The effect of decontamination procedures on the pharmacodynamics of venlafaxine in overdose

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WHAT IS ALREADY KNOW ABOUT THIS SUBJECT

• Single dose activated charcoal increases the clearance of venlafaxine in overdose. Combination of single dose activated charcoal and whole bowel irrigation decreases bioavailability of venlafaxine in overdose.
• There is an increased risk of seizures, a potential for cardiac toxicity and a higher rate of fatalities with venlafaxine overdose than other newer antidepressants.

WHAT THIS STUDY ADDS

• Single dose activated charcoal and combination of single dose activated charcoal and whole bowel irrigation decreases the probability of seizures that are caused by overdose of venlafaxine.

AIMS

To investigate the relationship between decontamination procedures and seizure events caused by venlafaxine overdose and to estimate the time at which 90% of patients would have had their first seizure in the presence and absence of decontamination.

METHODS

Data were collected from 319 patients who took an overdose of venlafaxine on 436 occasions. Seizures occurred on 24 of 436 occasions (5%). Patients received one of single dose activated charcoal (SDAC), whole bowel irrigation (WBI), a combination of either (SDAC/WBI) or no decontamination. Logistic regression and time to event analysis were used to investigate the influence of dose and decontamination on the probability of seizures and time to 90% ($t_{90}$) of seizure, respectively.

RESULTS

A linear logistic regression model described the data. Simulation from the model showed that the probability of seizure was 0.05 (0.03–0.08), 0.19 (0.09–0.35) and 0.75 (0.30–0.96) at 1000, 5000 and 10 000 mg, respectively (median and 95% credible interval). At the mean dose of 2100 mg the odds ratios (OR) in the presence of SDAC, WBI and SDAC/WBI were 0.48 (0.25–0.89), 0.71 (0.35–1.22) and 0.25 (0.08–0.62), respectively. A modified Gompertz model described the time to seizure events. Simulations from the Gompertz model showed that the $t_{90}$ values for first seizure was 26 h and was not affected by dose or decontamination procedure.

CONCLUSION

SDAC/WBI provided greater benefits than the sum of the independent effects of SDAC and WBI. Patients should be observed for at least 24 h for seizures based on the dose and risk of seizure occurring.
Introduction

Deliberate self-poisoning is a common problem throughout the world and accounts for an estimated 170 000 general hospital attendances in the United Kingdom alone annually [1, 2]. In the developed world up to one-fifth of overdoses involve ingestion of antidepressant medication and the rate of antidepressant overdose is increasing [3]. Serotonin re-uptake inhibitors, including venlafaxine make up the majority of these. This increase of SSRI overdose cases presenting to emergency departments means an understanding of the clinical course and treatment is increasingly important [4].

Venlafaxine appears to be more toxic in overdose than other newer antidepressants including other serotonin re-uptake inhibitors. Various studies have shown that there is an increased risk of seizures [5], a potential for cardiac toxicity [6] and a higher rate of fatalities [7] with venlafaxine overdose than with other antidepressants. However there are no studies on factors that predict these outcomes and no studies on the clinical benefits of decontamination for venlafaxine overdose.

Administration of single dose activated charcoal (SDAC) is a recognized decontamination procedure for drug overdose. However, the use of SDAC especially at times greater than 1 h after ingestion, has been the subject of intense debate [8]. We have previously shown the beneficial effects of SDAC for citalopram overdose where SDAC was administered greater than 1 h post-overdose in all but one case. In the citalopram overdose study SDAC reduced the risk of QT prolongation [9]. In contrast, for quetiapine overdose it was shown that administration of SDAC only marginally decreased the probability of intubation and did not affect the time to extubation [10]. The above studies suggest that the benefits SDAC are not necessarily generalizable for all drugs. It is therefore essential to assess the benefit of SDAC, and indeed other decontamination procedures, for each drug in overdose. We are unaware of any pharmacodynamic studies that have addressed the effects of whole bowel irrigation (WBI) or a combination of SDAC and WBI (SDAC/WBI).

We have recently shown in a population pharmacokinetic analysis of venlafaxine that SDAC when administered alone increases the clearance of venlafaxine by 35% and when administered in combination with WBI (SDAC/WBI) the combination reduces the bioavailability by 29% [4]. Data simulated from the final model of the venlafaxine PK study have shown that the administration of SDAC alone or a combination of SDAC and WBI to patients overdosed on venlafaxine decreases the AUC and $C_{\text{max}}$ of venlafaxine when compared with no decontamination. SDAC/WBI provides a greater reduction in $C_{\text{max}}$ when compared with SDAC alone. However it is unclear if these beneficial effects of decontamination procedures will translate into clinical benefit.

