Modelling the pharmacokinetics of antidepressant discontinuation syndrome

Mathematics AA HL Internal Assessment

1 Introduction

1.1 Rationale

I have always been fascinated by the interactions between chemical substances, the brain, and subjective experience, so I have found it interesting taking fluoxetine (Prozac), an antidepressant I am prescribed for anxiety. However, when I was reading about my medication, I discovered that stopping antidepressants can lead to very unpleasant withdrawal symptoms. Such "antidepressant discontinuation syndrome" occurs in more than half of all users, causing headaches, mood disturbances, dizziness, and other symptoms (Michelson et al., 2000) that can persist for months or years after the drug is stopped (Davies & Read, 2019). As I will likely stop or change medication at some point, I decided to explore the mathematical relationships between drug intake, its levels in the body, and incidence of discontinuation syndrome, so that I can find a dose-tapering regimen to help me avoid withdrawal symptoms.

1.2 Approach

I will:

1. Use ordinary differential equations and clinical data to derive and fit a pharmacokinetic (drug movement) model for the plasma concentration of a dose of fluoxetine in the body, as a function of time, and extend this function to model concentration with repeated oral dosing, of the sort seen in daily antidepressant dosing.
2. Investigate and identify a model for the relationship between the dose of fluoxetine taken and its effects.
3. Use this dose-response relationship, along with clinical recommendations on avoiding withdrawal symptoms, to derive a theoretically ideal fluoxetine tapering plan.
4. Use the dose-concentration model from step 1 to convert the theoretically ideal tapering plan into a target plasma concentration curve, then compare this ideal concentration trajectory with those produced by recommended antidepressant cessation regimens, to determine which of these schedules is best for preventing withdrawal symptoms.

2 Exploration

2.1 Modelling drug plasma concentrations

In order to understand the relationship between a given dosing regimen and the effects it has on the brain, we must first model the changes in plasma concentrations of the drug caused by a dose with time—that is, the amount of drug per unit volume of blood in systemic circulation (often measured in nanograms per millilitre, ng/mL). Typical concentration-time graphs of fluoxetine are shown in Figure 1, taken from a study comparing two different brands of it available in Japan. The two formula-

tions have virtually identical concentration-time curves; however, this investigation will use the Prozac brand data, as that is the brand I generally take.

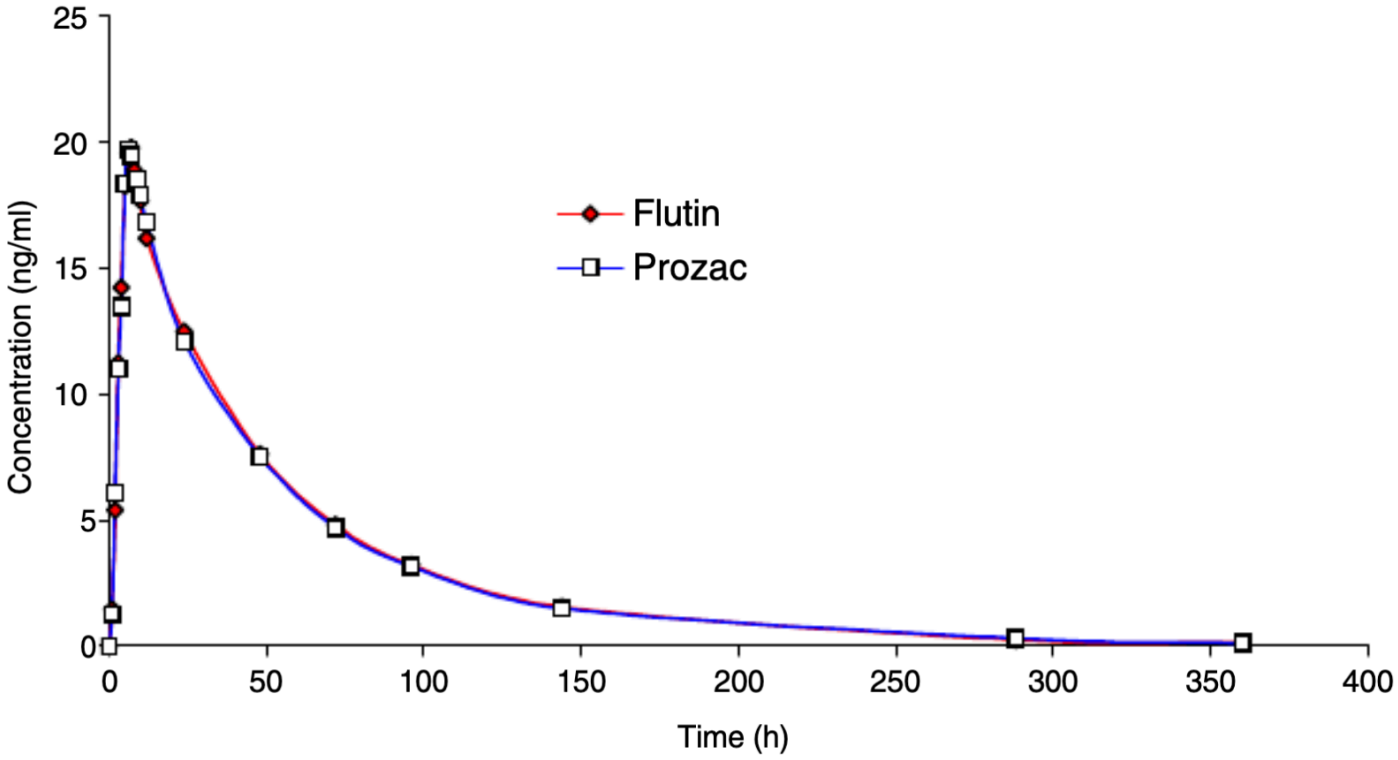


Figure 1: Mean plasma concentrations of two fluoxetine formulations (Najib et al., 2005)

This does not immediately resemble any common function. One could obtain a polynomial to approximate this curve using regression, but a more rational, mechanistic approach would be to construct a model based on the drug's movement in the body. Then, its parameters could be found by fitting the curve to the Prozac data.

2.1.1 A one-compartment model

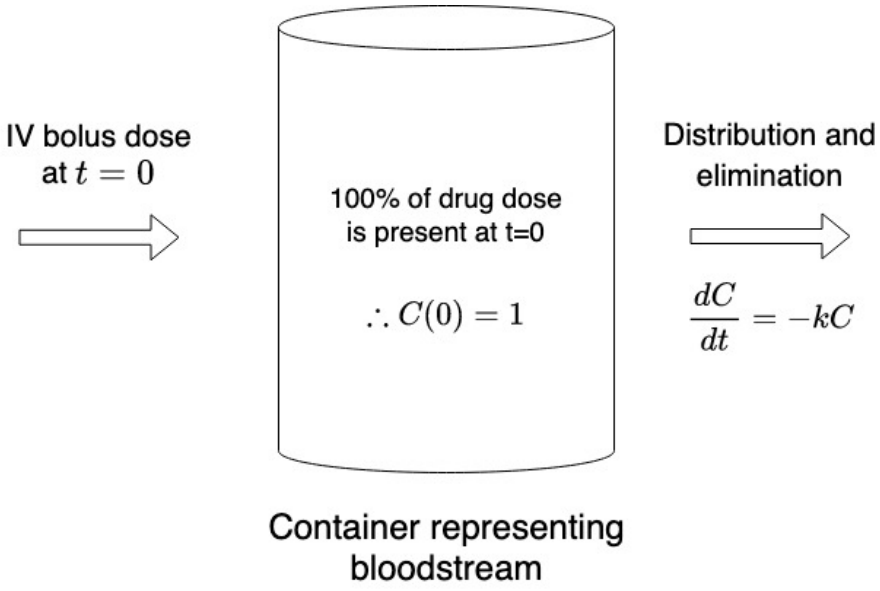


Figure 2: A diagram depicting a one-compartment pharmacokinetic model (own diagram)

One way to model this is with compartmental analysis. Compartmental models abstract away complicated bodily systems into 'compartments', homogeneous volumes through which the drug passes, at rates defined by differential equations, until

it is eliminated from the body (Gabrielsson et al., 2016; Duan, 2016). The simplest of these models is the one-compartment model. Used to model single intravenous drug doses ("bolus doses"), it treats the entire bloodstream as a compartment to which all the drug is added in the beginning, and from which the drug is continuously removed at a rate proportional to the remaining concentration of the drug (reflecting metabolism/excretion), as per Figure 2 (Gabrielsson et al., 2016).

In this model, the plasma concentration is described by the function $C(t)$, where t refers to time (usually in hours). As the rate of drug elimination is proportional to its remaining concentration (i.e. exponential decay), this can be represented by the first-order differential equation

$$\frac{dC}{dt} = -kC,$$

where k refers to a constant known as the elimination rate constant and $k > 0$. This differential equation explicitly states that the rate of concentration change, $\frac{dC}{dt}$, is negative (indicating decay), and its magnitude is equal to the concentration C multiplied by some constant k. As a separable differential equation, it can be solved by reciprocating and integrating:

$$\frac{dt}{dC} = \frac{1}{-kC}$$
$$\int \frac{dt}{dC}\, dC = \int \frac{1}{-kC}\, dC$$

The left-hand side simplifies to t, as $\int \frac{dt}{dC}\, dC \implies \int \frac{dC}{dC}\, dt \implies \int 1\, dt = t$, while on the right, the constant factor $\frac{-1}{k}$ comes out the front of the integral to yield

$$t = \frac{-1}{k} \int \frac{1}{C}\, dC.$$

Using the identity $\int \frac{1}{x}\, dx = \ln|x| + C$, and given that concentration is always positive (such that $C \equiv |C|$), the differential equation can be thus solved for $C(t)$:

$$\begin{aligned} t &= \frac{-1}{k} \ln C + A \\ -kt &= \ln C - kA \\ kA - kt &= \ln C \\ e^{k(A-t)} &= C(t) \\ \therefore C(t) &= e^{kA} e^{-kt} \\ &= Be^{-kt}, \end{aligned}$$

where A is the constant of integration, and the constant term e^{kA}, written as B, represents the initial concentration of the drug, as $C(0) = Be^0 = B$. This solution represents exponential decay from an initial maximum at $t = 0$.

