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Adaptation of Mixture Cure Model in Estimating Incidence and Latency for Major Depressive Disorder

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Abstract

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By Xingyue Huo

Background: Major Depressive Disorder is a serious mental health disease that may influence people's daily lives. Cognitive behavioral therapy and medications are the main treatments for depression and have been shown to be equally effective. However, there are still open questions as to compare time to response across different treatments, and possibly identifying when to discontinue the current treatment. We sought to determine if a mixture cure model that included nonresponse might fit the data in depression treatment and examine the data to see if there are indicators of when to discontinue or switch the current treatments.

Methods: We performed Cox proportional hazard regression and conditional survival analysis on a sample of 316 patients with the major depressive disorder to estimate the incidence and latency separately. We also proposed a mixture cure model for estimating the prevalence of response and the mean time to response, simultaneously. Due to a large response rate, we were forced to use two "nonresponse filters" in order to isolate the nonresponse signal.

Results: The results showed no clear evidence of a time to switch treatments since the survival curve were continuous and did not have any large plateaus. By comparing the results from Cox regression and conditional survival analysis, it might suggest that the incidence was responsible for the significant difference across treatments, and the CBT group was more likely to be nonresponders to traditional treatment. Without using "filters" to separate data in order to fit the mixture cure model, we cannot determine a significant association between treatment groups due to the high prevalence of response and therefore a solution closed to the boundary.

Discussion: We found it was inappropriate to use the mixture cure model with current clinical data due to high response prevalence. It emphasized the adaptation of a mixture model, the model might not fit the data with a high prevalence of the "cure". Our results also suggested the majority of patients had a response in the treatment of depression. CBT might take a longer time to respond than medications, but evidence of nonresponse in this group is limited. In addition, we did not identify when to discontinue or switch the current treatment because of the lack of a placebo group.

Keyword: depression, mixture cure model, response

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Introduction

1. Clinical Background

Mood disorders encompass a large group of psychiatric disorders in which pathological moods and related psychomotor disturbances dominate the clinical picture. Major depressive disorder (MDD), known also as unipolar depression, is classified as a mood disorder (Angst, Ajdacic-Gross, and Rossler 2015). It is a common and serious illness that refers to a state of low mood, which negatively affects how people feel, the way they think, and how they act (Mason, Brown, and Croarkin 2016). People with depression can lose interest in activities that the individual perceived as pleasurable, meanwhile, the disorder may alter appetite and sleep balance and other normal living habits, thereby leading to a variety of emotional and physical problems and can decrease a person's ability to function (Stanners et al. 2014).

Rating depression depends on the subjective assessment of mood status. In this case, self-report and interviews are used widely. The Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960), has a 17 or 24-item version scale based on the symptoms for depression, was developed in the late 1960s to evaluate and monitor the severity of major depression before, during, and after treatment(Williams 2001). Generally, items on the HRSD are scored from 0 to 2 or from 0 to 4, and the total score ranging from 0 to 50. Scores from 19 to 22 could be considered severe, and above 23 considered very severe. The HRSD has been used to evaluate the change in response to pharmacological and other interventions, and thus offers the advantage of comparability across a broad range of treatment trials (Zimmerman et al. 2013).

2. Treatments for depression

2.1 Psychotherapy

Psychotherapy consists of face to face conversation or discussion. Psychotherapy is typically used alone for treatment of mild depression, and also along with antidepressant medications for treatment of moderate to severe depression (Barrera and Spiegel 2014). Cognitive behavioral therapy (CBT) is one of the methods of psychotherapy that attempts to modify the interpretations of experiences that determine feelings and behaviors (Thoma, Pilecki, and McKay 2016).CBT examines distorted thinking and then helps people change their behaviors and thinking to lessen depression. The premise is that cognition (the process of acquiring knowledge and forming beliefs) can influence feelings and behaviors (Turkington, Kingdon, and Weiden 2006). Although there are various approaches to psychotherapy, CBT is the most widely studied. A meta-analysis revealed that between 42% and 66% of patients no longer meet the criteria for depression after CBT therapy(Anthes 2014).

