that, between days 67 and 80, we administer one-fifteenth of the final dose. The following dynamics result.

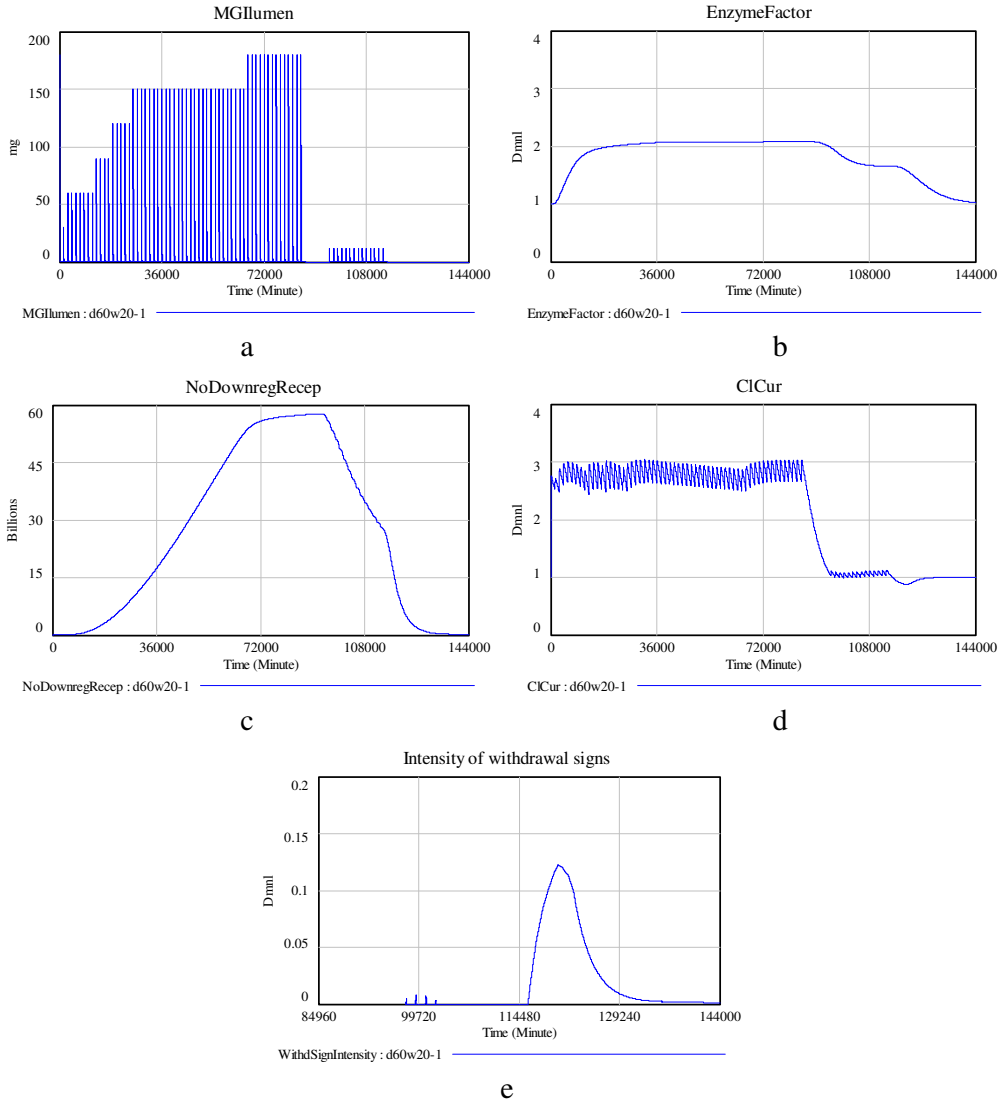

Figure 38. Results for an unsuccessful withdrawal regimen after complete dependence

Although chloride current is maintained in an appropriate range during the regimen so that both the down-regulated receptors and elevated enzyme levels are decreased (Figures 38b and 38c), re-adaptation is partial because the duration of withdrawal falls short. The result is a severe withdrawal syndrome as can be seen in Figure 38e.

6.2.2. A Successful Regimen

We prolong the duration of withdrawal to 30 days. Since the dosage in the previous regimen was shown to be appropriate, we only prolong the regimen. We assume that the user is supposed to take one-twentieth of the final dose for the following 10 days (i.e. between days 81 and 90). The following dynamics are observed.