This function effectively models the pharmacokinetics of a single IV bolus dose. However, in the case of an orally administered

drug such as fluoxetine, as is seen in Figure 1, concentrations of the drug do not follow simple exponential decay. Rather, they increase from zero at $t = 0$, reaching a peak concentration C_{max} before decaying. This is because fluoxetine, as an oral drug, first enters the gastrointestinal (GI) tract before being absorbed into the bloodstream. This can be modelled by treating the GI tract as another container interacting with the first, resulting in a two-compartment model.

2.1.2 Modelling oral dosing with a two-compartment model

When dealing with multi-compartment models, it can be useful to use drug amount X, instead of concentration, which is useless when discussing exact drug doses. The total amount of drug in the bloodstream X_B can be related to concentration C using

$$X_B = C \times V_D,$$

where V_D signifies the volume of distribution of the drug in the body, a quantity specific to a given drug that specifies the volume of plasma through which a drug circulates (Best, 2023). Figure 3 is a diagram of a two-compartment model.

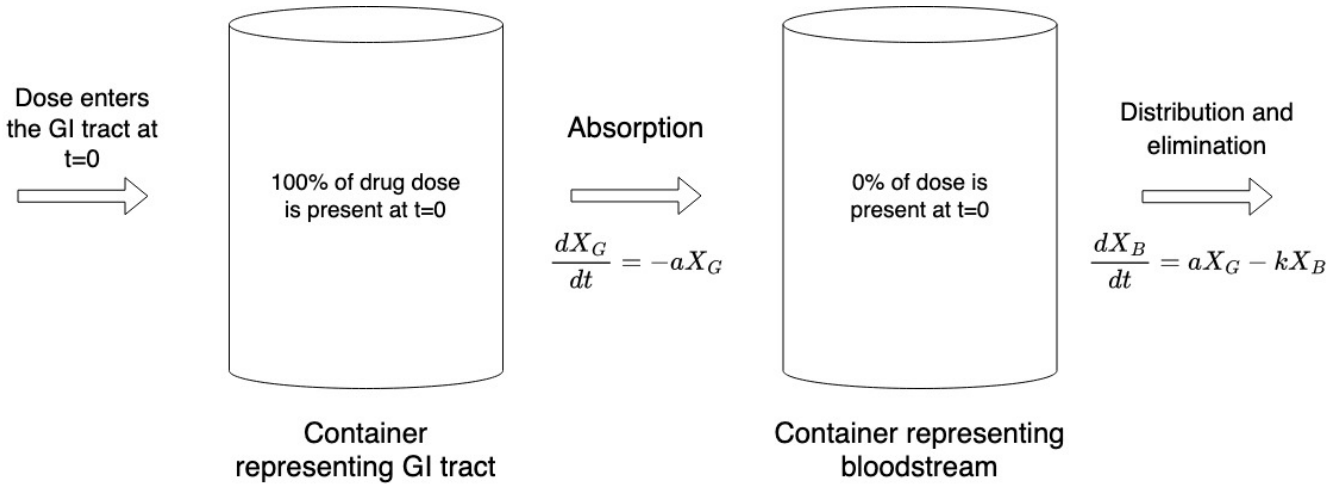


Figure 3: A diagram of a two-compartment pharmacokinetic model of oral dosing (own diagram)

In this model, 100% of the administered dose is present in the GI tract at $t = 0$, and is absorbed into the bloodstream at a rate proportional to the amount that remains in the GI tract. Therefore we can say, functionally identically to the one-compartment differential equation, that

$$\frac{dX_G}{dt} = -aX_G, \tag{1}$$

where X_G is the amount in the GI tract, and a is the rate constant of absorption. Furthermore, the drug is eliminated from the bloodstream at a rate proportional to the remaining bloodstream amount, so the rate of change of amount of drug in the bloodstream is the rate of elimination from the bloodstream subtracted from the rate of absorption from the GI tract. Thus,

$$\frac{dX_B}{dt} = aX_G - kX_B, \tag{2}$$

where X_B is the drug amount in the bloodstream, and k is the elimination rate constant.

The differential equation (1) is equivalent to that of the one-compartment model equation above, and so therefore has an

identical solution, exchanging $C \to X_G$ and $k \to a$:

$$\frac{dX_G}{dt} = -aX_G \iff \frac{dC}{dt} = -kC$$

$$\therefore C(t) = Be^{-kt} \iff X_G(t) = Be^{-at}.$$

As $B = X_G(0)$, the drug amount in the GI tract at $t = 0$, and $X_G(0)$ equals the entire dose administered, represented by D, this can also be written

$$X_G(t) = De^{-at}. \tag{3}$$

This solution equation (3) can be substituted into equation (2):

$$\begin{aligned}\frac{dX_B}{dt} &= aX_G - kX_B \\ &= a(De^{-at}) - kX_B\end{aligned}$$

As $X_B = V_D C$, where the volume of distribution is a constant parameter,

$$\frac{d}{dt}X_B = \frac{d}{dt}(V_D C) = V_D \frac{dC}{dt},$$

thus equation (2) can be written

$$V_D \frac{dC}{dt} = aDe^{-at} - k(V_D C),$$

and can be rearranged into the standard form of a linear differential equation:

$$\frac{dC}{dt} + kC = \frac{aDe^{-at}}{V_D}. \tag{4}$$

This differential equation is non-separable, so it cannot be solved in a similar manner to the one-compartment model equation. However, we can use the integrating factor method to solve this. For equations of the form

$$\frac{dy}{dx} + f(x)y = g(x),$$

where $f(x)$ and $g(x)$ are arbitrary functions in x only, the equation can be integrated by multiplying by an integrating factor $\mu(x)$, given by $\mu = e^{F(x)}$, where $F(x)$ is the antiderivative of $f(x)$, such that $F'(x) = f(x)$. In equation (4), the term kC corresponds to the $f(x)y$ term, where $C \equiv y$ and $f(x) \equiv k$, thus the integrating factor for equation (4) can be found like so:

$$IF = e^{F(x)} \Rightarrow e^{\int k\,dt} \Rightarrow e^{kt}$$

We can ignore the constant of integration here, as it cancels out during this process. We can then multiply equation (4) by the IF e^{kt}:

$$\frac{dC}{dt}e^{kt} + ke^{kt}C = \frac{aD}{V_D}e^{-at}e^{kt}$$

At this point, we have a complicated LHS. However, noticing that $ke^{kt} = \frac{d}{dt}e^{kt}$, the equation can then be written as:

$$\frac{dC}{dt}e^{kt} + \frac{d(e^{kt})}{dt}C = \frac{aD}{V_D}e^{-at}e^{kt}$$

This new LHS resembles the product rule $(uv)' = u'v + uv'$. If we let $u = C$ and $v = e^{kt}$, then $(Ce^{kt})' = C'e^{kt} + C(e^{kt})'$. Thus, we can simplify the LHS and rewrite the equation like so:

$$\begin{aligned}\frac{dC}{dt}e^{kt} + \frac{d(e^{kt})}{dt}C &= \frac{d}{dt}(Ce^{kt}) \\ \therefore \frac{d}{dt}(Ce^{kt}) &= \frac{aD}{V_D}e^{-at}e^{kt}.\end{aligned}$$

We can then integrate and simplify the equation like so:

$$\begin{aligned}\int \frac{d}{dt}(Ce^{kt})\,dt &= \int \frac{aD}{V_D}e^{(k-a)t}\,dt \\ Ce^{kt} &= \frac{aD}{V_D}\int e^{(k-a)t}\,dt \\ Ce^{kt} &= \frac{aD}{V_D(k-a)}e^{(k-a)t} + B,\end{aligned}$$

where B again represents the constant of integration for this operation. We can divide both sides by the integrating factor,

$$C(t) = \frac{aD}{V_D(k-a)}e^{-at} + Be^{-kt}, \tag{5}$$

then calculate the value of the constant term B using the initial condition that the initial bloodstream concentration is zero:

$$\begin{aligned}C(0) &= 0 \\ \therefore 0 &= \frac{aD}{V_D(k-a)}e^{0} + Be^{0} \\ B &= -\frac{aD}{V_D(k-a)}.\end{aligned}$$

And finally, we can substitute this term back into equation (5) to obtain a closed-form solution:

$$\begin{aligned}C(t) &= \frac{aD}{V_D(k-a)}e^{-at} + -\frac{aD}{V_D(k-a)}e^{-kt} \\ C(t) &= \frac{aD}{V_D(k-a)}(e^{-at} - e^{-kt})\end{aligned} \tag{6}$$

This biexponential factor ($e^{-at} - e^{-kt}$)—the difference between two exponential decay terms with different rate constants—is what underlies the characteristic plasma concentration-time curve in Figure 1 (Best, 2023). A graph of the function (6) using some arbitrary values of the constants with Desmos is shown in Figure 4.

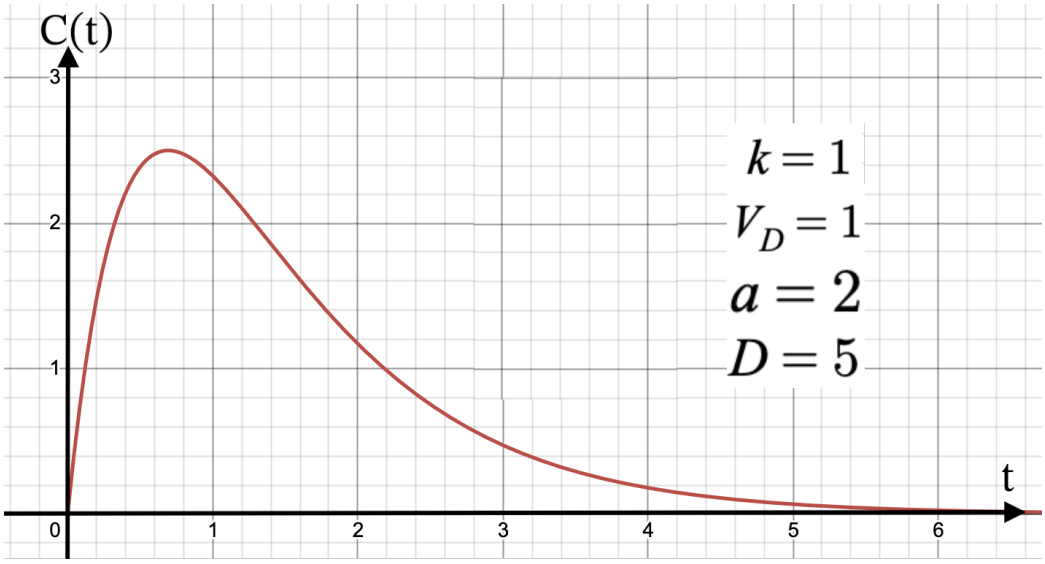


Figure 4: A graph of an arbitrary solution to the two-compartment model

2.1.3 Determining the pharmacokinetic parameters of fluoxetine

Now that a general concentration-time model of an orally administered drug has been established, it must be fit to model the fluoxetine data. Specifically, the parameters of fluoxetine a, k, and V_D must be solved for (Gabrielsson et al., 2016). One way of finding these is to computationally fit the model to existing data through regression. The data graphed in Figure 1 above, taken from a clinical trial comparing the pharmacokinetics of two brands of fluoxetine at doses of 40mg capsules in healthy male volunteers (Najib et al., 2005), will suffice. Though these properties can vary between individuals (Altamura et al., 1994), the averaged data from 24 volunteers in Najib et al. (2005) is a reasonable estimate of how the drug would behave in an otherwise healthy male, which I am.

