Delay discounting as a predictor of relapse following anti-depressant discontinuation

Analysis Plan

Giles Story, Isabel Berwian, Quentin Huys

Study Dataset

The existing study, described by Berwian et al. is a two-centre, longitudinal, naturalistic observational study of antidepressant discontinuation. Berwian et al. recruited participants who decided to discontinue their medication independently from study participation after they had a) experienced one severe or multiple depressive episodes, b) initiated antidepressant treatment during the last depressive episode and c) now achieved stable remission. The final sample included 104 patients (age: 34.86 (11.1), 77% female) and 57 healthy controls (age: 34.12 (10.6), 70% female). The study aimed to examine predictors of relapse following antidepressant discontinuation.

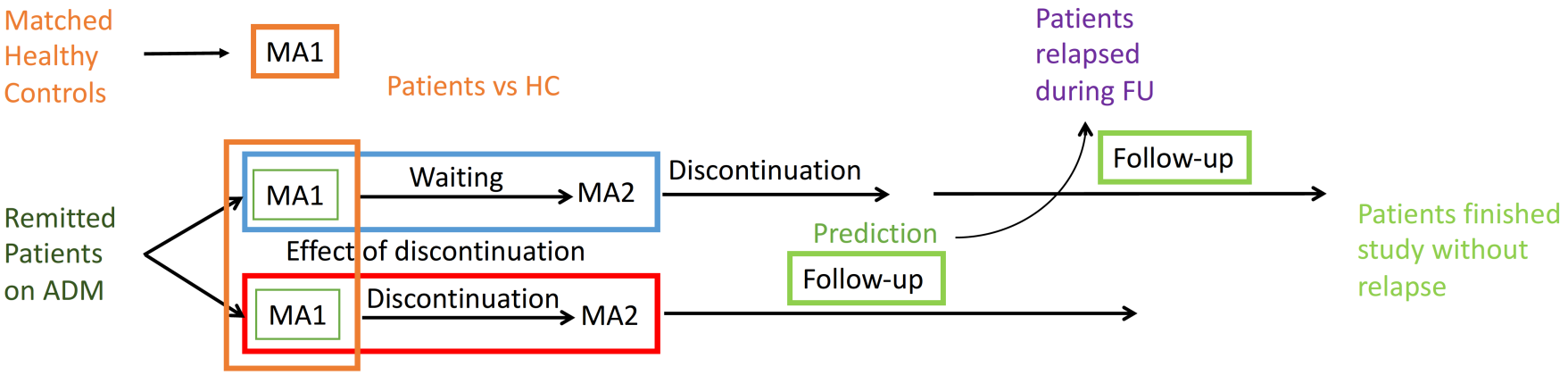

Figure 1. Study Protocol

As shown in Figure 1, participants were assessed and compared at main assessment 1 (MA1) to identify traits characterising the remitted, medicated state. Next, patients were randomised to either discontinue their medication until MA2 or enter a waiting period matched to the length of discontinuation time. Patients in the waiting group discontinued their ADM after MA2. After discontinuation, all patients entered the follow-up (FU) period of six months, whereas some patients had a relapse during this period and some patients finished this period without relapse.

Delay Discounting

Delay discounting is a widely used measure of impulsivity, which elicits a person's willingness to wait to obtain delayed rewards, rather than accept smaller immediate rewards. Impulsivity on this measure is summarised as an individual's discount rate, encapsulating the extent to which the value of reward decreases with delay. Delay discounting can be assessed by offering participants a series of choices,

termed intertemporal choices, between immediate and delayed rewards of varying magnitude. The existing study collected intertemporal choice data at MA1 and MA2.

Aims of current study

Previous studies have shown higher discount rates in people with depression compared with healthy controls. Previous work in humans has also revealed that discount rates increase following serotonin depletion, and are reduced by treatment with selective serotonin reuptake inhibitors. We therefore expect to observe increases in discounting following antidepressant discontinuation, offering a biomarker putatively predictive of subsequent relapse.

