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Non-random dropout and the relative efficacy of escitalopram and nortriptyline in treating major depressive disorder

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ABSTRACT

Most comparisons of the efficacy of antidepressants have relied on the assumption that missing data are randomly distributed. Dropout rates differ between drugs, suggesting this assumption may not hold true. This paper examines the effect of non-random dropout on a comparison of two antidepressant drugs, escitalopram and nortriptyline, in the treatment of major depressive disorder. The GENDEP study followed adult patients with major depressive disorder over 12 weeks of treatment, and the primary analysis found no difference in efficacy of the two antidepressants under missing at random assumption. By applying the recently developed Muthén–Roy model, we compared the relative efficacy of these two antidepressants taking into account non-random distribution of missing outcomes (NMAR). Individuals who dropped out of the study were those who were not responding to treatment. Based on the best fitting NMAR model, it was found that escitalopram reduced symptom scores by an additional 1.4 points on the Montgomery–Åsberg Depression Rating Scale ($p = 0.02$), equivalent to 5% of baseline depression severity, compared to nortriptyline. We conclude that association between dropout and worsening symptoms led to an overestimate of the effectiveness of treatment, especially with nortriptyline, in the primary analysis. These findings review the primary analysis of GENDEP and suggest that, when non-random dropout is accounted for, escitalopram is more effective than nortriptyline in reducing symptoms of major depression.

1. Introduction

Antidepressants are the primary treatment for moderate and severe depression. It can take up to 6–8 weeks of treatment for symptoms to decrease (Anderson et al., 2008; Uher et al., 2011). However many individuals do not complete treatment (Lingam and Scott, 2002; Olfson et al., 2006). The reasons for discontinuing treatment vary, and include lack of response, side-effects, and remission of symptoms. In a clinical trial these factors can make dropout systematically related to outcome. This is especially important in the comparison of antidepressants that differ in the burden of side-effects and the percentage of individuals who complete treatment. For example, clinical trials comparing tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have reported higher rates of drop-out in the TCAs (Arroll et al., 2005; Hirschfeld, 1999; MacGillivray et al., 2003; Uher et al., 2009b), potentially complicating the comparison of efficacy.

When making the decision whether to continue or stop medication, the patient and clinician often weigh the perceived therapeutic effect against the burden of side effects. This systematic relationship between efficacy, side effects and discontinuation can produce data not missing at random (NMAR) (Little and Rubin, 2002). This means that missing data differ systematically from

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observed values. It is often described as informative or non-ignorable missingness, and differs from data missing completely at random (MCAR) and data missing at random (MAR). With MCAR, the outcome variable is not related to the probability of dropout. In MAR, the observed values of the outcome variable are related to the probability of dropout, but the unobserved outcomes are not, after accounting for other covariates included in the analysis. In MNAR, the unobserved outcomes are related to the probability of dropout. An example of NMAR would be when individuals stop improving and dropout of the study before assessment, and so are lacking measurements showing the lack of improvement from which the cause of dropout could be established. Whether missing data are considered informative depends on the method of analysis, specifically which types of missingness it can account for. For instance, in general estimating equations both MAR and NMAR non-ignorable, while in likelihood based estimation only NMAR is non-ignorable. As a result, conventional methods of assessing and comparing the efficacy of antidepressants may produce biased results unless NMAR data are explicitly modelled and taken into account. In this case, the unobserved cause of missingness may be related to the trajectory of response to anti-depressants, and so captured by latent variables representing the slope or intercept of response. Several previous studies have shown the benefits of trajectory modelling in the analysis of clinical data (Gueorguieva et al., 2011; Marques et al., 2011; Stauffer et al., 2011; Uher et al., 2010a). A method based on trajectory modelling has been proposed to account for NMAR and has been previously applied to dropout in level I of the STAR*D study where all patients were treated with the same SSRI antidepressant (Muthén et al., 2011). This model looks for an association between patterns in dropout during the study and trajectories of response to treatment. It has also been used as a secondary analysis of a comparison of duloxetine against SSRIs and placebo treated groups (Gueorguieva et al., 2011). Here, we apply this method to the comparison of the efficacy of two antidepressants in the GENDEP study: escitalopram (an SSRI) and nortriptyline (a TCA). While the primary analysis of GENDEP showed no difference in efficacy between the two antidepressants (Uher et al., 2009b), they differed in percentage of individuals who dropped out of the study. Our aim is to examine if the differential dropout has affected the efficacy comparison.