2.2 Medication

Although the underlying pathophysiology of depression has not been clearly defined, clinical evidence suggests disturbances in serotonin (5-HT), norepinephrine (NE), and dopamine (DA) neurotransmitters in the central nervous system (Pringle et al. 2013). Medications used for depression work by ultimately effecting changes in brain chemistry and communication in brain nerve cells known to regulate mood, to help relieve depression (Latendresse, Elmore, and Deneris 2017). These medications are able to do

this by binding proteins, called neural transporters, which are responsible for carrying the chemicals between brain cells.

Older antidepressants included such things as monoamine oxidase (MAO) inhibitors(Thomas et al. 2015) as well as tricyclics(Kerr, McGuffie, and Wilkie 2001). These compounds are still considered as important third-line agents now. However, all of these had significant side effects and some diet restrictions made them difficult to take. Thus newer compounds were the target of development for pharmaceutical companies in the mid-1980s. Selective serotonin reuptake inhibitors (SSRIs) limit the reuptake of serotonin in the brain, raising serotonin levels in the central nervous system (CNS). In 1988, fluoxetine (Prozac) as the first SSRI was approved in the United States (Stokes and Holtz 1997), following with sertraline (Zoloft) (Muijsers, Plosker, and Noble 2002), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), and escitalopram (Lexapro). SSRIs ease depression by increasing levels of serotonin in the brain. SSRIs are called selective because they primarily affect certain proteins, serotonin (Oishi et al. 2010), while others are nonspecific because they bind to other neurotransmitters (the main difference from SNRIs). They are generally well tolerated, with a side-effect profile that includes nausea, dry mouth, and headache (Thoma, Pilecki, and McKay 2016). The development of the SSRIs is a significant milestone in the treatment of depression, and the SSRIs are still considered the front line treatment recommendation.

Serotonin-Norepinephrine reuptake inhibitors (SNRIs) are a group of medications that block both serotonin and norepinephrine, and are developed after the use of SSRIs became routine(Dale, Bang-Andersen, and Sanchez 2015). The addition of norepinephrine to the profile of the drug proposed to improve treatment

response(Silverstone, Entsuah, and Hackett 2002). Evidence suggests that norepinephrine is an important neurotransmitter in the pathophysiology and treatment of depression (Stahl and Stahl 2008), Antidepressants that enhance norepinephrine activity offer a therapeutic advantage over serotonin antidepressants in the treatment of certain symptoms. The SNRIs show at least equivalent antidepressant efficacy to the SSRIs, and there is evidence that they may be more effective than the SSRIs in achieving remission (Papakostas et al. 2007) . The SNRI used in the current study, duloxetine (Cymbalta), was approved by the FDA for treatment of MDD in 2004. It has also been used for other indications such as generalized anxiety and panic disorder. It was later approved for the treatment of chronic pain.

3. Time to response in depression treatment

The current study was originally designed to identify biomarker or predictors of ultimate treatment response. In order to identify treatment response predictors, a randomized controlled trial was designed where 3 different treatments were considered: SNRI (Cymbalta), SSRI (escitalopram), and CBT. It was known that each of the treatments was more or less equivalent in its ability to treat depression, but randomization was used to equalize possible prognostic factors across groups for the purposes of response prediction. However, it was not clear if the treatment would produce the same rates of response, or if the time to response would be the same across treatment groups.

In a recent study, time to response was compared using standard survival analysis methods, including the Kaplan-Meier curve and Cox regression models, to compare rates of response across treatments compared to placebo, while taking into account the

censored data (Stassen et al. 2007). They also used a 2-dimensional mixture ("cure") model to predict different aspects of response. More specifically, the depression response has two aspects, incidence and latency. Incidence is the proportion of patients in whom a response is induced, while latency is the time to onset (days/weeks) of improvement. In traditional Cox regression analysis, these two aspects are handled simultaneously through the survival function S(t). In order to separate these two aspects, a rather critical assumption must be made about the data; specifically that a subgroup of patients will never respond, or is not "susceptible" to response, (i.e., "cured"), which is the basis of conditional survival estimates.