The aim of the current study was to assess whether the beneficial effects of decontamination procedures on the pharmacokinetics of venlafaxine are associated with a beneficial effect on patient outcomes. The specific aims of the study were (i) to investigate the relationship between predictor variables including dose, SDAC, WBI and SDAC/WBI on the probability of seizures and (ii) to determine the time at which 90% of patients would have had their first seizure for those patients who experience a seizure event and if the decontamination procedure influences the time to first seizure.

Methods

Setting and study design

This was a cohort study of consecutive presentations of venlafaxine overdose to a tertiary toxicology unit. All presentations to the hospital were seen and treated by the toxicology service, including patients seen and discharged from the emergency department, admitted as inpatients or admitted to the intensive care unit. Data were collected for all patients treated by the toxicology service using a preformatted admission sheet. These data and any additional information taken from the medical record are entered into a relational database (Microsoft Access™). The use of this database for research purposes has previously been exempted by the Human Research Ethics Committee as an audit and approval was obtained for prospective collection of clinical data, blood samples and electrocardiograms from a subgroup of patients (see below).

Patient characteristics

Three hundred and nineteen patients who took a venlafaxine overdose on 436 occasions were included from January 1997 to December 2007.

A pharmacokinetic analysis on a subset (76 occasions) of these data and the estimated effects of decontamination on clearance and fraction of drug absorbed have been reported previously [4]. This report did not identify patient characteristics (such as age, weight and gender) as covariates for drug exposure. Therefore there was no benefit in considering individualized pharmacokinetic exposure profiles in this larger dataset with pharmacodynamic (PD) observations other than via dose. Table 1 summarizes the demographics of all the patients in the study. Briefly, the median reported dose in the data set was 1500 mg (75–13500 mg; note not all patients took an overdose). On 59.4% of occasions patients were not administered any decontamination. On 23.4%, 8.26% and 8.94% of occasions patients were administered SDAC, WBI and SDAC/WBI, respectively. Table 2 describes the characteristics of patients in different decontamination groups. The type of decontamination procedure administered to a patient depended on the treating toxicologist at the time of admission. Seizures
were considered the most commonly clinically important complication reported after venlafaxine overdose. In the study, patients had seizures on 5% of occasions after an overdose episode. The time of seizure was recorded. The number of occasions that a patient presented with an overdose ranged up to 16 occasions. The median time of first seizure was 6.17 h after the reported time of overdose.

Logistic regression was used to investigate the influence of dose, patient characteristics (age and gender), co-ingestants, formulation and decontamination procedures on the probability of seizure after a venlafaxine overdose. Time to event analysis was performed to estimate the time to 90% of seizure occurrence based on dose size and decontamination procedure. A fully Bayesian approach was undertaken for both the logistic regression and time to event analysis using WinBUGS 1.4.3.

### Bayesian analysis

The parameters of the models were estimated using WinBUGS. MATLAB 2008b, with MATBUGS (August, 2005), was used to call WinBUGS for analysis and then manipulate the exported CODA files from WinBUGS to produce output summaries. Low information priors were used for all the parameters for both logistic regression and time to event analysis. For further information see Appendix 1.

During model development, two Markov chains of 20,000 samples were run. The first 4000 samples (termed ‘burn-in’) were discarded. Model convergence was assessed by visual inspection of overlaid chains and BRG diagnostics available in WinBUGS [11].

#### Model selection criteria

For logistic regression models, selection was based on assessment of the deviance information criterion and a visual inspection of simplified Bayes marginal model plots (SBMMP) [12]. These plots were also used for both model discrimination as well as model evaluation purposes. The plots are explained in the model evaluation section.

For the time to event analysis the model selection was based on visual comparison between survival times predicted from the fitted model to those obtained from Kaplan-Meier plots. An acceptable model would be expected to have good agreement between the model predicted survival times with those obtained from Kaplan-Meier plots.