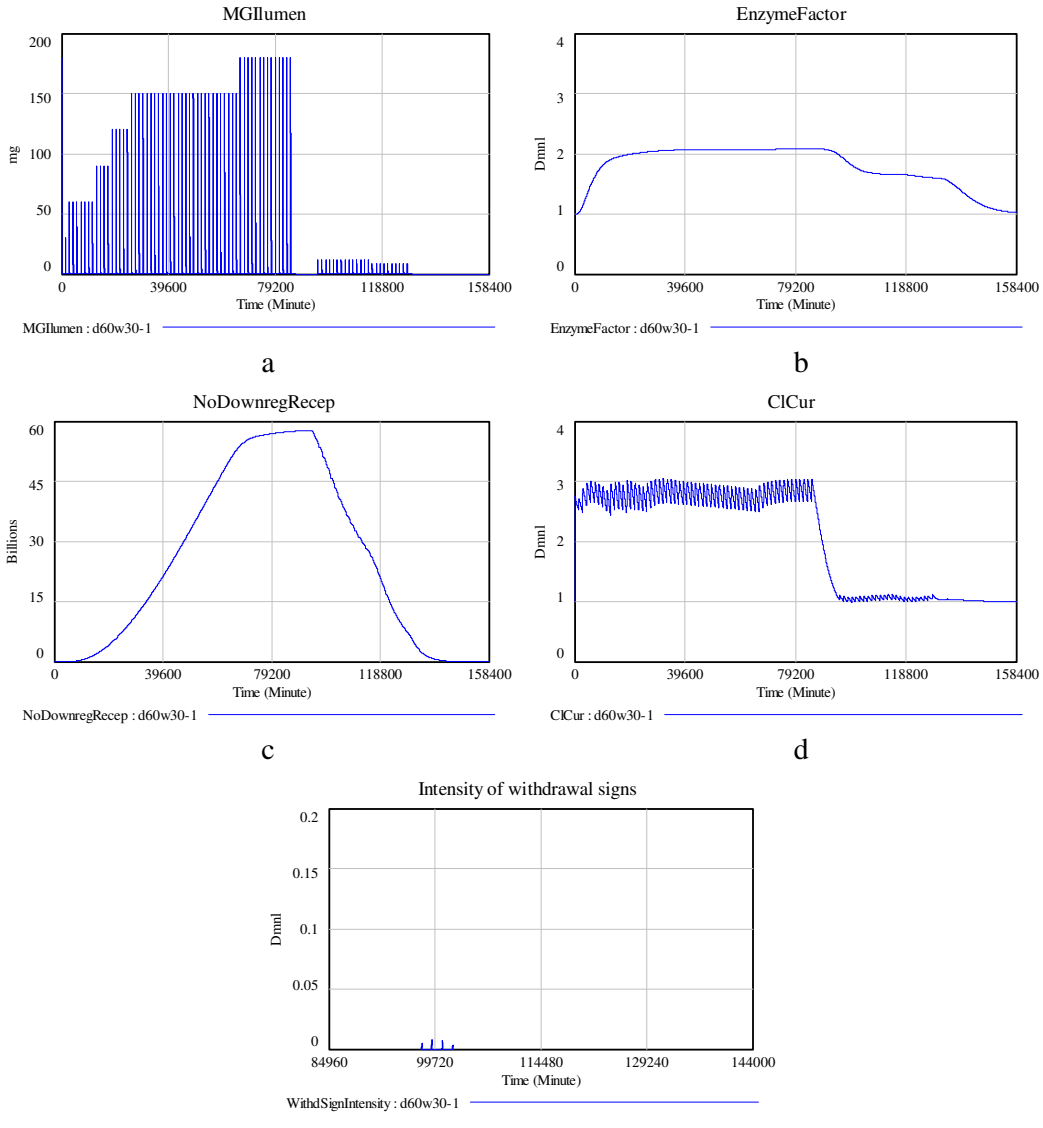

Figure 39. Results for a gradual withdrawal regimen of 30 days following a 60 day drug treatment

As anticipated, prolonging the last phase of the regimen cured the failure. The drug user experiences no rebound effects (Figure 39e). The duration of drug intake is long enough so that almost all down-regulated receptors are restored by the end of the 90^{th} day (Figure 39d).

7. CONCLUSIONS AND FUTURE DIRECTIONS

Although being replaced by safer drugs, a lot of people still use phenobarbital (PB) regularly for sedation or to help them fall asleep. The systemic model constructed in this thesis is a good representation of a regular barbiturate user and the consequences of chronic barbiturate use.

Adaptive changes have inertia. This gives birth to counter-intuitive dynamics that need to be addressed with good policies. Possible drug-drug interactions should also be taken into account if PB is being taken together with other chemicals. In this thesis, we study a drug-drug interaction involving only the liver. However, in epilepsy, several CNS active drugs may be prescribed and concurrent intake of these drugs would involve more complex dynamics especially in the CNS. Additionally, the consumption of alcohol while taking barbiturates has well-known lethal effects. As such, this could also be a future study.