In the cure model, it is assumed that there are a proportion of subjects who will never experience the event, thus the survival curve will eventually reach a plateau and never be zero. For example, when modeling the response time of medications to depression, some patients may have a response to the treatment, others may never have the response. The mixture model makes the assumption that there is a subset of subjects who cannot respond, and therefore time to response is only defined in those who respond, i.e. conditional on not being "cured".

Clinical evidence does show that some depressed patients do not respond to traditional treatments such as therapy and medications. These patients, if they have been ill for a long period of time, are considered to have treatment-resistant depression (TRD) (Koek and Luong 2019). Other additional treatment options for TRD could be considered based on psychiatrists' advice, for example, electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), and deep brain stimulation (DBS) (Koek et al. 2019). These subjects would be ideal candidates for a "not capable of response (cured)" group, if they could be

identified. The simplest way to approach the estimation of the conditional survival curve is to identify a group of “non-responders” using some criterion, and then to calculate the mean time to survival in only the responders. For the Stassen study (Stassen et al. 2007), they removed all “non-responders” as defined in the estimation of the survival curve and used these estimates as a first look at the conditional survival curve. However, it is not clear if some of those patients would go on to respond at a later time. Our study recently identified response profiles based on longitudinal trajectories (Kelley et al. 2018), and one of those groups, the longitudinal nonresponders, was shown to demonstrate more TRD- like qualities through an analysis of subsequent treatment data. In addition, throughout the study, endpoint nonresponse was defined as those with <30% response as an attempt to isolate more "treatment resistant" subjects. The use of the cure model is another way to estimate the conditional response curve by specifying the model to incorporate the two aspects of response, and use the data to estimate the “cure” or nonresponse rate. Thus, the current clinical question for this paper concerns comparing time to response across different treatments, and possibly identifying when it is prudent to discontinue the current treatment. To address this question, we applied a similar strategy as the Stassen study (Stassen et al. 2007) to our current data.

Methods

1. Study Population and Measurements

The study enrolled patients who met DSM-IV criteria for MDD and patients who had never received treatment with antidepressant previously. Patients who had received prior supportive therapy also were eligible, but they were not permitted to participate in such

psychotherapy during the study. 344 individuals, men and women aged 18-65 years, consented to participate in the study and were randomly assigned over 12 weeks: 114 to escitalopram (SCIT): 10–20 mg/d, 115 to CBT: 16 individual 1-hr sessions, 115 to duloxetine (DUL): 30–60 mg/d (Dunlop et al. 2017). 251 out of 344 subjects ultimately completed the 12-week study, 92 for escitalopram, 73 for CBT and 86 for duloxetine. In addition, 316 individuals took part in the study at least for one week, the remaining 28 individuals who never received treatment (have baseline only) were excluded from survival analysis.

The severity of depression was evaluated by HRSD at baseline, week 1 to 6 weekly, and week 8, 10 and 12 respectively. Criteria used for endpoint classification: remission (HRSD17 ≤7), response (≥50% improvement without reaching remission), partial response (30-50% improvement), and nonresponse (<30% improvement) (Dunlop et al. 2012). For the calculation of the survival function, we defined time to response as the week that subjects first met response criteria.