### Modelling the probability of seizure and influence of decontamination using logistic regression

A logistic regression model was used to quantify the influence of dose, SDAC, WBI and SDAC/WBI on the probability of seizures. The phenotypic covariates, gender and age were considered as well as the covariates formulation and co-ingested drugs in overdose (co-ingestants). Different functional forms of the logit model such as linear, log linear and polynomial forms were tested. An additive random effect indexed to the individual on the baseline seizure rate was also evaluated. Details of the modelling are given in the Appendix 2.

#### Effect of decontamination

Two separate approaches were used to estimate the influence of decontamination on the probability of seizure. In the first approach (which we term the naive model) we considered the effects of SDAC, WBI and SDAC/WBI as being independent. The decontamination procedure was assumed to influence the coefficient of dose only. In the case of the naive model three independent parameters were estimated each of which provided an estimate of the fractional effect of the particular decontamination procedure on the coefficient of dose.

A decontamination model which included an interaction similar to the one used in the pharmacokinetic analysis of venlafaxine overdose data was also considered [4] (see Appendix 2 for details on interaction model). In this approach on occasions when SDAC or WBI were administered alone to a patient they were estimated similar to the naive model. When SDAC/WBI was administered then an interaction model was used which allowed the combination of SDAC and WBI to be synergistic, antagonistic or additive. Note in this model the influence of the combination decontamination SDAC/WBI would also inform the estimated effect size of the decontamination procedure when either was used independently. The decontamination procedure was allowed to influence the coefficient of dose only.

The goodness of fit of the final model was evaluated using a simplified Bayes marginal model plot (SBMMP) [12].

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**Table 1**

<table>
<thead>
<tr>
<th>Number of occasions (n = 436)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported dose (mg); Median (IQR)</td>
</tr>
<tr>
<td>Phenotypic characteristics</td>
</tr>
<tr>
<td>Age (years); Median (IQR)</td>
</tr>
<tr>
<td>Gender Females, n (%)</td>
</tr>
<tr>
<td>Decontamination</td>
</tr>
<tr>
<td>No decontamination, n (%)</td>
</tr>
<tr>
<td>SDAC, n (%)</td>
</tr>
<tr>
<td>Whole bowel irrigation (WBI), n (%)</td>
</tr>
<tr>
<td>SDAC + WBI, n (%)</td>
</tr>
<tr>
<td>Formulation</td>
</tr>
<tr>
<td>Standard release (IR), n (%)</td>
</tr>
<tr>
<td>Extended release (SR), n (%)</td>
</tr>
<tr>
<td>Seizures, n (%)</td>
</tr>
<tr>
<td>Time of seizures (h)</td>
</tr>
</tbody>
</table>

The total number of patients in the study was 319; *18 patients took both standard and extended release.
Simulations from the model

From the final model the probability of seizure at different dose levels in the presence and absence of decontamination procedures was calculated. From these probability values the following values were estimated: (i) clinical significance: a decontamination procedure was arbitrarily assumed to be clinically significant if its effect changed the probability of seizure at a given dose by more than 20% and (ii) the odds ratio (OR) of having an event in presence of SDAC, WBI and SDAC/WBI.

Time at which 90% of first seizures occur using time to event analysis

Time to event analysis was conducted to determine the time at which 90% of patients would have had their first seizure for those patients in whom a seizure occurred. We denote this value as $t_{90}$. In the study only 5% of patients had seizures; hence the time of first seizure was available only for these patients. All other patients were assumed to be right censored with respect to their first seizure time, which was given by the time of discharge from the hospital. A variety of parametric models were considered to describe the seizure data including a Weibull survival model [13] and a modified Gompertz survival model [14]. A Weibull model was not considered suitable for such data as the probability of not having a seizure will asymptote to zero or, in other words, the Weibull model predicts that every patient will have a venlafaxine-induced seizure eventually, which is not true in this case. A modified Gompertz model, however, allows for a non-zero asymptote. The effect of decontamination on $t_{90}$ was estimated using an adjusted decontamination model similar to the logistic regression model. Full details of the model are presented in the Appendix 2.

The final model was used to simulate the $t_{90}$ values at different dose levels in the presence and absence of decontamination

Results

Probability of seizure and influence of decontamination

The best logistic regression model to describe the influence of seizure and decontamination was a linear model without random effects. An interaction model was used to estimate the influence of decontamination procedures on the probability of seizures. Age, gender, and formulation did not influence the probability of seizures. The immediate release (IR) formulation was ingested on about 50% of occasions and 12 seizures were recorded. The influence of formulation was considered in a model with an interaction between formulation and dose. The difference [median (95% credible interval)] in the effect of dose on seizures for IR vs. extended release (XR) was 0.01 (−0.35 to 3.67).

