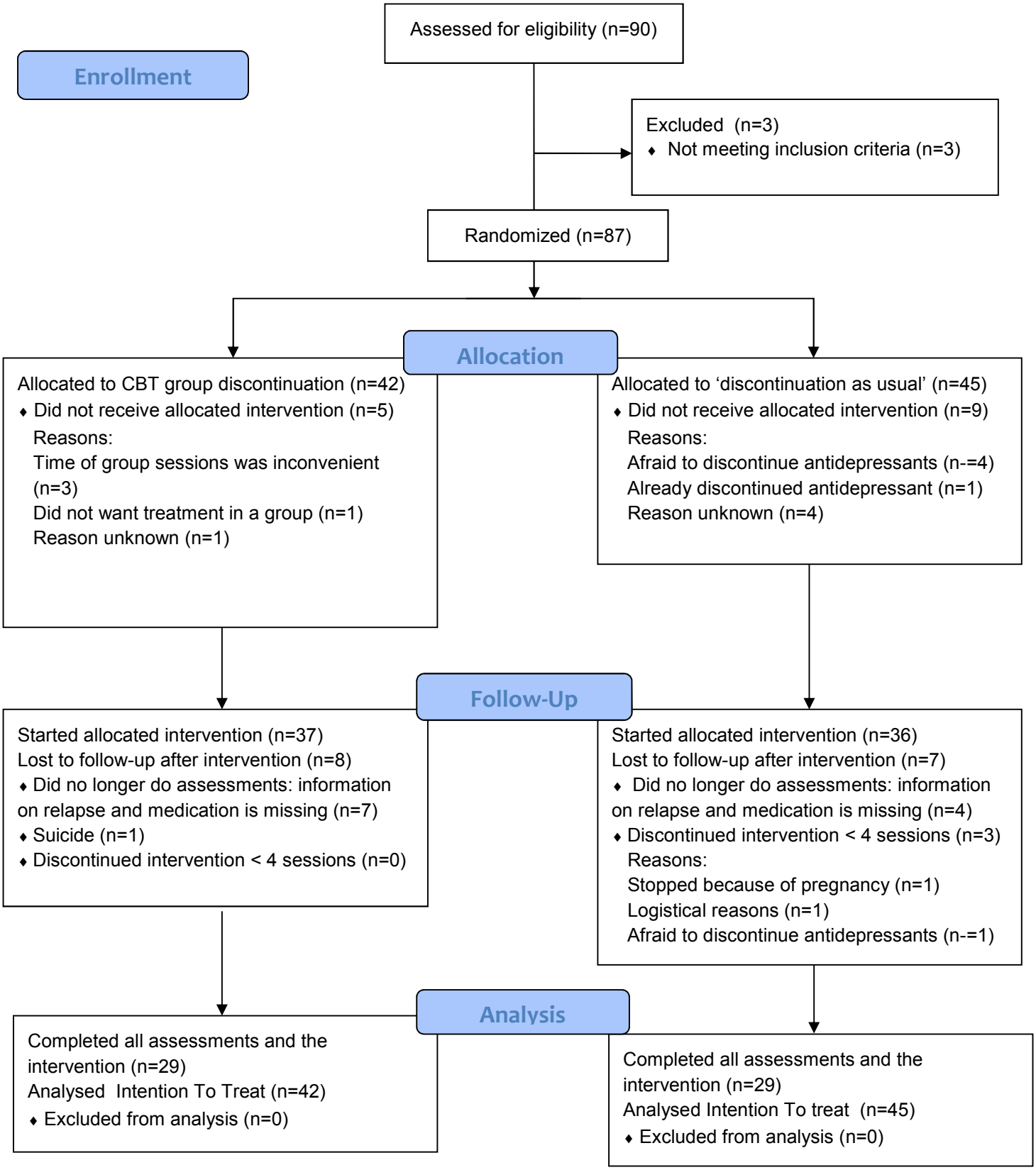
Online supplement

The efficacy of a group-CBT relapse prevention program for remitted anxiety disorder patients who discontinue antidepressant medication: a randomized controlled trial:

1. **Flow diagram**
2. **Design**
3. **CBT intervention**
4. **Discontinuation schedule antidepressants**
5. **Table: baseline characteristics**
6. **Survival curves**
7. **Table: relapse rates according to discontinuation**