2. Statistical Approach

2.1 Kaplan-Meier Estimator

If we defined survival "event" as first response, the survival function was used to describe the probability of an individual surviving beyond time x: $S(x) = \Pr(X > x)$. When X is a continuous variable, the survival function is the complement of the cumulative distribution function, that is, $S(x) = 1 - F(x)$, where $F(x) = Pr(X \leq x)$. Also, the survival function is:

$$S(x) = \Pr(X > x) = \int_x^{\infty} f(t)dt$$

The standard estimator of the survival function, is called the Product-Limit estimator. If the unique event times t_i are distinct and $t_1 < t_2 < \cdots < t_k$ denotes the ordered event times, D_i is the number of individuals who are at risk at timet_i, d_i is the number of individuals who had response at time t_i. d_i/D_i provides an estimate of the conditional probability that an individual who survives to just prior to time t_i experiences the event at time t_i:

$$\hat{S}(t) = \begin{cases} 1, & if \quad t < t_1 \\ \prod_{i:t_i \le t} [1 - \frac{d_i}{D_i}], & otherwise \end{cases}$$

The Product-Limit estimator is a step function with jumps at the observed event times. Survival analysis with the Kaplan-Meier curve is used to measure the fraction of patients 'surviving' at a given time. If an individual withdraws from a study, is lost to follow-up, or has no event occurrence at last follow-up. To examine time to response outcome, time to first response was calculated.

2.2 Cox Regression Model

The survival function above is the integral of the probability density function$f(x)$, thus:

$$f(x) = -\frac{dS(x)}{dx}$$

the hazard rate is defined by:

$$h(x) = \log_{\triangle x \to 0} \frac{P[x \le X < x + \triangle x | X \ge x]}{\triangle x}$$

the numerator of hazard rate is the conditional probability that the event will occur in the small time interval $[x, x + \triangle x)$, and the denominator is the time interval. When the

limitation of the time interval goes to zero, we have an instantaneous rate of occurrence, which also can be expressed as:

$$h(x) = \frac{f(x)}{S(x)} = -\frac{d}{dx} logS(x)$$

In this study, we defined Z as the design matrix of predictors to predict the probability of the indicator of nonresponse, $Z = (Z_1, Z_2 \dots Z_p)^T$, and $\beta = (\beta_1, \beta_2 \dots \beta_p)^T$ is an unknown parameters vector. $h(t|Z)$ is the hazard rate at time t for an individual with Z:

$$h(t|Z) = h_0(t) \ \exp(\beta Z)$$

where $h_0(t)$ is a baseline hazard rate. If we compare two individuals with covariate values Z_1 and Z_2, the ratio of their hazard rates is:

$$\frac{h(t|Z_1)}{h(t|Z_2)} = \frac{h_0(t)\exp(\beta Z_1)}{h_0(t)\exp(\beta Z_2)} = \exp[\beta(Z_1 - Z_2)]$$

Z_{im} is the mth covariate for each individual whose failure time is t_i and assuming Z_{im} is known for any time t_i at which the subject is under observation. $R(t_i)$ is the risk set at time t_i. The likelihood equation is:

$$L(\beta) = \prod_{i=1}^{n} \frac{\exp\left[\sum_{m=1}^{p} \beta_m \ Z_{im}\right]}{\sum_{j \in R(t_i)} \exp[\sum_{m=1}^{p} \beta_m Z_{jm}]}$$

where the numerator of likelihood depends on the subjects who had the response, whereas the denominator includes the data from all individuals who have not yet experienced the event or who will be censored.

2.3 Mixture Survival (Cure) Model

The mixture survival or "cure" model, explicitly models survival as a mixture of two groups of patients: those who are cured and those who are not cured. In this study, the

"cured" group is defined as those who are treatment resistant or "nonresponders". Typically, the probability a patient is cured is modeled with logistic regression, for patients who are uncured, the survival curve (S(t)) can be modeled using either a parametric model or the Cox semi-parametric model. For the mixture model, the predictors of incidence and latency can differ.