In order to extract the data from the graph, the online software plotdigitizer.com was used to convert the Prozac brand (the brand I take) points to a list of x, y values (see Appendix A), where the x-values represent time (in hours) and the y-values represent plasma concentration (in ng/mL). Then, the non-linear least-squares method of curve fitting was used to determine the optimum parameters of the biexponential model in equation (6), with the dose D fixed at 40 milligrams to match the clinical condition. (The code is contained in Appendix B.)

The curve fitting algorithm found that the following parameters for a, V_D, and k produced a biexponential curve that fit the empirical data to a coefficient of determination value of $R^2 = 0.9413$. A graph comparing the datapoints taken from Najib et al. (2005) with the fitted two-compartment model function (7) is shown in Figure 5.

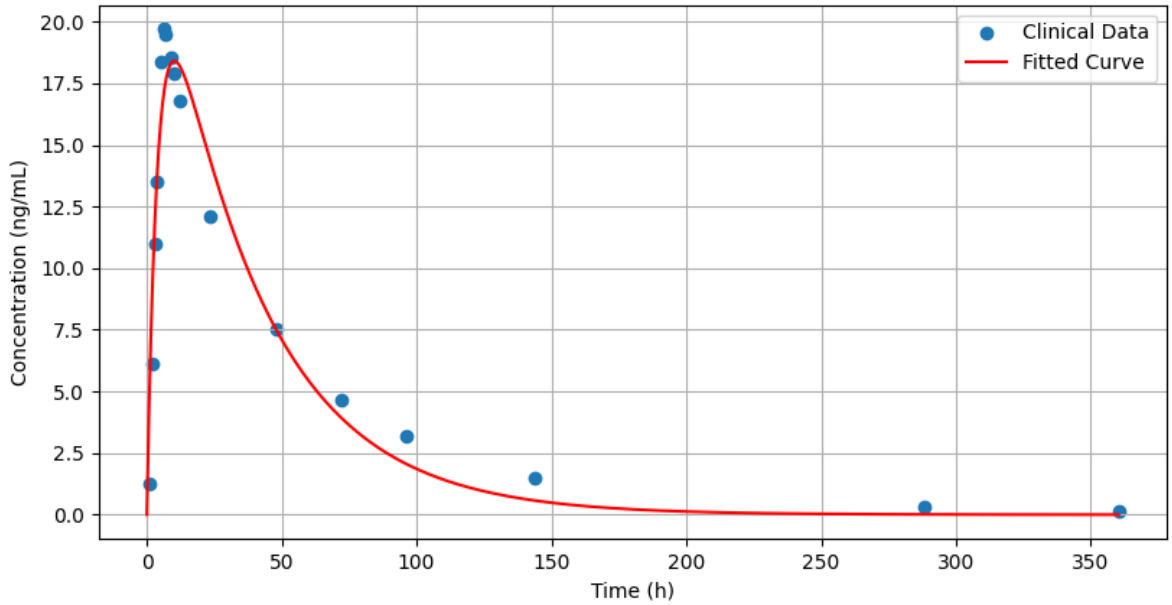


Figure 5: Biexponential model with optimum parameters for fluoxetine

Table 1: Optimum parameters for fluoxetine two-compartment curve (unitless)

a	k	V_D
0.02681751	0.24453773	0.18143838

This yields the function

$$\begin{aligned} C(t) &= \frac{0.02681751D}{0.18143838(0.24453773 - 0.02681751)}(e^{-0.02681751t} - e^{-0.24453773t}), \\ &= 0.678876D(e^{-0.0268175t} - e^{-0.244538t}). \end{aligned} \tag{7}$$

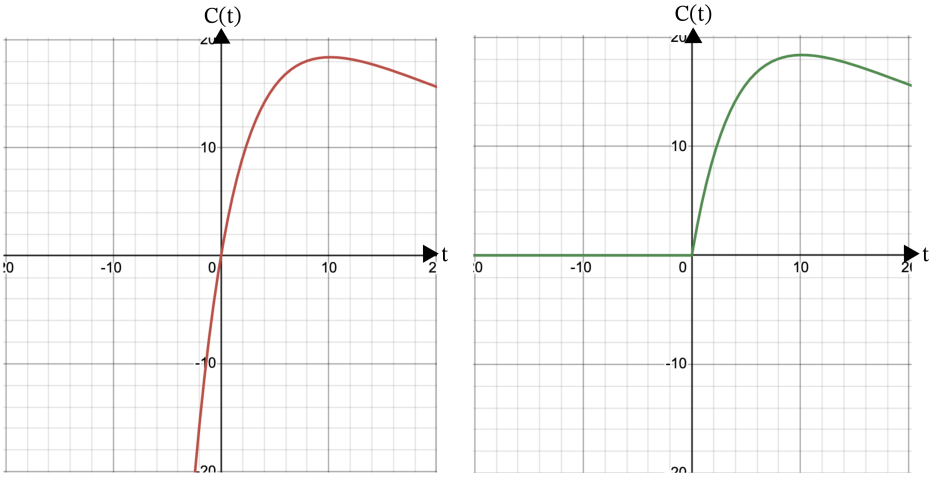
This function (7), then, is the solved two-compartment model, fine-tuned for fluoxetine. It gives the concentration of fluoxetine in the bloodstream, t hours an oral dose of D mg is administered, for $D > 0, t > 0$. (That the concentration is in nanongrams per litre while the dose is in milligrams is intentional—these are standard units for drug concentration and dosages.)

However, there is one further consideration: for values of $t < 0$, the function (7) does not accurately describe concentration. Before the drug is administered, the concentration should logically be zero, yet for $t < 0$, $C(t) < 0$, per Figure 6(a). To improve the accuracy of the model, we can use a piecewise definition to set $C(t) = 0$ for $t < 0$, producing the graph in Figure 6(b):

$$C(t) = \begin{cases} 0.678876D(e^{-0.0268175t} - e^{-0.244538t}) & \text{if } t \geq 0 \\ 0 & \text{if } t < 0 \end{cases} \tag{8}$$

Though limiting the domain of $C(t)$ to $t \geq 0$ achieves a visually similar result, it is in inaccurate, as the concentration

is simply zero, not undefined, before drug administration. This becomes relevant below when using the sum of horizontally offset concentration functions (e.g., $C(t)+C(t-N)+C(t-2N)\ldots$) to model repeated oral doses; the lower bound of the domain of this sum function is the time the most recent dose is given. Defining it as equal to zero before the administration ensures the concentration is modelled for all $t \geq 0$, and indeed, all $t \in \mathbb{R}$.



(a) Non-piecewise form (b) Piecewise form

Figure 6: Piecewise and non-piecewise forms of the biexponential model

2.1.4 Modelling repeated oral dosage

If we wish to examine the activity of fluoxetine as it causes withdrawal over time, we must model the concentration with time of repeated oral doses. Assuming that a dose D of fluoxetine is taken every τ hours, then the total plasma concentration t hours after the first administration, $C_r(t)$, can be thought of as the sum of multiple single-dose fluoxetine curves, each offset by τ hours:

$$C_r(t) = \sum_{n=0}^{\infty} C(t-n\tau) = C(t) + C(t-\tau) + C(t-2\tau) + \ldots$$

This assumes a dose is taken every τ hours for eternity. In practice, we can set a finite maximum value of n, say N, in the summation corresponding to the total number of concurrent doses administered. To sum the piecewise function using Desmos, it is necessary to rewrite it as an ordinary function. This can be done using the Heaviside step function $H(x)$ (Dawkins, 2022):

$$H(x) = \begin{cases} 0 & \text{if } x < 0 \\ 1 & \text{if } x \geq 0 \end{cases}$$

We can multiply the $t \geq 0$ case from equation (8) by $H(t)$ to attain the same function without multiple pieces. For $t \geq 0$, $H(t) = 1$, leaving $C(t)$ unaffected, and for $t < 0$, $H(t) = 0$, making $C(t) = 0$.

$$C(t) = 0.678876D(e^{-0.0268175t} - e^{-0.244538t})H(t) \tag{9}$$

Thus, we can rearrange the polynomial sum:

$$C_r(t) = \sum_{n=0}^{N-1} C(t-n\tau)$$

$$= \sum_{n=0}^{N-1} [0.678876D(e^{-0.0268175(t-n\tau)} - e^{-0.244538(t-n\tau)})H(t-n\tau)]$$

$$= 0.678876D \sum_{n=0}^{N-1} [(e^{-0.0268175(t-n\tau)} - e^{-0.244538(t-n\tau)})H(t-n\tau)] \quad (10)$$

(The upper bound of the sum is set to $N-1$ to represent N months, as the count begins at 0 instead of 1.) The graph of (10) for once-daily dosing ($\tau = 24$) of 1 Prozac capsule ($D = 20$) over 30 days ($N = 30$) is shown in Figure 7.