2. Materials and methods

2.1. Sample

The Genome-Based Therapeutic Drugs for Depression (GENDEP) project has been described in detail elsewhere (Uher et al., 2009a, 2010b). It incorporated 811 treatment-seeking adults of white European ancestry with a diagnosis of major depressive disorder and currently in a mild-to-moderate depressive episode, established in the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview, treated across 9 European centres (in Belgium, Croatia, Denmark, Germany, Italy, Poland, Slovenia and the UK). Personal or family history of bipolar affective disorder, mood-incongruent psychotic symptoms or active substance dependence were exclusion criteria. The present study uses 792 individuals (288 male and 504 female) who had available post baseline data on the primary outcome measure (Table 1). GENDEP was part-randomised as patients with no contraindications were allocated randomly to either escitalopram or nortriptyline. If an individual had a known history of side effects with one drug, they were non-randomly allocated to the other. This lead to 466 randomly allocated and 326 non-randomly allocated subjects (overall 56% on escitalopram). Symptoms were measured at weekly intervals, starting at week 0 (baseline) and continuing until week 12. The percentage of individuals missing data was 17% at week 4, 27% at week 8, and 36% at week 12. The 10-item Montgomery–Åsberg Depression Rating Scale (MADRS), rated by trained psychiatrists and psychologists with excellent inter-rater reliability (Uher et al., 2008), was the primary outcome measure and was used for all analyses. The GENDEP project was approved by ethics boards of participating centers, and all participants provided written informed consent.

Table 1
Clinical summary of drug groups in GENDEP.

Drug	*N*	Mean baseline MADRS (S.D.)	Percentage female	Percentage dropping out by:		
				Week 4	Week 8	Week 12
Escitalopram	446	28.3 (6.7)	62%	14.8	24.0	30.3
Nortriptyline	346	29.1 (6.8)	66%	20.2	32.4	45.1

2.2. Modelling of trajectories

To examine individuals' responses to antidepressants, growth mixture modelling (GMM) was used (Muthén et al., 2002). Here individuals' scores at each week are used to estimate latent variables, unobserved variables derived from the observed data, to create trajectories of response to antidepressants. From these trajectories an individual's scores at later weeks could be predicted. Three latent variables were defined: the intercept, slope, and curve (quadratic function) of symptom severity over time. Using a random effects model, the latent trajectory variables were used to classify individuals to classes which are relatively homogeneous in response to treatment. To evaluate the effects of NMAR data on treatment outcome, several models were examined which extended upon GMM. The first approach was a pattern mixture model (Little, 1995). This identified patterns of missingness within the data, e.g. complete data, dropping out at week 1, dropping out at week 2, etc. For this dummy variables were used, identifying the week of dropout. A model of response to treatment was estimated separately for each pattern, on the assumption that individuals who dropout at the same time are more alike than those that dropout at other times. Each pattern gave different estimates for the covariance between observations, and so the latent intercept, slope and quadratic variables. The results for each pattern were then weighted and averaged according to their frequency in the dataset. Those individuals dropping out in week 1 were only used for calculation of the intercept variable, as calculation of the slope or quadratic function requires multiple time points. For the same reason those dropping out in week 2 were not included in calculating the quadratic function, which required change over three time points to differentiate from linear change.