1. Flow Diagram



2. Design

Study	**I----------I----------I----------I----------I----------I**					
	T0	**T1**	**T2**	**T3**	**T4**	**T5**
	Baseline	4-months	7-months	10-months	13-months	16-months
Intervention	**I……..I**					
	CBT group discontinuation/					
	Discontinuation as usual					
	within four months					
Outcome	Remission of anxiety disorder (SCID)*	Relapse anxiety/ onset MDD** (SCID)	Relapse anxiety/ onset MDD (SCID)	Relapse anxiety/ onset MDD (SCID)	Relapse anxiety/ onset MDD (SCID)	Relapse anxiety/ onset MDD (SCID)
Predictors	Assessment*** of predictors					

***Remission of anxiety disorders was assessed using the Structured Clinical Interview for DSM IV axis I disorders (SCID-I). To be included, participants were required to have at least a lifetime but no current anxiety panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia and generalized anxiety disorder. Assessments were done via face-to-face interviews and at 7, 10 and 13 months through a telephone interview.

****Relapse or onset in the previous three of four months of: 1) the previous anxiety disorder (panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia and generalized anxiety disorder) AD were used for; 2) another anxiety disorder (i.e. the previous anxiety disorder or onset of a new anxiety disorder); and 3) any anxiety disorder (panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia and generalized anxiety disorder) or a Major Depressive Disorder (MDD), within 16 months after baseline (i.e. 12 months post-intervention). Diagnoses were assessed using the anxiety disorder and depression section of the SCID-I.

***Including the following putative predictors: age, gender, partner status, educational level attained (in years), duration of the remission at baseline from the anxiety disorder (months), and the number of anxiety disorders lifetime (1 or more than 1). Family history (first degree, not including offspring) of anxiety and depression was determined using the Family Tree Inventory [1]. Type of AD was assessed, as well as the duration of AD use (months), and how many times the person had previously attempted to discontinue AD. Severity of anxiety symptoms was measured using the 21-item Beck Anxiety Inventory (BAI, range 0-63), and avoidance symptoms were assessed using the 15-item Fear Questionnaire (FQ, range 0-120) [2]. Participants were asked if they had received psychological treatments in the past two years. Disability, in six domains of life (cognition; mobility; self-care; getting along with others; life activities and participation) in the past 30 days was measured using the 36-item WHO-Disability Assessment Schedule II (range 1-100) [3]. The Anxiety Sensitivity Index, a 16-item self-report questionnaire, was used to assess fear of anxiety-related somatic sensations [40. Neuroticism was assessed using the 12-item subscale 'neuroticism' (range 0-60) from the NEO personality questionnaire, a 60-item questionnaire measuring five personality domains [5]. The DESS was completed every two weeks during the discontinuation period and a total score was calculated (points being scored depending on the extent of suffering from a symptom; range 0-46).

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3. CBT intervention

The CBT intervention was based on available effective studies in this field: i) two small studies showed that discontinuing AD while undergoing CBT did not induce panic symptoms in patients with a panic disorder [1;2]; ii) adding CBT to discontinuation of benzodiazepines in patients with panic disorder or GAD facilitated stopping this medication [3-6], although this is a different kind of medication with different discontinuation symptoms; iii) CBT or mindfulness training prevented relapse in remitted depressive patients with a high risk of recurrent depression [7-10]; and iv) a CBT relapse prevention program provided to patients who were not using AD prevented relapse in patients with anxiety disorders [11;12]

The 8 sessions always contained: agenda setting; review of homework; agreement on a next step in discontinuation of AD according to a fixed schedule (**Supplement 2**); discussing discontinuation symptoms; explanation of CBT techniques; practicing techniques; and assignment of homework.

An effective CBT intervention to guide AD discontinuation targets known predictors of relapse and includes interventions based on the literature on effective relapse prevention studies [13]. Therefore the intervention was provided in group sessions, similar to effective psychological interventions in preventing depression. We attempted to do so by including the following aspects in the intervention. First, in each session, the presence of discontinuation symptoms was assessed using the DESS, and discontinuation symptoms were discussed. Many patients who discontinue AD experience discontinuation/withdrawal symptoms [14;15]. As discontinuation symptoms may mimic symptoms of an anxiety disorder, discontinuation symptoms were explicitly labeled as such to prevent potential catastrophic interpretations about re-emerging anxiety [5], which in turn may increase anxiety and result in relapse. In addition, slowly tapering AD was conducted to reduce the intensity and occurrence of discontinuation symptoms [16;17]. AD was tapered every two weeks according to a fixed tapering schedule as described in **Supplement 2** (depending on the dosage and type of AD). According to the schedule, full discontinuation was achieved well within four months. Second,