Benzodiazepines were the commonest co-ingestants in the study and were ingested on 126 occasions. A model was tested that included benzodiazepines and showed that benzodiazepine co-ingestants reduced the probability of seizure. Benzodiazepines reduced the probability of seizure by 45% at a venlafaxine dose of 4000 mg. However, the addition of benzodiazepines in the final model with decontamination did not change the magnitude of the effect of venlafaxine dose or decontamination on the probability of seizures. Pro-convulsant drugs were taken on six occasions, too few to determine if they influenced the risk of seizures in the final model.

The predictions from the fixed effects model had a close agreement to the empirical model (splines) up to a dose of 10 000 mg. Hence the model appeared to describe the data well for doses up to 10 000 mg. A model diagnostic plot for the logistic regression model is shown in Figure A1-B in Appendix 3.

Plots of the probability of seizure and dose show that the probability of seizure increases with dose. The probability of seizure was 0.05 (95% credible interval 0.03–0.08)
at 1000 mg, 0.19 (95% credible interval 0.09–0.35) at 5000 mg and 0.75 (95% credible interval 0.30–0.96) at 10 000 mg. Administration of SDAC and SDAC/WBI decreased the probability of seizure. Administration of WBI alone did not decrease the probability of seizure. The OR of having a seizure after an overdose episode in the presence of SDAC and SDAC/WBI are shown in Table 3. For the mean dose of 2100 mg the OR in presence of SDAC was 0.48 (95% credible interval 0.25–0.89), for WBI was 0.71 (95% credible interval 0.35–1.22) and for the combination SDAC/WBI was 0.25 (95% credible interval 0.08–0.62).

**Time to event analysis**

The modified Gompertz survival model without random effects provided an adequate description of the data (diagnostic shown in Figure 1). Since no effect of decontamination can be seen in the time to first seizure the effects of decontamination are not shown in this figure. Simulation from the final model showed that the median $t_{90}$ value at 1500 mg was 26 h and the value did not change with a change in dose nor was it affected by any decontamination procedure. The median $t_{90}$ values at different dose levels are shown in Table A1 in Appendix 3. Appendix 3, Figure A1-A shows the time to seizure at different dose levels. The graph shows that 23% of seizures occurred 8 h or more post-ingestion, 11% at 16 h or greater, and 4% 24 h or greater. In the study only one seizure occurred after 24 h.

**Discussion**

The results of the logistic regression model indicate that the probability of seizures increases with an increase in dose. SDAC and a combination of SDAC and WBI decrease the probability of seizures while WBI alone does not decrease the probability of seizures. Formulation did not influence the risk of seizures although co-ingesting a benzodiazepine reduced the probability of seizures and reduced this by 45% for 4000 mg of venlafaxine. The time to event analysis suggests that the majority of first seizures occur in the first 16 h.

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Interventions</th>
<th>OR</th>
<th>95% CrI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>-</td>
<td>2.16</td>
<td>1.51–3.15</td>
</tr>
<tr>
<td>Seizures</td>
<td>SDAC</td>
<td>0.48</td>
<td>0.25–0.89</td>
</tr>
<tr>
<td></td>
<td>Whole bowel irrigation (WBI)</td>
<td>0.71</td>
<td>0.35–1.22</td>
</tr>
<tr>
<td></td>
<td>SDAC/WBI</td>
<td>0.25</td>
<td>0.08–0.62</td>
</tr>
</tbody>
</table>

*95% credible interval.

The results of the logistic regression model are in accord with those from the pharmacokinetic analysis previously published. In the pharmacokinetic analysis it was shown that the combination of SDAC and WBI provides a greater decrease in the maximum concentration values when compared with SDAC alone. In accord with this in the current analysis we see that at 2100 mg the OR of having a seizure was 0.25 and 0.48 in presence of the combination and SDAC alone, respectively. WBI did not affect the probability of seizures. This could be because there were only a few patients in the WBI alone group so despite the OR being 0.71 in favour of WBI, the credible interval was large and included 1. A larger study may need to be conducted in order to confirm these results. A clinical interpretation of the statistically significant decontamination effects are provided in Figure 2.