Dropout in trials has been attributed to several factors linked to distinct responses to treatment (e.g. remission of symptoms and non-response to treatment), which are not incorporated in pattern mixture models. Therefore, two models were proposed to identify latent classes in the missingness patterns, reflecting different categories of dropout. The Roy (2003) model created classes from dummy variables representing the week an individual dropped out of the study, seeking to summarise this information into dropout patterns. The slope, intercept and quadratic latent variables were then estimated independently for each class. This accounts for the possibility that not all individuals dropping out at the same week did so for the same reason and that these reasons were unlikely to be unique to that week. In the Muthén–Roy model (Muthén et al., 2011), two types of classes were defined: a dropout class and an outcome class. The former was derived in the same way as in the Roy model, from the information on an individual's week of dropout. The latter was derived from the latent trajectory variables (intercept, slope and quadratic) and represented the response to

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treatment, or outcome. Each individual was then assigned to one class which represented their dropout status and another class representing their outcome. Different combinations of the dropout classes and outcome classes were examined, providing an exhaustive classification of the possible relationships between dropout and outcome. This approach avoids confounding of dropout classes with outcome classes.

The Bayesian Information Criterion (BIC) was used to decide on the optimal number of classes within each model and to compare the models. BIC is a measure of how well the model fits the data. It is derived from the log likelihood of the parameters given the data with a penalty for number of parameters in a model. This favours parsimonious models over complex ones, and avoids over-fitting. The model with the lowest BIC is considered to provide the best fit. All models were first run with the assumption of equal (linear) spacing between weekly observations and then with time coded on a logarithmic scale, where spacing of time points in the model was week 0 = log 1, week 1 = log 2, etc. This was to more accurately models the large changes in the early weeks of treatment and progressively decreasing rate of change in later weeks. This affected the calculations of the trajectory gradients, which obviously depend on the spacing of each time point within the model. This was particularly relevant for classes which represented individuals who had dropped out of the study. All models were fitted in M*plus* 6.1 (Muthén, 1998–2010), using scripts adapted from Muthén et al. (2011) (http://www.statmodel.com/examples/penn.shtml#stard).

2.3. Comparison of treatment groups

To test the impact of this difference in dropout in a more traditional analysis framework, the optimum model's results were incorporated into the drug comparison by linear regression. Model estimates, derived as the average of each trajectory's estimated mean score for that week weighted by an individual's probability of belonging to each trajectory class, were used to replace missing measurements in individuals who dropped out of the study. The effect of drug was tested in a linear regression model with week 12 scores as the outcome, accounting for covariates. Two sensitivity analysis were then performed. First, the above method of a single imputation of missing values was tested again by linear regression including only randomised individuals. However, while this two-stage procedure of estimating drug differences with includes the mean scores by class, it does not account for the differing variance between classes and the uncertainty in estimating class membership. Therefore, we performed a second sensitivity analysis by incorporating treatment group into the optimal model. In this analysis, treatment group was used as a covariate for response (the slope and quadratic latent variables) and class. The mean difference in week 12 scores between the two treatment groups was then included as a parameter within the model and estimated. This was again run including only randomised individuals, to remove the possibility of confounding by indication and avoid the overly complex model needed to correct for differences in the non-randomised individuals. The weakness of this model was that the proportion of individuals belonging to each class for each drug could not be derived by the model itself but set at values from the results of the optimum model in the primary analysis.

3. Results

3.1. Modelling informative dropout

A comparison of model BIC scores (Table 2) shows two trends. Firstly, the Muthén–Roy model outperformed the pattern mixture model and Roy model. Secondly, models with time on a logarithmic scale improved model fit over models with linear time. In the Roy model, a 2-class model with a logarithmic time scale produced the best fit. These two classes were labelled as a dropout and non-dropout class, for which 18% and 71% of individuals completed the study respectively. This suggested that there were no distinct patterns of dropout within those individuals failing to complete the trial, only between those that completed the study and those that did not. The class made up primarily of those individuals dropping out showed no improvement at week 12 score over baseline. In contrast the class made up primarily of completers showed a drop of 17 points, or 61% of the baseline score.