cognitive therapy interventions were provided focusing on diminishing underlying dysfunctional attitudes (and not as in acute treatment on dysfunctional automatic thoughts). This strategy has shown promise in preventing relapse in patients with a recurrent depression [7]. Third, we focused on diminishing anxiety sensitivity, i.e. the tendency to interpret bodily sensations as catastrophic, because some studies have shown increased anxiety sensitivity to be predictive of relapse in anxiety disorder patients [18;19]. Moreover, anxiety sensitivity can be influenced by using CBT [20]. Therefore, we aimed to do so by altering dysfunctional attitudes and by including interoceptive exposure techniques in the protocol. Fourth, exposure exercises were included to diminish residual avoidance behavior, as this may be associated with an increased relapse risk [21-24]. Fifth, participants formulated a personal relapse prevention plan, including personal predictors for relapse, early signs and symptoms, and strategies to cope with relapse symptoms. This is recommended in international guidelines for patients who have initially remitted, and moreover, has proved to be effective in preventing relapse in OCD as part of a relapse prevention program [11]. A final phenomenon that may be of influence on relapse is state-dependent learning. In state-dependent learning, learning is associated with a specific chemically altered state, such that the learned information cannot be recalled or used unless the subject is restored to the state that existed when learning first occurred. We therefore not only offered CBT interventions during tapering medication, but also after full discontinuation. In this way, patients experience learning new behavior in a medication-free state. Optimal timing of CBT when discontinuing AD is important[25;26].

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4.Discontinuation schedule antidepressants

Antidepressant	Dose	Session							
	Mg	1	2	3	4	5	6	7	8
(Es)citalopram[a]	60 mg	50	40	30	20	10	0		
	50	40	30	20	10	0			
	40	30	20	10	0				
	30	20	10	0					
	20	10	0						
	10	0							
Fluoxetine	All	0							
Fluvoxamine	300	250	200	150	100	50	0		
	250	200	150	100	50	0			
	200	150	100	50	0				
	150	100	50	0					
	100	50	0						
	50	0							
Paroxetine	60	45	30	20	10	5	2.5	0	0
	50	40	30	20	10	5	2.5	0	
	40	30	20	10	5	2.5	0		
	30	20	10	5	2.5	0			
	20	10	5	2.5	0				
	10	5	2.5	0					
Sertraline	200	150	100	50	0				
	150	100	50	0					
	100	50	0						
	50	0							
Venlafaxine	225	187.5	150	112.5	75	37.5	0		
	187.5	150	112.5	75	37.5	0			
	150	112.5	75	37.5	0				
	112.5	75	37.5	0					
	75	37.5	0						
	37.5	0							
Clomipramine	250	150	75	50	25	0			
	150	75	50	25	0				
	75	50	25	0					
	50	25	0						