When considering the question of how long to monitor a patient for a seizure when no seizure has occurred was formed on the basis of determining the time at which 90% of seizures would have occurred. An observation period of 24 h was chosen arbitrarily because the median predicted time to 90% of seizures was 26 h which is longer than the median length of stay (16 h) for overdose patients that was observed in a previous study on valproate [15]. However, the credible interval on the time to 90% seizures was diffuse and hence this recommendation may in some circumstances be overly conservative because only one seizure occurred after 24 h. In contrast it might be regarded as not sufficiently conservative by some clinicians. This should be considered in relation to the
probable patient characteristics and bioavailability or clearance since we found no clear link between observations and estimates of actual dose [3]. In the latter case, it is implausible to believe that clinicians assigned decontamination to those patients with lower bioavailability or greater clearance since we found no clear link between observable patient characteristics and bioavailability or clearance [3]. It is worth noting that any inherent bias in the results would tend to favor more seizures in the decontamination group since this group appeared to have received the larger dose.

Normal therapeutic doses including doses as low as 75 mg were included in the study. This was because in studies of this nature it is useful to have patients who have taken low doses or ideally no dose at all, to enable the baseline incidence of events to be established. Note in our model we estimate the baseline probability of a seizure to be 0.018 which is similar to the prevalence of seizures in the normal population. We do not claim that all patients have necessarily taken an overdose by the amount of drug ingested, but the intention in these patients was still deliberate self-harm.

It is also of interest that the PK predicted a 35% increase in CL with SDAC which in the absence of pharmacodynamic data may be considered as a borderline improvement, albeit significantly greater than the 20% arbitrarily required for clinical significance in that study [3]. We see here however that the 35% increase in CL corresponded to a 32% reduction in seizure probability at 5000 mg indicating that PK provided a good biomarker of perceived clinical benefits in venlafaxine overdose.

The results of logistic regression analysis concur with the results from a previous pharmacokinetic study of venlafaxine overdose which supports the effect of decontamination on the dose exposure relationship. Figure 2 provides the probability of a seizure based on the ingested dose, with and without the SDAC/WBI combination, and can guide clinical management including the use of decontamination. Although the OR with either SDAC or the combination of SDAC and WBI suggests a highly beneficial effect this must be balanced with the relative low event rate of seizures and the potential low morbidity from a self-limiting seizure occurring in hospital. However, the observation period of 24 h for the first seizure is then a significant observation since an out of hospital seizure would have a much higher morbidity.

Together the results obtained from the logistic regression and time to event analysis may help clinicians make a decision regarding the length of time a patient requires observation based on the reported dose of venlafaxine. From Figure 2 it can be seen that for smaller overdoses (<4000 mg) the probability of seizure is low, less than 0.1 or 10%, and hence these patients may not require observation for an extended period and could be potentially discharged if otherwise well. However, for larger overdoses (>4000 mg) the probability of seizure is greater than 0.1 and there may be benefit in observing patients for 24 h. In the current study the number of occasions on which the dose was greater than 4000 mg was 13 (0.03% of cases).

We conclude that venlafaxine causes seizures in a dose dependent manner in overdose, the combination of SDAC and WBI appeared to provide greater benefit at reducing seizures than the sum of the independent effects of SDAC and WBI and that an observation time of about 24 h may be a clinically relevant period to observe for the potential for seizures, particularly for large venlafaxine overdoses.
Competing Interests

There are no competing interests to declare.

Appendix 1

Priors

For the logistic regression the prior probability distribution of the parameters was set to provide low information priors and was given by a multivariate normal distribution with the mean of 0 and variance of 100. The prior for the inverse of the variance of the between subject variability was assumed to be a low information gamma distribution for the univariate case and a low information Wishart for the multivariate case with degrees of freedom equal to the dimension of the Wishart distribution.

In the case of the time to event analysis the prior probability distribution of each parameter was described by a normal distribution with a mean of 0 and variance of 10. Similar to the logistic regression, the prior for the inverse of the variance of the between subject variability was assumed to be a low information gamma distribution for the univariate case and a low information Wishart for the multivariate case with degrees of freedom equal to number of parameters.