Table 2
Summary of models fitted and Bayesian information criterion (BIC) scores. The lowest BIC score is considered the best fit, and shown in bold for each model. The Muthén–Roy without distal outcome model shows only the results for combinations with 2 dropout classes and a variable number of trajectory classes.

Model	No of classes	BIC score with linear time scale	BIC score with logarithmic time scale
Pattern mixture analysis (NMAR)	1	50968.5	50825.41
Roy latent dropout analysis (NMAR)	**2**	**50856.9**	**50701.22**
	3	50870.4	50750.47
Muthén–Roy without distal outcome (NMAR)	2	50869.3	50725.16
	4	**50797.3**	**50660.34**
	6	50799.2	50685.71
Growth mixture model (MAR)	1	50961.4	50751.69
	2	50906.2	50715.95
	3	50878.4	50693.46
	4	**50869.3**	**50681.2**
	5	50871.3	50692.5

On the basis of the Roy model results, two dropout classes were used in the Muthén–Roy model, which was run with an increasing number of outcome trajectory classes until the addition of a further outcome class no longer improved the fit. The best fit was found with a Muthén–Roy model with 2 dropout classes and 2 trajectory classes (giving 4 class combinations) and a logarithmic time scale. The 4 classes estimated in the best-fitting Muthén–Roy model are summarised in Table 3, and shown in Fig. 1. They can be interpreted as gradual responders, dramatic responders, non-responders and transient responders. The majority of individuals (73%) were in the gradual responder class which showed a gradual decrease in symptoms. The dramatic responder class showed even greater and more rapid improvement, though accounted for only 10% of individuals. In both these classes over 70% of individuals completed the study. In the non-responder class only 31% of individuals completed the study, and overall the class showed little improvement in MADRS score. The transient response class (containing 1% of individuals) was so named as it showed a large decrease in symptom levels by week 3 but then a subsequent increase to well beyond baseline score by week 12. This class's trajectory was largely based on changes in the early weeks, with all but one individual dropping out in the first half of the study. Its pattern shown in Fig. 1 reflects model-based extrapolation of smaller worsening immediately proceeding dropout.

3.2. Drug comparison

The primary analysis of GENDEP data showed equal efficacy for nortriptyline and escitalopram (Uher et al., 2009b). We were interested to find out the extent to which uneven dropout across treatment group may have affected this analysis. Multinomial logistic regression was performed on class membership estimated from the Muthén–Roy model classes to examine the effects of age, age of onset, sex, number of episodes and drug, weighted by an

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Table 3
Summary of Muthén–Roy model classes with logarithmic time scale.

Class	Number of individuals (%)	Percentage reaching week 12	Mean baseline MADRS score	Percentage change in MADRS score by week 12	Percentage of individuals who respond/remit in class	Percentage of individuals who respond/remit with estimated missing values	Percentage of individuals treated with escitalopram
Non responders	125 (16%)	31%	32	−17%	3%/0%	1%/0%	50%
Transient Responders	7 (1%)	14%	27	45%	0%/0%	0%/0%	86%
Dramatic responders	79 (10%)	72%	32	−77%	91%/62%	85%/44%	56%
Gradual Responders	581 (73%)	72%	27	−62%	69%/40%	66%/36%	57%

Response to treatment was defined by a 50% reduction in symptoms, and remission by a reduction of symptoms to a MADRS score below 7. Estimated values were constructed from the Muthén–Roy model, using estimated trajectory values at each week and individuals' probability of belonging in each class.

individual's probability of belonging to latent trajectory class. Only drug treatment group was found to be significant ($p < 0.005$), with larger numbers of individuals taking nortriptyline in the non-responder and transient responder classes. This was confirmed in a sensitivity analysis restricted to individuals randomly allocated to treatment.