Let $\Theta = (t_i,\ \delta_i, Z_i, X_i)$ be the observed data for each individual, we define the matrix of predictors for latency as above, i.e. Z. We use X as the design matrix of predictors to predict the time to response, then the model can be presented as:

$$S(t|X,Z) = \pi(Z)S(t|X) + 1 - \pi(Z)$$

Where $1 - \pi(Z)$ is the probability of patients being cured based on Z, and $\pi(Z)$ represents the "incidence", $S(t|X)$ is the survival function of the uncured patients given X, which represents the "latency". For our study, we will implement the Cox proportional hazards version of the mixture model (proportional hazards mixture cure model, PHMC) (Maller and Zhou 2002). The distribution of failure time of uncured patients (latency) can be modeled using the PH model. Let Y be the indicator that an individual will experience the event (Y=1). We define a new $\Theta = (t_i,\ \ \delta_i, Z_i, X_i, y_i)$ with $y = (y_1, y_2, \dots \dots y_n)$, the likelihood for the mixture cure model is :

$$L(\beta) = \prod_{i=1}^{n} [1 - \pi(Z_i)]^{1-y_i}\, \pi(Z_i)^{y_i} h(t_i|y = 1, X_i)^{\delta_i y_i} S(t_i|y = 1, X_i)^{y_i}$$

where h(·) is the hazard function corresponding to S(·).

The Expectation-Maximization (EM) algorithm is used to estimate the unknown parameters in the mixture model. The E-step in the EM algorithm computes the expected value of y, i.e. the prevalence of response, the M-step then uses the estimated prevalence

to solve the standard cox regression maximization. This algorithm continues until convergence to the solution. Due to the fact that EM does not automatically calculate standard errors, the current package uses bootstrap resampling to estimate the standard errors (Cai et al. 2012).

3. Analysis Approach

First, we computed S(t) using Cox regression for the group of subjects with at least one follow-up (n=316), getting estimated rates of response and mean time to response within the 3 treatment groups. For treatment group comparisons, we used the escitalopram (SCIT) group as the baseline. For comparison we did a "simple" assessment of incidence and latency differences by separating into two models: logistic regression for prevalence and conditional (responders only) Cox regression to calculate time to response. We then fit the mixture model to simultaneously estimate incidence and latency.

Results

Looking at the raw data (Table 1), the CBT group had both the lowest prevalence of response (61.0%), and the longest time to response at 7.36 weeks (SE=0.39). For the medication groups, Dulox group had the lower prevalence of response (75.5%) than SCIT group (78.1%), as well as the longer time to response at 6.16 weeks (SE=0.41) than SCIT group, which had the mean time to response at 5.84 weeks (SE=0.39) . The results of the standard Cox regression indicate that the CBT group was significantly different from SCIT treatment groups (p=0.007), whereas there was no significant difference between

two medication groups (p=0.670). However, using the standard Cox regression testing, we cannot determine whether incidence or latency was responsible for the significance. In order to separate the effects of incidence and latency on significance, we used two models to test the incidence and latency separately: 1) Logistic regression was used to predict the response prevalence for all patients, and 2) Conditional survival analysis based on patients who have response (n=226) was used to test latency (Table 1). The comparison of response rates showed a significantly lower prevalence for the CBT group (61.0%) than SCIT group (78.1%) (p=0.008), but no significant difference of prevalence between two medication groups (p=0.652) was evidence that the response prevalence of the CBT group is significantly different from medication groups. The conditional survival analysis indicated that the mean time to response was 4.51 weeks (SE=0.33) for SCIT group and 4.81weeks (SE=0.37) for Dulox group, but, there was no significant difference between them (p=0.337). Even though the CBT group had the longest average time to response of 5.27 weeks (SE=0.34), it was not significantly different from SCIT group (p=0.180), which showed some differences from the result using Cox regression above. By comparing the results from Cox regression and conditional survival analysis, the results might suggest that the incidence was responsible for the significance. However, can we test the response prevalence and mean time to response simultaneously using a mixture model?