Analysis Plan

We will first find the parameters of a discount function which best explains the intertemporal choice data for each participant, at MA1 and MA2. This will yield a discount rate, referred to as K, for each participant at each of the two time points. Higher K reflects greater impulsivity. The logarithm of K is approximately normally distributed in the population.

We will go on to examine relationships between K and other variables of interest. Our planned analyses are described in Table 1.

Table 1. Planned Analyses

Analysis	***Dependent Variable***	***Independent Variable(s)***	***Hypothesis***	***Statistical Method***	***Contrast of Interest***	***Intention-to-Treat***
Impulsivity in depressed patients vs healthy controls	Log *K* at MA1	Group: patient vs control	At MA1 log *K* is greater in patients than controls	Two sample *t*-test	Main effect of Group	No
Impulsivity as a function of antidepressant discontinuation	Log *K* at MA1 and MA2	Group: early vs late discontinuation	Discontinuation is associated with an increase in log *K* between MA1 and MA2	Linear mixed effects regression modelling	Group x Time interaction	Yes
Impulsivity as a function of questionnaire data	Log *K* at MA1	HAM-D[1]	HAM-D scores are positively correlated with log *K*	Linear regression modelling, *t*-test on slope	Main effect of HAM-D	No
		SWLS[1]	SWLS scores are negatively correlated with log *K*	Linear regression modelling, *t*-test on slope	Main effect of SWLS	No
		ACE[1]	ACE scores are positively correlated with log *K*	Linear regression modelling, *t*-test on slope	Main effect of ACE	No
		HAM-D, ERQ, BSCS, SWLS, ACE, CTQ, TLEQ, MWT-B[1]	Exploratory analysis: a combination of questionnaire measures (and/or their latent factor structure) is associated with discounting	Linear regression modelling; sparse partial least squares regression, *t*-tests on slope	Main effects of questionnaire measures, or corresponding factors	No

		HAM-D, ERQ, BSCS, SWLS, ACE, CTQ, TLEQ, MWT-B[1]	Exploratory analysis: a combination of questionnaire measures (and/or their latent factor structure) *predicts* discounting	Lasso regression modelling; leave one out cross validation within Zurich sample; test prediction on Berlin sample as a hold out	Main effects of questionnaire data, or corresponding factors	No
Relapse rate over time as a function of impulsivity	Relapse in both patient groups	Log *K* at MA1	Higher log *K* at MA1 is associated with greater odds of relapse	Cox proportional hazard modelling	*K* x Hazard interaction	Yes
			Higher log *K* at MA1 *predicts* relapse	Lasso regression modelling; leave one out cross validation within Zurich sample; test prediction on Berlin sample as a hold out	Main effect of *K*	No

Relapse over time in the patient group as a function of change in impulsivity following antidepressant discontinuation	Relapse in early discontinuation patient group	Log *K* at MA1 and MA2	Increase in log *K* between MA1 and MA2 is associated with greater odds of subsequent relapse	Cox proportional hazard modelling	*K* x Time x Hazard interaction	Yes
			Increase in log *K* between MA1 and MA2 *predicts* subsequent relapse	Lasso regression modelling; leave one out cross validation within Zurich sample; test prediction on Berlin sample as a hold out	*K* x Time interaction	No
Depression score over time as a function of impulsivity	Hamilton Depression Scale (HAM-D) scores	Log *K* at MA1	Higher log *K* at MA1 is associated with reduced recovery in HAM-D score over time	Linear mixed effects regression modelling	*K* x Time interaction	Yes

1. Hamilton Depression Scale (HAM-D), Emotion Regulation Questionnaire (ERQ), Brief Self-Control Scale (BSCS), Daily Hassles, Satisfaction with Life Scale (SWLS), Adverse Childhood Experience (ACE), Childhood Trauma Questionnaire (CTQ), Traumatic Life Events Questionnaire (TLEQ), Digit Span and the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B).