In regression analysis of week 12 scores (including estimated missing values from the model) correcting for age, sex, and baseline MADRS score, treatment group had a significant effect on outcome ($p = 0.02$). Regression analysis (adjusted for age, sex and baseline score) found that, by week 12, individuals treated with escitalopram improved by 1.4 MADRS points more than those treated with nortriptyline, with an average week 12 MADRS score for escitalopram at 12.7 and nortriptyline at 14.4 (Fig. 2). This translates to an additional decrease of 5% of baseline MADRS score for those treated with escitalopram, or 10% of week twelve outcome scores. Whether an individual was randomly allocated to treatment or not was not significantly associated with outcome. The slightly larger difference between the averages than the result of the regression analysis is due to differences in average baseline scores between the two drugs. This difference in average baseline score was not present in the randomised individuals. When analysis was restricted to only those individuals who were randomised the effect remained equally strong (1.3 MADRS points, $p = 0.12$). The second sensitivity analysis incorporating the effects of drug into the model produced results that were consistent with the single imputation, showing a mean difference of 1.7 MADRS points and a p value of 0.21, with a reduced improvement again seen in nortriptyline. While not significant, comparison with the results for randomised individuals in single imputation method show them to be capturing the same effect and that differing variance between classes has little influence on results. Lastly, due to the transient response class consisting of only a small minority of individuals ($n = 7$) showing a unique pattern of response that was largely extrapolated, we wanted to test the sensitivity of our results to their inclusion. Removal of this class before imputing missing outcomes led to a minor change in effect size from 1.4 to 1.5 MADRS points but increased significance ($p = 0.008$).

4. Discussion

Dropout poses a problem for drug comparisons, potentially biasing results towards making treatments seem more similar than they actually are when those who are not responding leave the trial. A less well tolerated and less effective drug would lose more individuals to low response to treatment relative to a better tolerated drug, masking the difference in average severity by the end of the trial. Our results demonstrate this effect in the GENDEP study, where initial analysis found no difference in average response to escitalopram and nortriptyline. In this study the Muthén–Roy model was found to best account for the effects of missing data and, when used to estimate missing values, the treatment groups were found to have significantly different outcomes. It appears that greater dropout in nortriptyline hid a lower level of response, as more non-responders dropped out of the study. With a well established difference in dropout rates between TCAs and SSRIs (Arroll et al., 2005), this is particularly relevant to comparisons of these two classes of anti-depressants. However, this phenomenon poses a problem to drug comparisons in general.

Our results also demonstrate that the incorporation of models accounting for NMAR data leads to an increase in average severity of symptoms and a decrease in the estimate of response to treatment by the end of the trial. This is best seen in the Muthén–Roy model where those classes made up of a majority of dropout

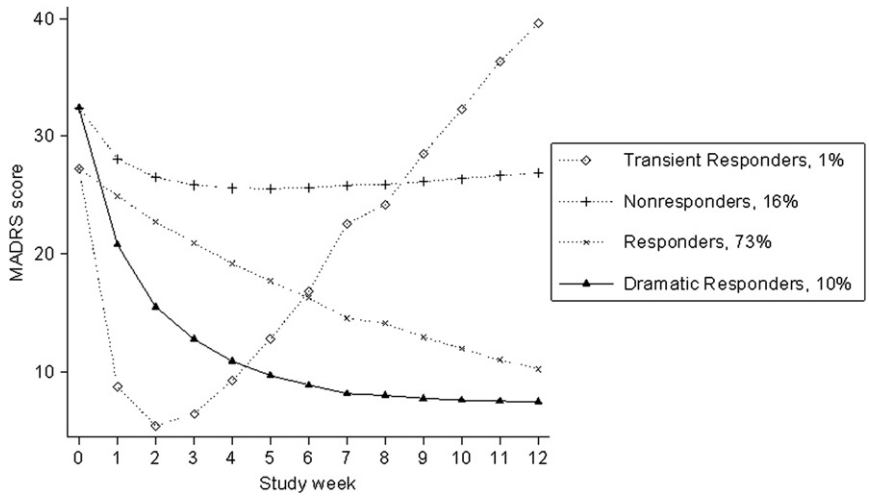

Fig. 1. Muthén–Roy 2 outcome 2 trajectory classes with logarithmic time scale, showing estimated mean MADRS score at each week.