Our initial attempt to fit the mixture model to all data (n=316) resulted in a boundary solution (almost all subjects are responders) and therefore had invalid estimates. In order to isolate the nonresponse “signal” to fit the mixture model, we defined subgroups of the data where the response was less prevalent. Two "filters" were used to attempt to isolate

more TRD-like patients or nonresponse patient subgroups. 1) The subgroups of nonresponders or minimal response based on longitudinal trajectories, 2) The subgroups of nonresponse (<30% response) or partial response (<50% response) at endpoint.

For extracted subgroups of patients with minimal response or nonresponse in trajectory analysis (n=138), medication groups had very high response prevalence (93.8% for SCIT and 99.9% for Dulox), as well a slower mean time to response: 9.39 weeks (SE=0.10) for SCIT group, 9.96 weeks (SE=0.12) for Dulox group. In addition, the lowest response prevalence was 81.0% that was predicted within CBT group, whose response time of 10.36 weeks (SE=0.13) was the longest response time in all treatment groups (Table 1). However, we cannot determine whether there was any significant association between treatment groups since the prevalence was too high (close to 100%), and therefore a solution close to the boundary (variance approaching infinity).

The mixture model on the second isolated subgroup showed rational estimated response prevalence among treatment groups (n=84). As expected it was lower than the total group due to the filter. Similarly, the CBT treatment group showed the lowest (only 30.0%) response rate and longest mean response time of 10.25 weeks (SE=0.13) among all treatment groups, while SCIT had the highest response prevalence (52.4%) and the shortest response time of 8.07 weeks (SE=0.09), we noticed that there was no significant difference in response prevalence (p=0.161) and response time (p=0.179) between CBT and SCIT groups, respectively. Meanwhile, the Dulox group had 38.9% of responders and 9.40 weeks (SE=0.11) to response on average, also, it suggested no difference between medication groups in terms of incidence (p=0.439) and latency (p=0.474).

Although there was no significant difference between treatments on both response rate and mean time to response, the OR of nonresponse in the CBT group was 2.56, indicating the odds of nonresponse in the CBT group were 2.56 times as large as the odds of nonresponse for SCIT group. It was a particularly large effect size. Similarly, the HR of time to nonresponse in the CBT group was 1.93. Thus it may be that the current sample was too small (underpowered) to test these effects. However, there was evidence that the CBT group were more likely to be nonresponders to traditional treatment.

We compared survival curves for all patients in three different treatment groups (Figure 1). A vertical gap meant that at any specific time point during the treatment, the CBT group had a greater proportion of subjects who did not experience the response, whereas medication groups had a lower rate of response. But in contrast, the conditional survival curve for only responders showed that it took a shorter time for the treatment groups to experience response because we removed nonresponders who were censored at 12 weeks. (Figure 2). Comparing the median time to response in all patients with those in the responder group, we noticed that the median time to response of all patients group was one week less than that of the responder group in CBT and Dulox group, whereas it remained the same for SCIT group. This might suggest the SCIT group had a higher response prevalence. Since the cure was continuous and did not have any large plateaus, there was no clear evidence of a time to switch treatments.

Discussion

Principal Findings

We have proposed a mixture cure model for estimating the prevalence of response and the mean time to response, simultaneously. We found the current data did not indicate that the two medications were for the most part equally successful, however patients in the SCIT group had higher response prevalence and took a shorter time to respond. However, the raw data indicated CBT was different. The CBT patients were less likely to respond, but data on time to response was inconclusive, although there was evidence perhaps these subjects took longer to respond.

Fitting the mixture model without manipulating the data resulted in a boundary solution and therefore had invalid estimates. We assumed this was because response was highly prevalent in depression and therefore the use of the cure model might not be warranted like it was for cancer. The previous study had placebo groups which probably helped estimation of nonresponse. Then we proposed a filter approach to isolate subgroups of the data where the response was less prevalent. Although the filter strategy helped with estimation in the mixture model, it was not completely successful because reducing the sample size led to underpowered estimates.