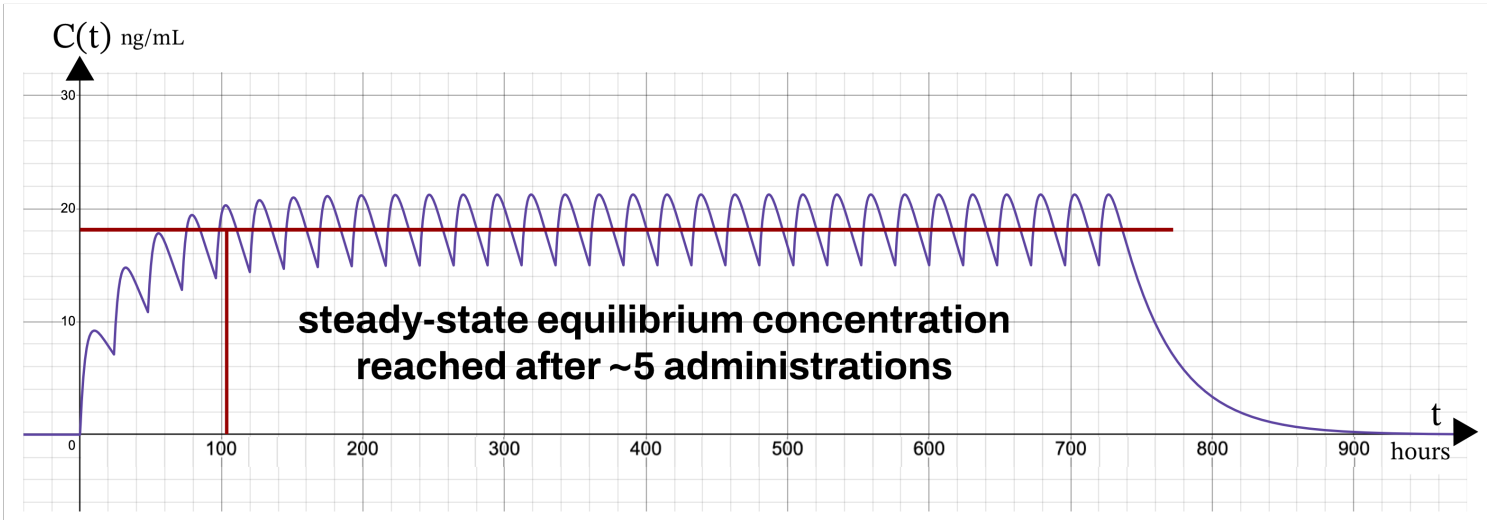


Figure 7: Concentration-time graph of daily 20mg fluoxetine over a month

A clear feature of the graph in Figure 7 is that after ~5 administrations, the concentration fluctuates around an apparently constant equilibrium concentration until dosing is ceased, after which it gradually decays. This property will be useful later when analysing this graph in terms of the biological substrates upon which fluoxetine acts.

2.2 Modelling the action of fluoxetine in the brain

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is thought to exert its antidepressive effects primarily by inhibiting serotonin transporters, proteins in the brain that reduce levels of the neurotransmitter serotonin (Sohel et al., 2024). Furthermore, it is also thought that antidepressant withdrawal symptoms are caused by the abrupt drop in serotonin levels that occurs when the antidepressant is stopped and SERT is thus disinhibited (Sohel et al., 2024). The brain contains many SERTs, and a drug's effect on them is generally quantified as the proportion of the SERTs that the drug inhibits, referred to as percentage occupancy.

Counterintuitively, the relationship between the concentration of fluoxetine in the blood and its occupancy of SERTs is not linear, but rather hyperbolic (Sørensen et al., 2022). Figure 8 is a scatter plot, adapted from Sørensen et al. (2022), showing the observed relationship between the fluoxetine dose and the percentage of the serotonin transporters occupied in a part of the brain, after a month of someone taking that dose every day. Per Figure 7, equilibrium concentrations are reached after only about 5 doses given 24 hours apart, so fluoxetine concentrations at 30 days in should reflect those at any point after 5 days of daily administration ("chronic dosing").

In biological modelling, enzyme kinetic reactions such as this are often modelled using the Michaelis-Menten model, a type of hyperbolic function (Sørensen et al., 2022):

$$f(x) = \frac{V_m x}{K + x} \tag{11}$$

where $f(x)$ represents the receptor occupancy proportion for a dose x, V_m represents the maximum occupancy possible, and K is the dose which causes occupancy equal to 50% of V_m. The use of this function in modelling fluoxetine is justified, as the curve plotted in Figure 8 was produced by nonlinear least squares regression using the Michaelis-Menten equation, and yielded a strong fit of $R^2 = 0.939$ for the following parameters: $V_m = 86.12, K = 1.89$ (Sørensen et al., 2022). (Full data can be found in Appendix C.) With this, we have now a model that relates the dose of fluoxetine taken to the level of SERT occupancy in the brain produced, during chronic dosing.

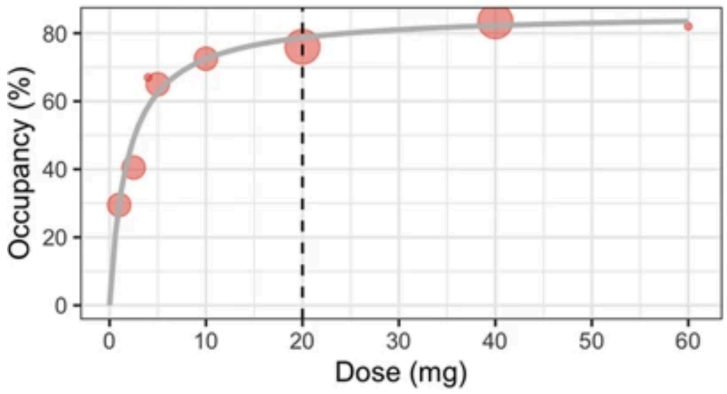


Figure 8: Plot of fluoxetine dose vs SERT occupancy (Sørensen et al., 2022)

This relationship is significant because, per Figure 8, tapering the antidepressant dose by decreasing in fixed increments will lead to disproportionate decreases in SERT occupancy. Per Appendix C, a dramatic 30mg dose reduction from 40mg to 10mg will only decrease SERT occupancy by 11%, while a small decrease of just 3mg (4mg to 1mg), will decrease SERT occupancy by 37.5%. Thus, it is clear that this must be considered when designing a taper.

Additionally, it is important to identify the rate at which SERT occupancy should be decreased to prevent withdrawal symptoms. In research, much research has converged on 10% reductions in SERT occupancy at each step, commonly weekly or monthly, to prevent withdrawal (Ruhe et al., 2019). Monthly changes were associated with a reduced incidence of antidepressant withdrawal syndrome, so I will use this recommendation.

2.3 Finding the optimal fluoxetine taper to prevent withdrawal

With these quantities and their relationships in mind (see Figure 9 for a summary), we can mathematically design an ideal taper regimen to help me cease my daily 20mg fluoxetine while avoiding antidepressant withdrawal syndrome.

2.3.1 Fluoxetine dosing regimen in terms of target SERT reduction

With a target of 10% SERT reduction per month (= 24 hours/day $\times$ 30 days/month = 720h), we can use the Michaelis-Menten equation with the fluoxetine-specific parameters above to calculate the corresponding dose of fluoxetine desired per month.