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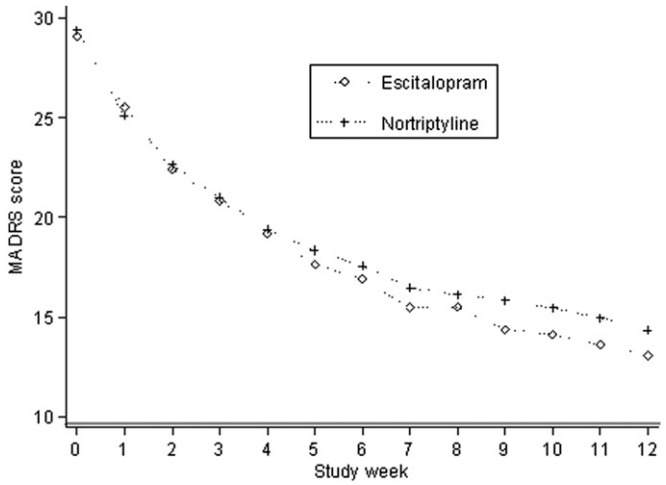

Fig. 2. Drug comparison of mean score at each week including estimated missing values from Muthén–Roy model. Missing values were estimate using the predicted mean scores for the 4 classes weighted by the probability of an individual belonging to each class.

individuals having latent trajectories predicting more severe scores and the least response to treatment. The conclusion is that those dropping out were unlikely to respond to treatment, and so models which do not account for NMAR data risk overestimating the efficacy of treatment. A similar finding has been reported in the secondary analysis of a similarly designed study looking at antidepressant response with the Muthén–Roy model (Gueorguieva et al., 2011). Our study provides further evidence of non-random dropout posing a problem to the design and analysis of clinical trials.

With the exception of the transient response class, it is also interesting to note that our results highlight that response to antidepressants occurs mostly in the first two weeks (Uher et al., 2010a). This is largely captured in the quadratic function of our model, suggesting the widespread use of a linear component in trajectory modelling may not be necessary. The transient response class is also primarily driven by the quadratic function. While only a very small minority of individuals belonged to this class and its values in later weeks were largely extrapolated, this response pattern has been previously reported (Muthén et al., 2011) and its removal only strengthened the significance of our findings.

The demonstration that escitalopram may have superior efficacy to nortriptyline is based on the assumption of homogeneity within the four classes estimated in the best fitting model. While estimates from this model are likely to be closer to truth than results of analyses carried out under the MAR assumption, the limited sample size and relatively complex parametrization of the models limit the accuracy of these estimates. This complexity may lead to over-fitting of the model, though the limited sample size makes it difficult to perform cross validation by splitting the sample into discovery and replication sub-samples. This is especially true when multiple treatment groups are compared, or the optimum model accounting for NMAR data is one with a large number of latent classes (rather than the 4 class model in this study). In addition, the estimated difference between escitalopram and nortriptyline, while significant, does not reach the criteria for clinical significance (NICE). Therefore, we refrain from drawing conclusions on the efficacy of nortriptyline or other tricyclic antidepressants based on these findings.

In conclusion, our findings review the primary analysis of the GENDEP study and suggest that when non-random dropout is accounted for, escitalopram shows slight yet significant improvement in outcome over nortriptyline. This provides further evidence for the importance of accounting for NMAR in clinical trials comparing treatments that differ in terms of tolerability and dropout.

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Contributors

Rudolf Uher designed the analysis and was the primary supervisor across all stages. Robert Power performed the main analysis and drafted the manuscript. Bengt Muthén provided advice on the analysis and the writing of the manuscript. Neven Henigsberg, Ole Mors, Anna Placentino, Julien Mendlewicz, and Wolfgang Maier all revised the manuscript, providing insight from their experience in collecting and supervising the GENDEP study. Peter McGuffin and Cathryn M. Lewis provided supervision, statistical advice and input to the manuscript.

Author disclosure

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