Appendix 2

Logistic regression

**Base model**

The seizure response ($y_{ij}$) for the $i^{th}$ patient on the $j^{th}$ occasion was described as 0 no seizure or 1 for seizure and was assumed to be an independent Bernoulli trial with the probability of seizure ($\pi_{ij}$) as a function of exploratory variables ($X_{ij}$) such as dose ($D_{ij}$) and decontamination procedures as shown in Equation 1.

$$
\log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) = f(X_{ij}, \beta_i)
$$

(1)

Where $\beta_i$ are the $i^{th}$ patient parameters of the model and $f(X_{ij}, \beta_i)$ is the functional form of the model. The left hand side of Equation 1 represents the log odds of having a seizure at $D_{ij}$ for any given decontamination procedure. Various functional forms of $f(D_{ij}, \beta_i)$ such as linear, log-linear, $E_{max}$ and up to a second order polynomial were considered. An additive random effect on the baseline seizure rate was also considered.

**Interaction model**

The interaction model is shown in Equation 2.

$$
f(X_{ij}, \beta_i) = \beta_0 + \beta_1 \times D_{ij} \times (\beta_2 \times SDAC_i + \beta_3 \times WBI_i + \beta_4 \times b_{ij})
$$

(2)

Note that in the above notation the probability of baseline seizure (i.e. a seizure in the absence of venlafaxine) was allowed to vary between patients. However the coefficients for the exploratory variables (dose and decontamination procedure) were assumed to be the same for all patients. A random effects model was also considered.

In all cases the decontamination procedure was an indicator variable that took the value of 1 when given and 0 when not. In this model $\beta_4$ is an interaction parameter that allows the effect of SDAC and WBI when used in combination to be additive ($\beta_4 = 1$), synergistic ($\beta_4 < 1$) or antagonistic ($\beta_4 > 1$).

**Time to event analysis**

**Modified Gompertz model**

A modified Gompertz model is described here.

The instantaneous hazard of having a seizure is given by Equation 3

$$
hz_{ij} = \exp(\alpha + \gamma \times t_{ij} + f(X_{ij}, \beta))
$$

(3)

Where $hz_{ij}$ is the instantaneous hazard of having a seizure for the $i^{th}$ patient on the $j^{th}$ occasion at time $t_{ij}$; $\alpha_i$ is the baseline hazard and its value was constrained to be greater than zero. $\gamma$ is the rate of change of the logarithm of the hazard and its value was constrained to be less than zero. $\beta$ is the coefficient of exploratory variables $X_i$. Note that the $f(X_{ij}, \beta)$ used in this hazard model is identical to the one used in logistic regression model but the parameter vector is a different set of parameters.

The corresponding survivorship ($S_{ij}$) is parameterised as shown in Equation 4

$$
S_{ij} = \exp\{\exp(f(X_{ij}, \theta)) \times \lambda^{-1} \times \alpha \times [1 - \exp(\lambda \times t_{ij})]\}
$$

(4)

The hazard and survival functions as defined in Equations 3 and 4 were used to write a closed form solution for the likelihood

$$
L(\alpha, \gamma, \beta) = \prod_{i=1}^{N} \prod_{j=1}^{m_i} (S_{ij} \times hz_{ij}^{\delta_{ij}})
$$

(5)

where $\delta_{ij}$ is a censoring variable and has a value of 0 if censored or 1 if the patient had a seizure. $N$ is the total number of patients in the data set and $m_i$ is the total number of occasions on which a given patient presented with an overdose.
Appendix 3

Results

![Graph A1](image1.png)

**Figure A1**

(A) The predicted survival at different dose levels (1500, 3000 and 5000 mg). KM plot (—); Dose 3000mg (—); Dose 1500mg (—); Dose 5000mg (—). (B) SBMMP for linear model without random effects. The solid lines are 5th, 50th and 95th percentile of model predictions, the dashed lines are the 5th, 50th and 95th percentile of the spline. The vertical solid line represents the region up to which the model predictions can be relied on.

![Graph B1](image2.png)

**Table A1**

Time to 90% of seizures to occur at different dose levels of venlafaxine

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>( t_{90} ) Dose only*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1500</td>
<td>25.82 (15.37–55.10)</td>
</tr>
<tr>
<td>3000</td>
<td>25.69 (15.29–55.70)</td>
</tr>
<tr>
<td>4500</td>
<td>25.49 (15.18–54.10)</td>
</tr>
<tr>
<td>6000</td>
<td>25.18 (15.00–53.08)</td>
</tr>
<tr>
<td>7500</td>
<td>24.60 (14.70–51.53)</td>
</tr>
<tr>
<td>9000</td>
<td>23.70 (14.23–49.32)</td>
</tr>
</tbody>
</table>

*All values are (median (credible interval)).

REFERENCES