In order to determine when to switch the treatment, a flat plateau would be expected in the survival curve. However, the Kaplan-Meier curves showed gradually decreasing changes in curves. The time to response was on average within 2-6 weeks. Thus the current data did not provide much information as to when to change the treatment strategies.

Limitations

One of the questions for this paper concerned how to identify when it was prudent to discontinue or switch the current treatment thus it would be helpful to test the effects across treatments compared to placebo. Unfortunately, in this study, we had several treatment groups but no placebo group due to observation study. In addition, this dataset only included the treatments of CBT and two medications, therefore, these results might not be appropriate for application to all main-stream treatment methods for depression. The invalid result of the implementation of the mixture cure model indicated that this model might not fit the data with a high prevalence of the "cure", because we had to use subgroups. Therefore, another limitation for this study might be underpowered statistics. We would need a much larger sample size in order to estimate the proportion of the nonresponse subjects more accurately.

Future Research

Although this study identified a potential method in implementing the mixture model in the response of depression treatment, the method itself did not isolate successfully the nonresponse subgroups. We had to use subgroups in order to get a better signal. Future research could identify criteria to isolate the nonresponse subgroups and use the methods discussed throughout this paper.

Additionally, identifying when to discontinue or switch the current treatments was not obvious in the current data. It would be beneficial to have a placebo group in order to identify the effect of the treatments. Also, CBT in conjunction with medication treatment would be an alternative way. Studies comparing CBT or other psychotherapies and medication for depression showed that psychotherapy delivered in conjunction with

medication is significantly more efficacious in treating depression than was medication alone (Cuijpers et al. 2013).

Conclusions

We found it inappropriate to use the mixture cure model with current clinical data due to high response prevalence. By defining subgroups to isolate the nonresponse, we were able to identify treatment nonresponders. Consequently, our results suggested that the vast majority of patients had the response in the treatment of depression. Our analyses did not identify when to discontinue or switch the current treatment. Additionally, the CBT group had a lower response prevalence, although CBT might take a longer time to respond than medications, such as SCIT and Dulox. These findings emphasized the adaptation of a mixture model, the model might not fit the data with a high prevalence of the "cure".

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Table and Graphs

Table 1: survival analysis estimates outcome: response

	Treatment Group	Response Prevalence	OR	OR SIG	Mean(Se) Time To Response	HR	HR SIG
Cox Regression	SCIT	78.1			5.84 (0.39)	1.000	- -
for All Patients	CBT	61.0			7.36 (0.39)	0.638	0.007
(N=316)	DUL	75.5			6.16 (0.41)	0.935	0.670
Logistic	SCIT	78.1	1.000	- -	NA	- -	- -
Regression	CBT	61.0	0.437	0.008+	NA	- -	- -
(N=316)	DUL	75.5	0.863	0.652+	NA	- -	- -
Cox Regression	SCIT	100	NA	- -	4.51 (0.33)	1.000	- -
for Responders	CBT	100	NA	- -	5.27 (0.34)	0.799	0.180
Only (N=226)	DUL	100	NA	- -	4.81 (0.37)	0.859	0.337
Mixture cure	SCIT	93.8	1.000	- -	9.39 (0.10)	1.000	- -
model (Filter 1)	CBT	81.0	0.283	*	10.36 (0.13)	0.676	*
(N=138)	DUL	99.9	73.49	*	9.96 (0.12)	0.680	*
Mixture cure	SCIT	52.4	1.000	- -	8.07 (0.09)	1.000	- -
model (Filter 2)	CBT	30.0	0.390	0.161	10.25 (0.13)	0.518	0.742
(N=84)	DUL	38.9	0.579	0.463	9.40 (0.11)	0.709	0.540

Significance values are for model estimates with baseline (SCIT)

+ OR from logistic regression of proportions of response by treatment group

* Log-lik converged before variable 1, beta may be infinite.