The model provides an experimental platform to test different dose intake schemes and dose adjustment policies during regular use. We experiment with different dosing frequencies and show that the more frequent the doses, the better it is in terms of tolerance and dependence development. However, we neglect the possible impracticality of too frequent doses. Since we explicitly model arterial blood drug content, the model could also be used to imitate clinical settings such as constant intravenous infusion where the infusion of drug is more continuous contrary to cases studied in this thesis.

Literature reports and also we show that when a dependent user abruptly discontinues PB use, harmful rebound effects are experienced. To avoid, the doses should be reduced gradually in time. We have proposed relatively efficient withdrawal regimens for both partial and complete dependence cases. As anticipated, a longer period of withdrawal was necessary in complete dependence. The duration of the withdrawal period was at least half the actual treatment duration in both cases. The method of search for feasible withdrawal regimens was rather intuitive. Therefore, a more systematic approach could prove useful in the future. It may be interesting to define the problem as an optimization problem where it is tried to minimize both the duration of the withdrawal period and the amount of doses while keeping the resulting intensity of withdrawal signs at minimum.

The model does not take into account neuroadaptation dynamics in the excitatory neurotransmission system. It is likely that when inhibitory neurotransmission is potentiated by PB, besides desensitizing inhibitory receptors to counteract potentiation, neuroadaptation could up-regulate excitatory neurotransmission as well. We have neglected this issue in our model. However, the direction of effect of these neuroadaptive mechanisms at different sites is the same and we may argue that these are confounded in our formulation.

Finally, the model is built using rather generic structures and generic assumptions. This is especially true for the pharmacokinetic sector. The parameters can be modified

so that a different CNS-active drug can be modeled as well. Receptor down-regulation is also a rather common mechanism of neuroadaptation. Therefore, the parameters in the CNS sector of the model can be modified to capture the dynamics of a different drug that causes receptor down-regulation.

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APPENDIX. EQUATIONS OF THE MODEL

Equations of the model are given below for one-a-day treatment lasting for 20 days and ending with abrupt withdrawal (Studied in Section 4.3.2).

Dose=INTEG (DoseIncr,30)

I4=IF THEN ELSE(MODULO(Time,1440)>=1437,1,0)

LoadDose=180

MGIlumen=INTEG (Intake2+Intake3+Intake4+Intake5+Intake1-Absorption, LoadDose)

*DoseIncr=I1*I2*I3*I4*10*

I3=IF THEN ELSE(Time>1440, 1 ,0)

I1=IF THEN ELSE(ClCur<ThresholdSedat, 1 , 0)

*Adaptation=EffSatur*RealAdptnRate*

*RealAdptnRate=SMOOTH3(IndAdptnRate , 15*1440)/15*

*Readaptation=EffPBReadptn*ReadptnFrac*NoDownregRecep*

ReadptnFrac=0.000325

*VenousToArterial=QTotal*CVenous*

MVenous=INTEG(ArterialToVenous+BrainToVenous+FatToVenous+KidneyToVenous +LiverToVenous+MuscleToVenous-VenousToArterial,0)

*Excretion=MKidney*Kexcr*

MArterial= INTEG (VenousToArterial-ArterialToMuscle-ArterialToLiver-ArterialToKidney-ArterialToGItis-ArterialToFat-ArterialToBrain-ArterialToVenous,0)

*ArterialToVenous=CArterial*QHeart*

MFat= INTEG (ArterialToFat-FatToVenous,0)

*FatToVenous=QFat*CFat/PFat*

*ArterialToFat=QFat*CArterial*

VFat=16.394

PFat=1

CFat=MFat/VFat

QFat=0.26

Intake3=0

Intake4=0

Intake5=0

MKidney= INTEG (ArterialToKidney-KidneyToVenous-Excretion,0)

TotalNoRecep=60

EffAdptnOnNormClCur= WITH LOOKUP (NoDownregRecep/TotalNoRecep,
([(0,0.6)-(1,1)],(0,1),(0.0825688,0.829825),(0.100917,0.807018),
(0.131498,0.784211),(0.153333,0.77193),(0.186544,0.764912),
(0.266055,0.750877),(0.33945,0.742105),(1,0.7)))

EffSatur= WITH LOOKUP (NoDownregRecep/TotalNoRecep,
([(0.8,0)-(1,1)],(0,1),(0.8,1),(0.8263,0.969298),(0.849541,0.907895),
(0.877676,0.758772),(0.899083,0.605263),(0.933945,0.179825),
(0.944342,0.100877),(0.95841,0.0351),(0.975535,0),(1,0)))