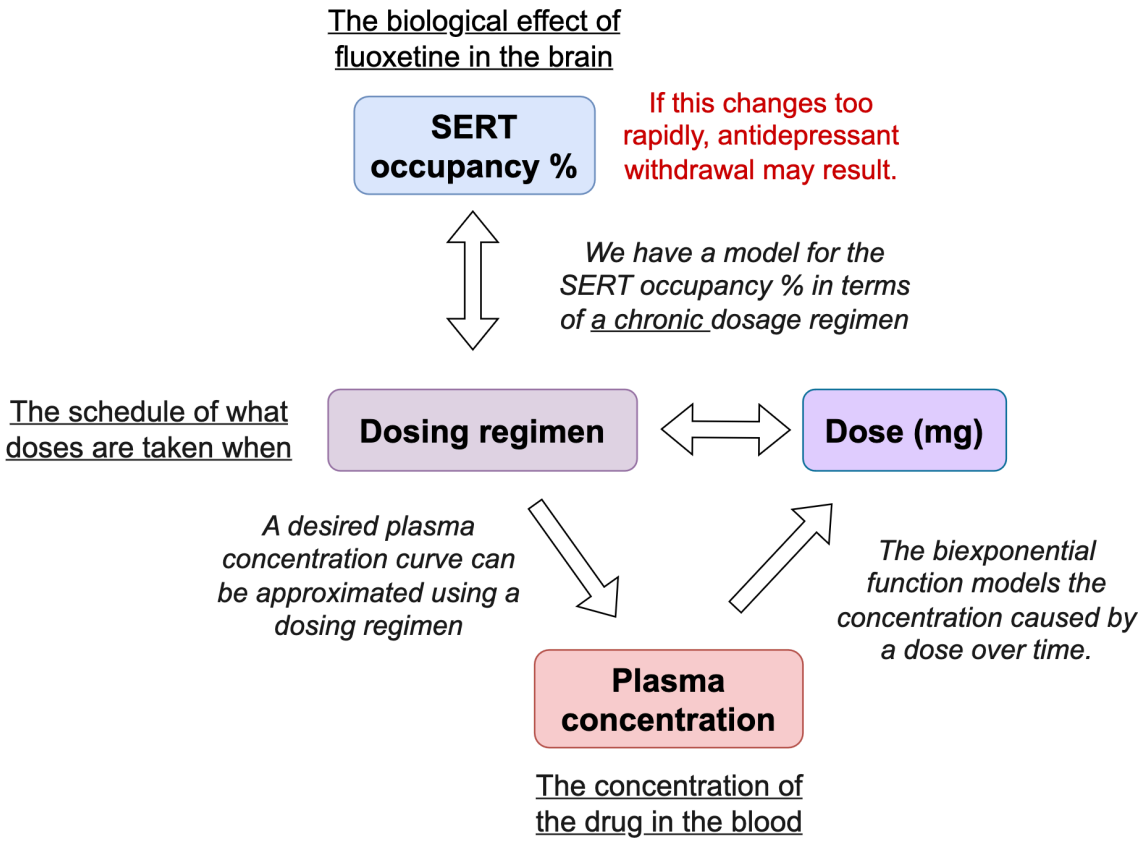


Figure 9: Summary of quantities and their relationships pertinent to tapering

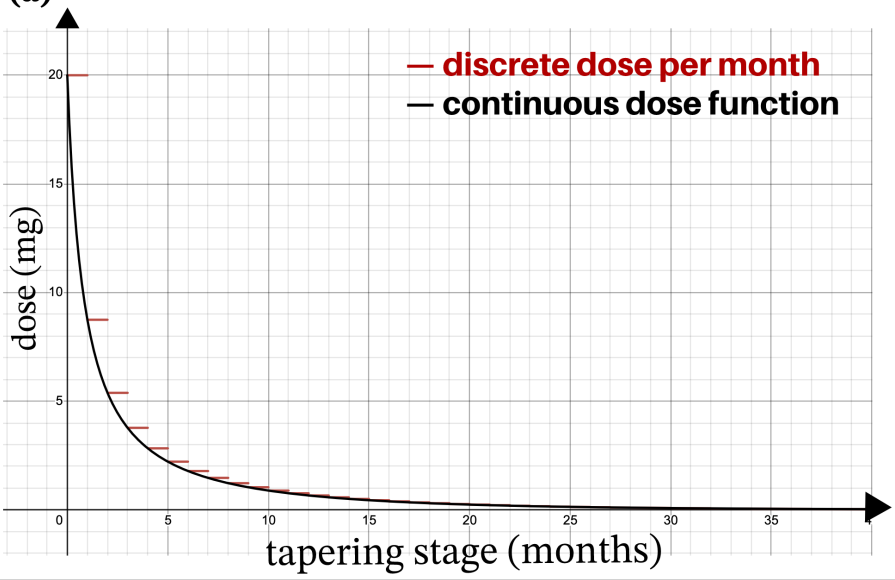
The equation for my target daily dose $D(n)$ milligrams of fluoxetine n months into the taper (where $n \in \mathbb{N}$) would be

$$D(n) = f^{-1}(0.9^n f(20)), \tag{12}$$

where $f(x)$ and $f^{-1}(x)$ are the function and inverse of the function (11), respectively, with the above fluoxetine parameters. This function takes the SERT occupation induced by the initial 20mg dose of fluoxetine $f(20)$, applies a 10% exponential decay for n months (0.9^n) and then uses the inverse function $f^{-1}(x)$ to find which dose would produce the reduced occupation. Thus, the function prescribes a daily dose of fluoxetine, which changes each month, to produce a 10% step-wise decrease in dose each month. The graph of this function (12), is shown in Figure 10(a). Although this curve is continuous, we only care about the (discrete) monthly doses, given by $D(n)$ for $n \in \mathbb{Z}^+$, which are shown in Figure 10(b).

The dosing schedule outlined by (12) is optimal in that following it would produce a 10% monthly reduction in SERT occupancy to prevent withdrawal. However, it is not overly practical, in that per the chart, maintaining the desired 10% reduction in SERT occupancy would require extremely precise dose increments. Fluoxetine is available only in 20mg formulations, some of which may be broken into 10mg halves or 5mg quarters, which is not sufficient for making such fractional adjustments to the dose. Furthermore, the nature of the exponentially decaying dosing this plan uses means that, even if I were able to obtain arbitrarily specific dosages of fluoxetine, the taper would never end; I would have to keep taking ever-decreasing microscopic doses of fluoxetine forever. Clearly, this is not a practical regimen.

(a)



(b)

n	D(n)
0	20
1	8.7457868
2	5.3812475
3	3.7698355
4	2.8286742
5	2.2144078
6	1.7839632
7	1.467097
8	1.2252819
9	1.035619
10	0.88364138

Figure 10: Graph and table of monthly dose increments to achieve 10%/month SERT taper

2.4 Evaluating the suitability of recommended antidepressant cessation regimens

2.4.1 Target plasma concentrations from ideal dosing regimen

Though it may be infeasible to adhere to the optimal regimen above, we can model the concentration of fluoxetine it would produce in the bloodstream, and then search for more convenient regimens that approximate this ideal concentration curve. In order to do this, we will need to modify the fluoxetine dose-concentration function (10). Specifically, this new function, $C_{\text{mr}}(t)$ (**C**oncentration of **m**onthly **r**egimen) must have reached the equilibrium concentration associated with a 20mg dose before $t = 0$ (as I have been taking fluoxetine for years), and incorporate both the monthly dose changes according to the function (12) and the constant daily dosing within the monthly interval. For sake of convenience, we will henceforth use a 30-day month.

First, let $C_r(t; D, N, \tau)$ represent the repeated dosing function from (10), except now it is:

- Parameterised for a dosage D mg given N times at intervals spaced τ hours apart, and
- Defined piecewise (again!) to be equal to the regular $C_r(t)$ function if $t > 0$, and to zero if not. This ensures the concentration exists, and that $\forall t \in \mathbb{R}, C_r(t)$ is defined.

Furthermore, let $D(n, D_0)$ refer to a parameterised form of the dose-taper function (12) for any starting dose D_0, that gives the nth month's fluoxetine dose for a 10% SERT decrease:

$$D(n, D_0) = f^{-1}(0.9^n f(D_0))$$

Therefore, the concentration curve produced by a month of administering an arbitrary dose D_0 every 24 hours is represented by $C_r(t; D_0, 30, 24)$. To model a changing dose, starting at 20mg every month for M months with the function $C_{\text{mr}}(t)$,

we can write:

$$C_{\text{mr}}(t) = \sum_{m=0}^{M-1} C_r((t - 720m)\,, D(m, 20), 30, 24) \tag{13}$$

This in turn makes use of the Michaelis-Menten function (11), $f(x)$, and its inverse function $f^{-1}(x)$, using the fluoxetine-specific parameters identified by Sørensen et al. (2022).

The function (13) models, from $m = 0$ to $m = (M-1)$ months, 30 days of daily oral dosing using that month's appropriate daily dose as determined by $D(m, 20)$. Then, each successive month's concentration curve is offset from the last by 30 days = 720 hours so that they are equally spaced along the x-axis. However, per Figure 11(a), it does not start from $t = 0$ at an equilibrium concentration, but must build up to it during the yellow highlighted period of time. A simple way to fix this would be to add a duplicate of the 0th month concentration term and offset it by 720 hours in the direction of the $-x$ axis, such that by $t = 0$ there has been daily dosing for one month prior:

$$C_{\text{mr}}(t) = \sum_{m=0}^{M-1} [C_R((t - 720m)\,, D(m, 20), 30, 24)] + C_R((t + 720)\,, D(0, 20), 30, 24) \tag{14}$$

The choice of one month of prior fluoxetine therapy is arbitrary, as it is apparent from Figure 7 that the equilibrium concentration is established after approximately 5 administrations. The graph of (14) is shown in Figure 11(b).

2.4.2 Modelling and testing the recommended tapering regimens

Knowing the ideal fluoxetine concentration-time course for preventing withdrawal, we can model and compare various recommended tapering programs on the extent to which their plasma concentration trajectories approximate the ideal. While it would be ideal to mathematically design from the bottom up a dosing regimen based on the available doses of fluoxetine and the ideal curve, this problem is fundamentally hard, in the computational sense: to simply compare every possible combination of doses—say there were 5 options, 0mg, 5mg, 10mg, 15mg, and 20mg, over 365 days—would require calculating the concentration curve for 5^{365} different permutations—incomprehensibly larger than the number of atoms in the universe, ~10^{80} (Kiernan, n.d.). As a result, it is more sensible to compare existing regimens—as it were, other people have, through experience, narrowed the search space.

Though the ideal hyperbolic taper in theory continues forever, asymptotically approaching zero, a majority of recommended tapering plans take less than 6 months, so I will compare them within the interval $t = 0$ to $t = 6 \times 30 \times 24 = 4320$ days. Some plans begin with an initial month of regular dosing, while others immediately begin a taper. The ideal concentration function C_{mr} and many other tapering regimens were constructed in the former way, so for fair comparison of dosing with time, tapering regimens of the latter sort will be adjusted to fit this standard when creating functions.

Clinical guidelines' tapering regimens were gathered from the review "Clinical practice guideline recommendations on tapering and discontinuing antidepressants for depression: a systematic review" by Sørensen et al. (2022). Many of these guidelines