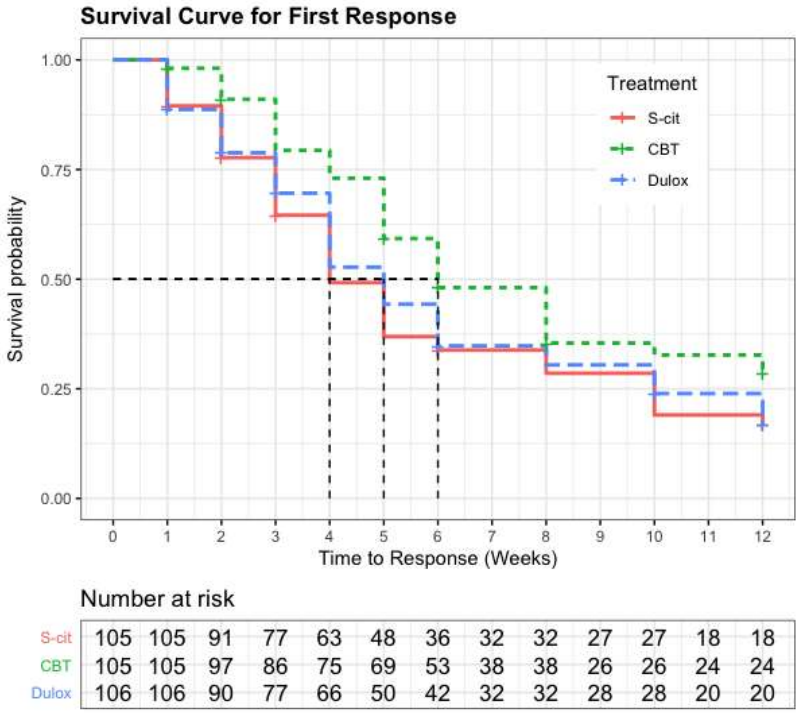

Figure 1. Survival curve for all patients

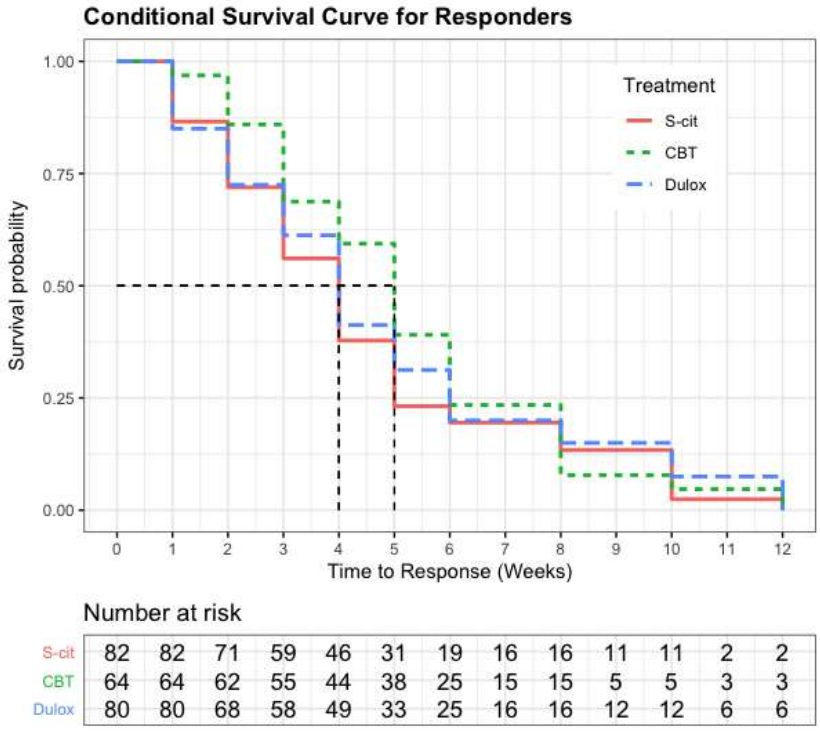

Figure 2. Conditional survival curve for responders