ThresholdSedat=2.5

Intake2=0

kout= LN(2)/HalflifeEnzyme

HalflifeEnzyme=2880

Rin=LN(2)/(HalflifeEnzyme)

*Intake1=(Dose/TIME STEP)*PULSE TRAIN(1440, TIME STEP,*
*1440,DaysTreatment*1440+TIME STEP)*

DaysTreatment=19

*I2=IF THEN ELSE(Time<DaysTreatment*1440,1,0)*

CLiver=MLiver/VLiver

CMuscle=MMuscle/VMuscle

CVenous=MVenous/VVenous

CArterial=MArterial/VArterial

CBraincapil=MBraincapil/VBraincapil

CBraintis=MBraintis/VBraintis

CGItissue=MGItissue/VGItissue

CKidney=MKidney/VKidney

Kexcr=0.0035

VKidney=0.308

VArterial=1.556

VBraincapil=0.0447

VMuscle=28

VGItissue=1.19

VLiver=1.925

VVenous=3.811

MBraincapil= INTEG (ArterialToBrain+BraintisToBraincapil-BrainToVenous-BraincapilToBraintis,0)

*EffPB=CBraintis*600/(2.79+CBraintis)*

WithdSignIntensity=-(ClCur-1)

*NormClCur=ClCurWOPB*EffAdptnOnNormClCur*

*ReaIInducbyPB=SMOOTH3(IndInducByPB, 2*1440)*

Synthesis=Rin(1+ReaIInducbyPB)*

EffPBReadptn= WITH LOOKUP (EffPB,([(0,0)-(800,1)],(0,1),(10.7034,0.938596),(18.9602,0.850877),(25.9939,0.714912),(42.5076,0.232456),(46.1774,0.144737),(52.9052,0.0614035),(60.367,0.0175),(70,0),(600,0)))

IndAdptnRate= WITH LOOKUP (ClCur/ClCurWOPB,([(0,0)-(6,0.04)],(0,0),(1.5,0),(1.88991,0.0008635),(2.04587,0.00185025),

(2.20183,0.003455),(2.37156,0.0061675),(2.52294,0.009375),(2.66972,0.013322 5),(2.78899,0.0173925),(3,0.028125),(3.04465,0.03),(3.13211,0.0317544), (3.23976,0.0331579),(3.40061,0.0342105),(3.61468,0.035),(4,0.035614),(6,0.035 61)))

ClCur=NormClCur(1+EffPB/100)*

ClCurWOPB=1

NoDownregRecep= INTEG (Adaptation-Readaptation,0)

*Kmet=NormKmet*EnzymeFactor*

*Metabolism=CLiver*Kmet*

MBraintis= INTEG (BraincapilToBraintis-BraintisToBraincapil, 0)

*BraincapilToBraintis=VBraintis*DR*CBraincapil/(1+Bplasma)*

*BraintisToBraincapil=VBraintis*DR*CBraintis*FR*

*Absorption=MGIlumen*Kabs*

*ArterialToBrain=QBrain*CArterial*

*ArterialToGItis=CArterial*QGItissue*

*ArterialToKidney=CArterial*QKidney*

*ArterialToLiver=CArterial*QLiver*

*ArterialToMuscle=QMuscle*CArterial*

Bplasma=0.438

*BrainToVenous=QBrain*CBraincapil*

*Degradation=(EnzymeFactor)*kout*

DR=0.02

EnzymeFactor= INTEG (Synthesis-Degradation,1)

FR=1.75

MGItissue= INTEG (Absorption+ArterialToGItis-GItissueToLiver,

*GItissueToLiver=QGItissue*CGItissue/PGItissue*

Kabs=0.02

*KidneyToVenous=QKidney*CKidney/PKidney*

NormKmet=3.14/1000

MLiver= INTEG (ArterialToLiver+GItissueToLiver-LiverToVenous-Metabolism,
0)

*LiverToVenous=(QLiver+QGItissue)*CLiver/PLiver*

*MuscleToVenous=QMuscle*CMuscle/PMuscle*

MMuscle= INTEG (ArterialToMuscle-MuscleToVenous,0)

PGItissue=1

PKidney=2.05

PLiver=2.25

PMuscle=1.12

QBrain=0.57

QGItissue=0.9

QHeart=0.2

QKidney=0.875

QLiver=0.235

QMuscle=1.67

QTotal=4.475

*IndInducByPB=1.15*CLiver/(1+CLiver)*

VBraintis=1.3553