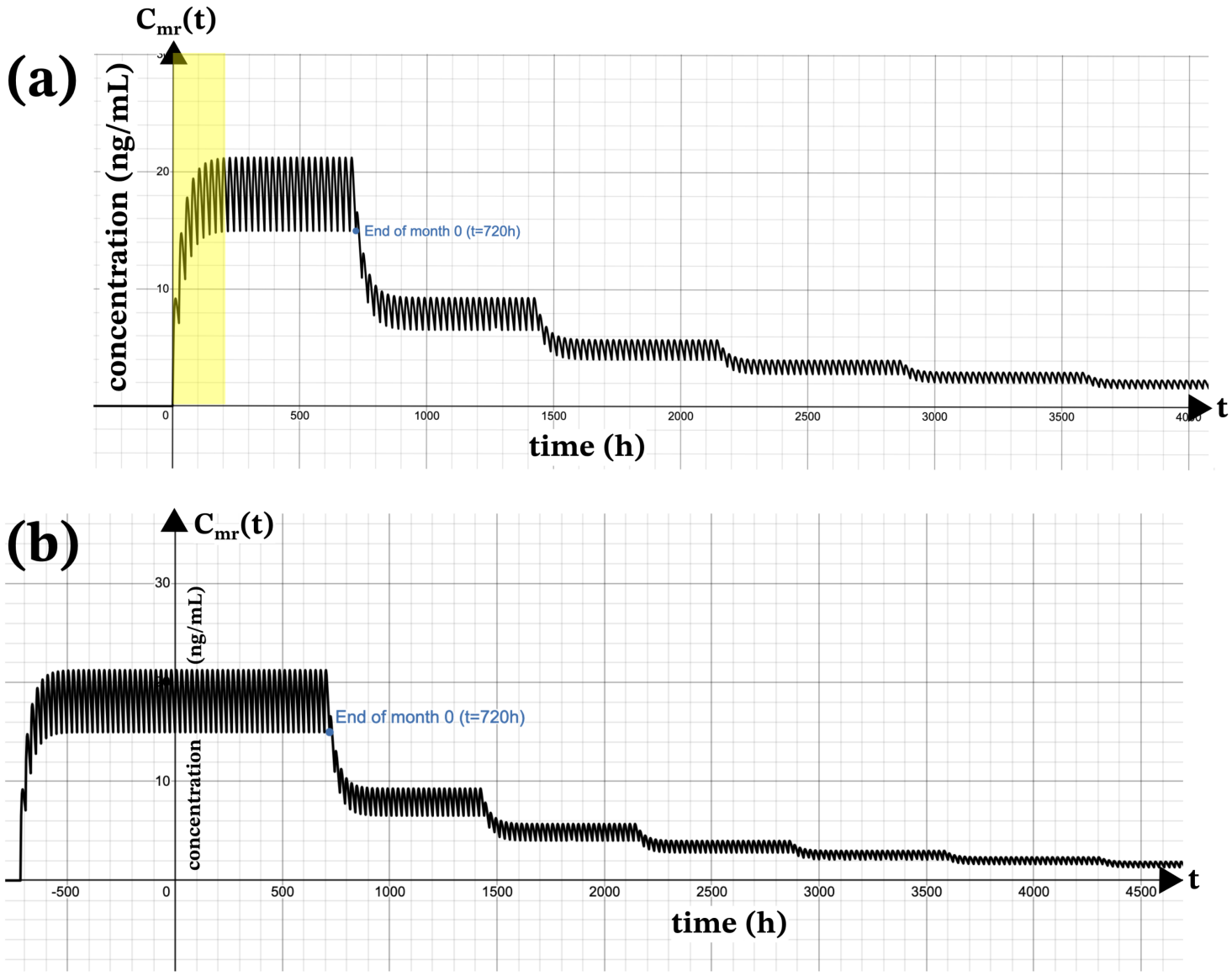


Figure 11: The ideal fluoxetine tapering concentration curves with (b) and without (a) steady-state reached at t=0

were equivocal or vague in terms of dosing plans. Other tapering regimens were obtained from an online tool, drugtaper.com, which purports to design an optimal individualised tapering regimen based on the specific drug taken, the starting dose, the desired duration of the taper (6 months), available dose increments (quartered 20mg tablets, or 5mg), and the desired tapering approach (with options such as 'exponential', 'linear', and 'hyperbolic'). The complete dosing regimens this website provided can be found in Appendix D. The table in Figure 12 below compares the various tapering recommendations, the resulting concentration functions they produce, and the MSE (mean-squared error) value between each recommended concentration curve and the ideal concentration curve over a six-month interval starting at $t = 0$. The MSE is a measure of closeness of approximation, quantifying the total absolute deviation of candidate functions' values from the ideal's over time. This is calculated by the program in Appendix E, which will compare the functions' values every hour over the interval (4320 comparisons in total).

Concentration functions were produced using the parameterised repeated concentration function. For example, the UK NICE guidelines' function is given by

$$C(t) = C_r(t + 720; 20, 30, 24) + C_r(t; 20, 30, 24) + C_r(t - 720; 20, 15, 48),$$

where the first term establishes a month of dosing prior to $t = 0$ to achieve steady state, the second represents the 0th month of 20mg daily dosing, and the third represents the alternate-day dosing pattern they recommend (detailed explanations of each guidelines' translation to a concentration curve, and Python code, are given in Appendices D and E respectively). When the intervals between dose changes are not explicitly stated, one month intervals will be used, as recommended by Ruhe et al., (2019).

Source	**Recommendation**	**Interpretation**	**MSE**
NICE clinical guidelines (UK)	"Fluoxetine's prolonged duration of action means that it can sometimes be safely stopped in the following way: in people taking 20 mg fluoxetine a day, a period of alternate day dosing can provide a suitable dose reduction..." (NICE, 2022)	20mg daily for the 0th month; 20 mg once every two days (48h) for the 1st month; and 0mg from the second month onwards.	9.516
	Function: $C(t) = C_r(t + 720; 20,30,24) + C_r(t; 20,30,24) + C_r(t - 720; 20,15,48)$		
RANZGP clinical guidelines (AU/NZ)	"...the first step is to reduce the dose to the minimal effective dose. Following this, the dose should be halved, and after a week, the dose should be reduced more slowly in small decrements (allowing 2 weeks for each dose reduction), according to how the tablet can be divided." (Malhi et al., 2021)	20mg daily for the 0th month (minimal effective dose); 10mg daily for one week; 5mg for two weeks (smallest division); then cessation.	12.49
	Function: $C(t) = C_r(t + 720; 20,30,24) + C_r(t; 20,30,24) + C_r(t - 720; 10,7,24) + C_r(t - 888; 5,14,24)$		
DrugTaper website: Linear taper	Used online tapering calculator website *DrugTaper.com* to generate a tapering regimen based on the following parameters: current daily dose = 20mg, tapering duration = 180 days (6 months), tapering method = linear. Gave list of doses for 180 days (see Appendix D). Converted into an array of doses D_L and used a sum to index $D_L[n]$ for $n \in [0,180]$: *Function*: $C(t) = C_r(t + 720,20,60,24) + \sum_{n=0}^{180} C_R(t - 24(n + 30), D_L[n], 1,24)$		30.21
DrugTaper website: Hyperbolic taper	Used online tapering calculator website *DrugTaper.com* to generate a tapering regimen based on the following parameters: current daily dose = 20mg, tapering duration = 180 days (6 months), tapering method = hyperbolic. Gave list of doses for 180 days (see Appendix D). Converted into an array of doses D_L and used a sum to index daily doses, $D_H[n]$, for $n \in [0,180]$: *Function*: $C(t) = C_r(t + 720,20,60,24) + \sum_{n=0}^{180} C_R(t - 24(n + 30), D_L[n], 1,24)$		2.134

NB: All concentration curves include one month of daily dosing at 20mg prior to t=0 (month -1) to establish a steady state level. MSE quoted to 4 significant digits.

Figure 12: The MSE values of various tapering routines' plasma values vs. the ideal

Figure 13 provides a graphical comparison of the various taping regimens compared to the ideal.

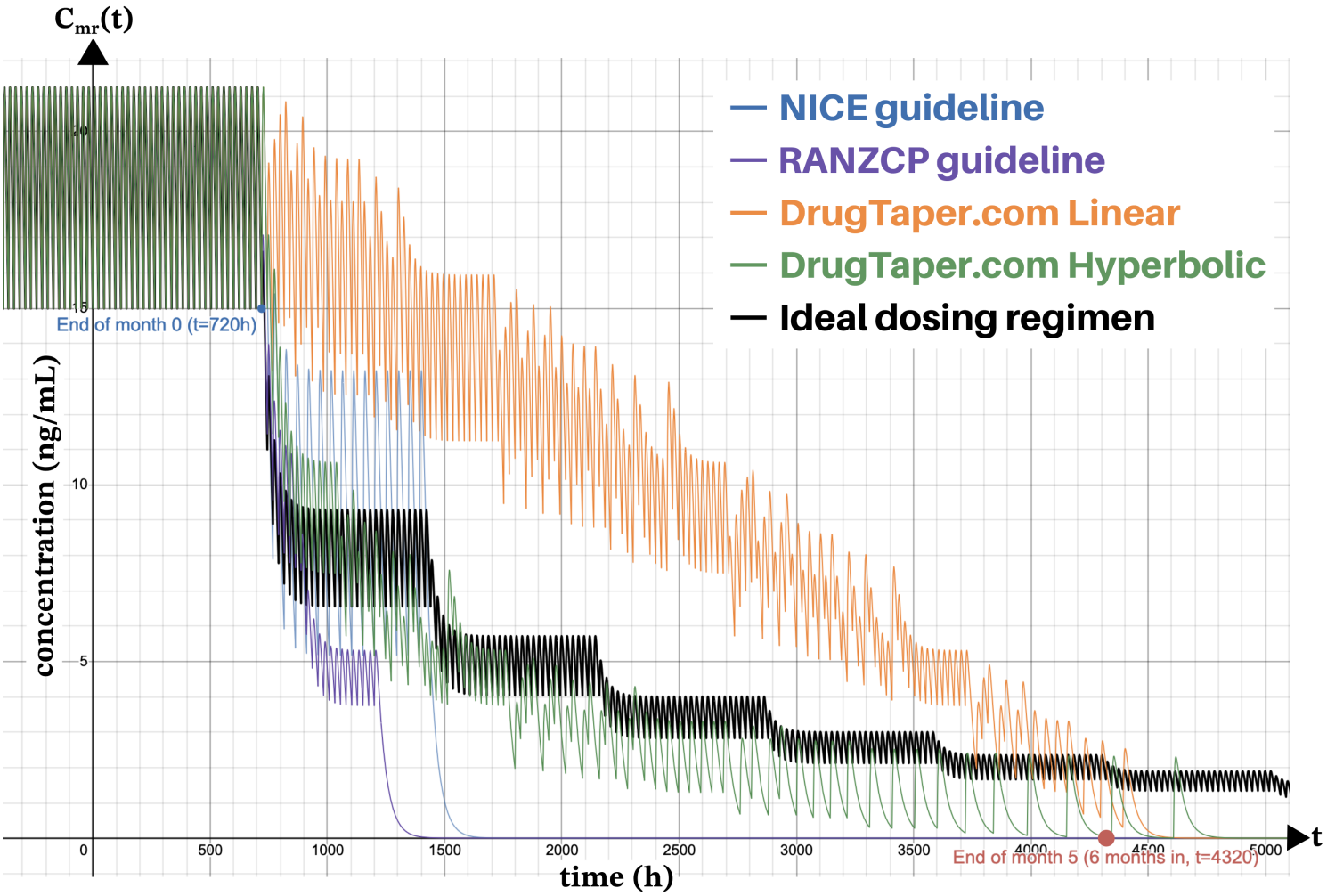


Figure 13: Graph of various tapering routines' plasma concentrations vs the ideal

As can be seen from the table, the regimen with the lowest MSE in plasma concentrations compared to ideal plasma concentrations is given by the DrugTaper.com hyperbolic taper. For my dosage, the specific series of doses it recommends (see Appendix E) very closely matched the ideal plasma concentrations, as can be qualitatively appreciated from the graph in Figure 13, as well as its MSE of 2.134, the lowest identified. Furthermore, while the two clinically recommended tapers from the UK's NICE and Australia/New Zealand's RANZCP initially approximate the ideal curve reasonably well, they both drop to zero plasma concentration far earlier than the ideal curve, producing subpar MSEs of 9.516 and 12.49 respectively. Perhaps clinical wisdom is accurate, and there is little harm in dropping from these lower concentrations to zero after some step-wise decrements over a few months; there is insufficient data to determine this. However, what can be said is that the best way to completely avoid withdrawal syndrome, according to the established dose-response relationships of fluoxetine, is to follow the "hyperbolic" tapering routine given, in Appendix D, by DrugTaper.com.

