



## 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.

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### 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 MNAR 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 MNAR non-ignorable, while in likelihood based estimation only MNAR is non-ignorable. As a result, conventional methods of assessing and comparing the efficacy of antidepressants may produce biased results unless MNAR 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 MNAR 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 led 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

**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

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.

### 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 MNAR 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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