Curiously, the "linear" taper option from DrugTaper.com is notable for having the highest MSE of all routines tested. Despite achieving a smooth, approximately linearly decreasing dose trajectory by modulating doses that certainly appears more "gradual" than several other options in Figure 13, it had a very high MSE of 30.21.

2.5 Conclusion

The aim of this exploration was to model the relationship fluoxetine dosing, its concentration in the body, and its effects, to help me find a dose tapering regimen to prevent the incidence of antidepressant discontinuation syndrome. Using differential equations, a two-compartment pharmacokinetic model of drug concentration vs time for a given dose was derived, and fine-tuned based on clinical data. Next, this model was extended and parameterised to model multiple doses taken at regular occurring intervals.

Using biological data, I investigated the relationship between the dose of fluoxetine taken and the corresponding effect it has on the brain. Finding this relationship was hyperbolic, I found a hyperbolic Michaelis-Menten model to describe it. Then, I designed a function, using the dose-response function and its inverse function, that would give nth dose necessary to achieve the recommended 10% step-wise reduction in SERT occupancy.

This dosing function thus outlined an ideal fluoxetine tapering regimen; however, it required impractically precise dose adjustments, so I instead modelled the plasma concentrations that the ideal tapering regimen would produce, then compared it to the plasma concentration curves produced by several popular regimens, to find the optimum practical tapering regimen. The practical tapering regimen which best approximated the ideal regimen was the hyperbolic taper given by the online calculator DrugTaper.com (Appendix D).

3 Evaluation and reflection

On the whole, the exploration was successful, as I was able to mathematically model the dose-response and dose-concentration relationships of fluoxetine, and combine this with clinical data to produce an ideal concentration curve. I then was able to compare numerous popular tapering regimens to the ideal curve, to find the one closest to the ideal hyperbolic concentration decrease. The tapering regimen which I identified very closely matched the ideal function, and I now feel confident in my ability to taper and quit fluoxetine when I need to, without fear of withdrawals. However, these results are not without their caveats.

While the two compartment model's use is generally justified in modelling oral dosing, some research suggests fluoxetine's metabolism and activity are significantly more complicated than can be represented by a two-compartment system. This is because fluoxetine inhibits the enzyme that metabolises it, causing higher concentrations of the drug (Altamura et al., 1994). As a result, the half-life of fluoxetine depends on how much is already present in the body, and fluoxetine has a nonlinear pharmacokinetic profile, meaning that higher doses of fluoxetine are associated with plasma concentrations disproportionately higher than lower doses (Altamura et al., 1994). However, the two-compartment model that I fit to the clinical data of fluoxetine has dose D as a linear parameter, encoding the implicit assumption that the concentration function, which was fitted to data taken from a study of 40mg fluoxetine dosing, would be able to model a 20mg dose by linearly scaling the

output. With nonlinear pharmacokinetics, this may not be valid, thus potentially invalidating the concentration curve used for my 20mg dose. Additionally, modelling the entire body as two homogeneous volumes is a simplification that may not accurately represent the mechanics of the drug's metabolism. This may explain why, although the two-compartment model closely modelled the empirical concentration curve, with a coefficient of determination of $R^2 = 0.9413$, the shape of the curve did not perfectly fit the data; several datapoints were not on the line in Figure 5.

Another limitation is the lack of available research on the mechanisms underlying antidepressant withdrawal. Though there is some empirical evidence to support hyperbolic tapering, many questions are still raised. What rate of SERT occupancy reduction is ideal for reducing withdrawal? How often should doses be decreased? At what point is the SERT occupancy so low that the hyperbolic taper can be abandoned, instead of asymptotically approaching zero but never reaching it? I have not been able to find evidence-based answers to these, so instead I have relied upon somewhat arbitrary 'best practice' guidelines, like aiming for 10% reduction in SERT occupancy every month, or tapering for no longer than six months. Whether these assumptions are accurate is not clear.

Furthermore, the use of mean-squared error (MSE) in comparing candidate regimens' concentration curves to the ideal's prompts further consideration. While MSE is generally a fine way of quantifying the extent to which one function matches another, it is worth considering what degree of 'similarity' with the ideal curve is most important for preventing withdrawal. Is it simply the absolute distance between the function and each point, as the MSE quantifies, or is it some other quantity, such as the slope of the curve, that is most important here? How much deviation from this curve is acceptable? For instance, both clinical guidelines' curves significantly differ from the ideal curve in duration, yet still score favourably in terms of MSE compared to the linear taper, despite the fact that the linear taper's concentration trajectory appears qualitatively much more gradual than the guidelines'. It is not apparent whether or not MSE appropriately captures the unsuitability of a dosing regimen—perhaps other metrics, informed by neurobiology, could provide a more accurate picture.

Finally, the chemical that fluoxetine is partially metabolised into, norfluoxetine, has similar effects to fluoxetine with a longer half-life, which could potentially serve to cushion withdrawal by prolonging the combined half-life of these chemicals in the body (Altamura et al., 1994). This could explain why many medical guidelines recommend much shorter tapers than what this investigation would identify as ideal; the drug could (to an extent) 'taper itself' in the body. To accurately model this, future investigations could model a proportion of the fluoxetine eliminated from the body being added back into the bloodstream as norfluoxetine, before being eliminated itself (into an inactive form) at a rate proportional to its remaining amount. Given Y_B is the amount of norfluoxetine in the bloodstream, we can write

$$\frac{dY_B}{dt} = \lambda k X_B - j Y_B,$$

namely that the rate of change of norfluoxetine amount is equal to a proportion (denoted by λ) of the rate of fluoxetine's

elimination (kX_B, from equation (2)), minus the rate of norfluoxetine's own elimination, with rate constant j. However, the solution of this extended model is beyond the scope of this investigation.

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Appendix A — Fluoxetine concentration time-series data

Table 2: Concentration of fluoxetine vs time

Time (h)	Concentration (ng/mL)
1.001	1.252
2.002	6.093
3.003	10.98
3.670	13.48
5.004	18.36
6.339	19.70
7.006	19.49
9.008	18.53
10.01	17.90
12.01	16.82
23.69	12.10
48.04	7.513
72.06	4.674
96.08	3.172
143.8	1.503
288.2	0.2922
360.3	0.1252

Adapted from Najib, et al. (2005) using plotdigitizer.com. Values quoted to 4 significant figures.

Appendix B — Python code to perform curve-fitting of fluoxetine data onto biexponential function

The following code uses the `numpy`, `scipy`, and `matplotlib` Python modules to perform non-linear least-squares curve-fitting of the data taken from a graph by Najib, et al. (2005).

```
import numpy as np
import matplotlib.pyplot as plt
from scipy.optimize import curve_fit

x_values = [1.00083402835696,2.00166805671392,3.00250208507089,3.6697247706422,5.00417014178482,
6.33861551292743,7.00583819849874,9.00750625521267,10.0083402835696,12.0100083402835,
23.6864053377814,48.0400333611342,72.0600500417014,96.0800667222685,143.786488740617,
288.240200166805,360.300250208507] # Array of x-coordinate datapoints (time, hours)
y_values = [1.25208681135225,6.09348914858096,10.9766277128547,13.4808013355592,18.363939899833,
19.6994991652754,19.49081803005,18.5308848080133,17.9048414023372,16.8196994991652,
12.1035058430717,7.51252086811352,4.67445742904841,3.1719532554257,1.5025041736227,
0.292153589315525,0.125208681135225] # Array of y-coordinate datapoints (concentration, ng/mL)

def model(t, a, V_D, k):  # The biexponential model function takes t->C(t)
    D = 40  # Fix dosage at 40mg
    # Avoid division by zero or invalid values
    if (k == a):  # Check if k is equal to a
        return np.nan  # Return NaN if k == a to avoid division by zero
    else:
        return (a * D) / (V_D * (k - a)) * (np.exp(-a * t) - np.exp(-k * t))

# Convert data to numpy arrays
x_data = np.array(x_values)
y_data = np.array(y_values)

try:
    # Provide initial guesses for parameters-iterative algorithm
    popt, pcov = curve_fit(model, x_data, y_data, p0=(0.1, 1, 1))
except RuntimeError:
    print("Error - curve_fit failed to converge")

a_fit, V_D_fit, k_fit = popt # Extract fitted parameters
D = 40  # Fixed value for D
```

```
x_fit = np.linspace(min(x_data), max(x_data), 100)
y_fit = model(x_fit, *popt) # Generate points for the fitted curve

# Calculate R-squared value
residuals = y_data - model(x_data, *popt)
ss_res = np.sum(residuals**2)
ss_tot = np.sum((y_data - np.mean(y_data)) ** 2)
r_squared = 1 - (ss_res / ss_tot)
print("R-squared:", r_squared)
print(popt)

# Plot the original data and the fitted curve
plt.scatter(x_data, y_data, label="Data")
plt.plot(x_fit, y_fit, "r-", label="Fitted Curve")
plt.xlabel("t")
plt.ylabel("C(t)")
plt.title("Fitted Curve")
plt.legend()
plt.grid(True)
plt.show()
```

Appendix C — Fluoxetine dose-occupancy curve data

Table 3: Dose of fluoxetine vs striatal SERT occupancy

Dose (mg)	Striatal SERT occupancy (%)
1	29.5
2.5	40.5
4	67
5	65
10	72.5
20	76
40	83.5
60	82

Data taken from Sørensen et al. (2022).

Appendix D — Tapering regimens and explanations

NICE clinical guidelines

According to the guidelines published by England's National Institute for Health and Care Excellence, a suitable tapering method for fluoxetine is as follows (NICE, 2022)

> "Fluoxetine's prolonged duration of action means that it can sometimes be safely stopped in the following way: in people taking 20 mg fluoxetine a day, a period of alternate day dosing can provide a suitable dose reduction. In people taking higher doses (40 mg to 60 mg fluoxetine a day), use a gradual withdrawal schedule. Allow 1 to 2 weeks to evaluate the effects of dose reduction before considering further dose reductions."

Using the general guidance from earlier in the guidelines to reduce doses at monthly or weekly intervals, as I take 20mg fluoxetine, for me this entails taking 20mg once a day (24h) for the 0th month, 20 mg once every two days (48h) for the 1st month, and 0mg from the second month onwards. We can model this using the parameterised form of (10), $C_r(t; D, N, \tau)$:

$$C(t) = C_r(t + 720; 20, 30, 24) + C_r(t; 20, 30, 24) + C_r(t - 720; 20, 15, 48)$$

where the first term establishes a month of dosing prior to $t = 0$ to achieve steady state, the second represents the 0th month of 20mg daily dosing, and the third represents the alternate-day dosing pattern.

RANZCP clinical guidelines

The tapering advice given by the Royal Australian and New Zealand College of Psychiatrists is:

> "…the first step is to reduce the dose to the minimal effective dose. Following this, the dose should be halved, and after a week, the dose should be reduced more slowly in small decrements (allowing 2 weeks for each dose reduction), according to how the tablet can be divided." (Malhi et al., 2021)

Starting from 20mg daily for the 0th month, then taking a half dose daily for one week, and then halving that dose to 5mg daily for two weeks, before ceasing, can be modelled using the parameterised form of (10), $C_r(t; D, N, \tau)$:

$$C\left(t\right) = C_r\left(t + 720; 20, 30, 24\right) + C_r\left(t; 20, 30, 24\right) + C_r\left(t - 720; 10, 7, 24\right) + C_r\left(t - 888; 5, 14, 24\right)$$

where the first term establishes a month of dosing prior to $t = 0$ to achieve steady state, the second represents the 0th month of 20mg daily dosing, the third represents the week of 10mg daily dosing of fluoxetine, and the fourth and final represents the two weeks of 5mg daily dosing.

DrugTaper.com personalised tapers

This is the linear taper function, however, the hyperbolic function is almost identical:

$$C\left(t\right)=C_r\left(t+720;20,60,24\right)+\sum_{n=0}^{180}C_R\left(t-24\left(n+30\right),D_L\left[n\right],1,24\right)$$

The first term here establishes two months of dosing at 20mg daily; one prior to $t\ =\ 0$ to establish a steady state, and one immediately after $t\ =\ 0$, to standardise this regimen with the others which begin with the first period of time at the starting dosage. The second term sums the parameterised C_R dosing function for 6 months = 180 days, each term in the sum modelling the nth dose given by the dosing array, D_L, and separated from the other by $(n+30)$ days. The $n+30$ is needed to offset the entire taper from 0th month of initial dosing described by the first term.

The only difference between the hyperbolic and lis that the hyperbolic taper takes the nth dose from the D_H array, and the linear takes its nth dose from the D_L array.

The tapering regimens were generated for 180 days, under the constraint of 5, 10, and 20 milligram fluoxetine formulations being available. The complete day-by-day taper arrays are as follows:

D_H = [20, 15, 20, 20, 20, 15, 20, 20, 15, 20, 15, 20, 15, 20, 15, 20, 15, 20, 15, 15, 20, 15, 15, 15, 20, 15, 15, 15, 15, 15, 15, 15, 15, 15, 15, 15, 15, 15, 15, 15, 15, 15, 10, 15, 15, 15, 10, 15, 15, 10, 15, 15, 10, 15, 10, 15, 10, 15, 10, 15, 10, 10, 15, 10, 10, 10, 15, 10, 10, 10, 10, 10, 15, 10, 10, 10, 10, 10, 10, 10, 10, 10, 10, 5, 10, 10, 10, 10, 5, 10, 10, 5, 10, 10, 5, 10, 5, 10, 5, 10, 5, 10, 5, 5, 10, 5, 5, 10, 5, 5, 5, 5, 10, 5, 5, 5, 5, 5, 5, 5, 5, 5, 5, 5, 5, 5, 0, 5, 5, 5, 0, 5, 5, 0, 5, 5, 0, 5, 0, 5, 0, 5, 0, 5, 0, 0, 5, 0, 0, 5, 0, 0, 0, 5, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0]

D_L = [20, 10, 15, 10, 10, 10, 10, 10, 10, 10, 10, 10, 10, 10, 5, 10, 10, 5, 10, 5, 10, 5, 5, 10, 5, 5, 10, 5, 5, 5, 5, 5, 5, 10, 5, 5, 5, 5, 5, 5, 5, 5, 5, 5, 0, 5, 5, 5, 5, 0, 5, 5, 5, 0, 5, 5, 0, 5, 5, 0, 5, 5, 0, 5, 0, 5, 5, 0, 5, 0, 5, 0, 5, 0, 5, 0, 5, 0, 5, 0, 5, 0, 5, 0, 0, 5, 0, 5, 0, 0, 5, 0, 5, 0, 0, 5, 0, 0, 5, 0, 0, 5, 0, 0, 5, 0, 0, 0, 5, 0, 0, 0, 5, 0, 0, 0, 5, 0, 0, 0, 5, 0, 0, 0, 0, 5, 0, 0, 0, 0, 5, 0, 0, 0, 0, 5, 0, 0, 0, 0, 0, 5, 0, 0, 0, 0, 0, 0, 5, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 5, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0]

5 Appendix E — MSE calculation program

```
import numpy as np
import matplotlib.pyplot as plt

# linear fluoxetine taper doses generated by drugtaper.com
drug_taper_linear = [
    20,15,20,20,20,15,20,20,15,20,15,20,15,20,15,20,15,20,
    15,15,20,15,15,15,20,15,15,15,15,15,15,15,15,15,15,15,
```

```
    15,15,15,15,15,15,10,15,15,15,10,15,15,10,15,15,10,15,
    10,15,10,15,10,15,10,10,15,10,10,10,15,10,10,10,10,10,
    15,10,10,10,10,10,10,10,10,10,10,5,10,10,10,10,5,10,10,
    5,10,10,5,10,5,10,5,10,5,10,5,5,10,5,5,10,5,5,5,5,10,5,
    5,5,5,5,5,5,5,5,5,5,5,5,0,5,5,5,0,5,5,0,5,5,0,5,0,5,0,
    5,0,5,0,0,5,0,0,5,0,0,0,5,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
    0,0,0,0,0,0,0,0,0,0,0,0,0]

# hyperbolic fluoxetine taper generated by drugtaper.com
drug_taper_hyperbolic = [
    20,10,15,10,10,10,10,10,10,10,10,10,10,10,5,10,10,5,10,
    5,10,5,5,10,5,5,10,5,5,5,5,5,10,5,5,5,5,5,5,5,5,5,5,5,
    0,5,5,5,5,0,5,5,5,0,5,5,0,5,5,0,5,5,0,5,0,5,5,0,5,0,5,
    0,5,0,5,0,5,0,5,0,5,0,5,0,0,5,0,5,0,0,5,0,5,0,0,5,0,0,
    5,0,0,5,0,0,5,0,0,0,5,0,0,0,5,0,0,0,5,0,0,0,5,0,0,0,0,
    5,0,0,0,0,5,0,0,0,0,0,5,0,0,0,0,0,0,5,0,0,0,0,0,0,0,5,
    0,0,0,0,0,0,0,0,0,0,5,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
    0,0,0,0,0]

def heaviside(x):
    return 0.5 * (np.sign(x) + 1)

def f(x):
    return 86.1209 * x / (1.89012 + x)

def inverse_f(y):
    return (1.89012 * y) / (86.1209 - y)

def C_Ru(t, D_f, N, T):
    return (0.678876 * D_f * np.sum((np.exp(-0.0268175 * (t - n * T)) - np.exp(-0.244538 * (t - n * T)))
    * heaviside(t - n * T) for n in range(N))

def C_R(t, D_f, N, T):
    return np.where(t > 0, C_Ru(t, D_f, N, T), 0)

def D(n, D_0):
    return inverse_f(0.9**n * f(D_0))

def C_mr(t, M=10, D_0=20, N=30, T=24):
```

```
    result = 0
    for m in range(M):
        result += C_R(t - 720 * m, D(m, D_0), N, T)
    result += C_R(t + 720, D(0, D_0), N, T)
    return result

def C_trend(t):
    return 21.7872*1.00089**(-t)+1.28299

def nice(t):
    return C_R(t + 720, 20, 30, 24) +C_R(t, 20, 30, 24) + C_R(t - 720, 20, 15, 48)

def ranzcp(t):
    return (C_R(t+720,20,30,24)
        + C_R(t,20,30,24)
        + C_R(t-720, 10,7,24)
        + C_R(t-888, 5,14,24))

def custom_dose_array(t, regimen):
    result = 0
    for _, dose in enumerate(regimen):
        result += C_R(t - 24*(_+30), dose, 1, 24)
    # A month at steady state before t=0
    # and one after to standardise
    result += C_R(t+720,20,60,24)
    return result

def linear(t):
    return custom_dose_array(t, drug_taper_linear)
def hyperbolic(t):
    return custom_dose_array(t, drug_taper_hyperbolic)
def mse(f, g, x_range):
    x_values = np.linspace(x_range[0], x_range[1], num=4320)
    y_f = f(x_values)
    y_g = g(x_values)
    return np.mean((y_f - y_g) ** 2)

# Define the range of x values
x_range = (0,4320)
```

```
# Calculate MSE
print("Mean Squared Error NICE:", mse(C_mr, nice, x_range))
print("Mean Squared Error RANZCP:", mse(C_mr, ranzcp, x_range))
print("Mean Squared Error LINEAR:", mse(C_mr, linear, x_range))
print("Mean Squared Error HYPERB:", mse(C_mr, hyperbolic, x_range))
```