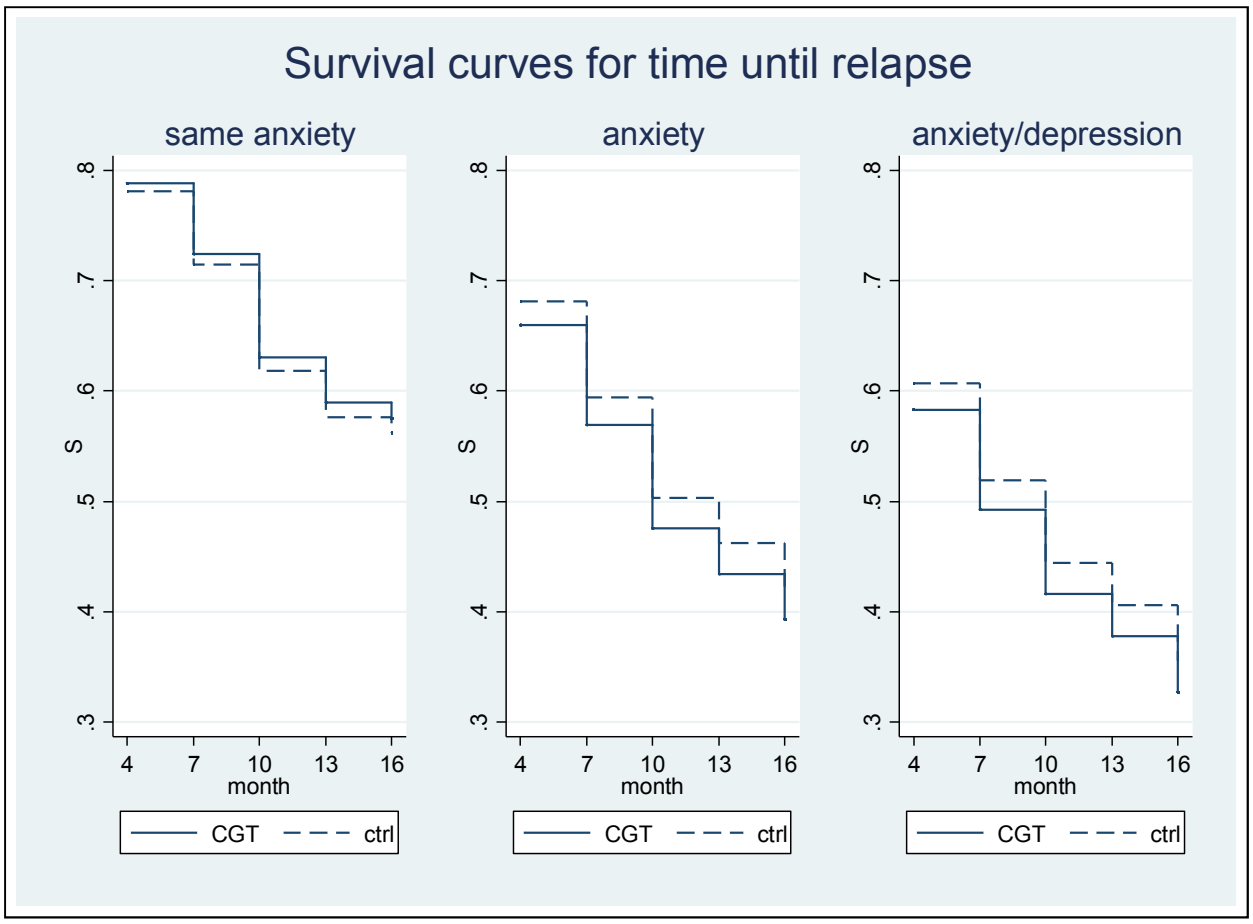
[a]At the time patients were included in this study the maximum dose was 50 or 60mg, but in the meantime the maximum is lowered to 40 mg.

5. Sociodemographics, illness-related variables and psychosocial vulnerabilities at baseline (n=87)

Characteristics	CBT Group discontinuation (n=42)	Discontinuation as usual (n=45)
Age in years, Mean (SD)	42.7 (11.9)	40.8 (13.4)
Female gender %	60 (n=25)	60 (n=27)
Education level attained (years), Mean (SD)	11.2 (7.3)	11.8 (7.7)
Current partner %	79	74
Lifetime anxiety disorder according to the SCID (in remission at baseline) %:		
Panic disorder (without agoraphobia)	21 (n=9)	24 (n=11)
Panic disorder (with agoraphobia)	57 (n=24)	66 (n=30)
Agoraphobia alone	-	-
Social phobia	24 (n=10)	13 (n=6)
Generalised anxiety disorder	12 (n=5)	8 (n=4)
Obsessive-compulsive disorder	2 (n=1)	-
Lifetime depression	52 (n=22)	55 (n=25)
Number of years ago anxiety disorder started Mean (SD)	15.9 (11.3)	12.9 (8.3)
Remission of anxiety disorder in months, Mean (SD)	30.7 (34.2)	43.3 (44.2)
>1 anxiety or depressive disorder lifetime %	57 (n=24)	60 (n=27)
Family history of anxiety or depression prevalent %	88 (n=37)	97 (n=44)
Type of antidepressant medication %:		
SSRI	76 (n=32)	82 (n=37)
SNRI	19 (n=8)	13 (n=6)
TCA	2 (n=1)	2 (n=1)
Mirtazepine	2 (n=1)	2 (n=1)
Duration of AD use in months, Mean (SD)	77.0 (61.4)	77.9 (60.3)
Tried to discontinue AD before %	71 (n=30)	67 (n=30)
1 time	67 (n=20)	47 (n=14)
> 1 time	33 (n=10)	53 (n=16)
Severity of avoidance symptoms (FQ), Mean (SD)	21.6 (15.7)	15.0 (16.6)
Severity of anxiety symptoms (BAI), Mean (SD)	9.8 (7.2)	7.7 (6.5)
Use of psychological treatment in past 2 years %	57 (n=24)	64 (n=29)
Disability (WHODAS), Mean (SD)	18.1 (11.7)	14.5 (11.0)
Anxiety Sensitivity, Mean (SD)	16.2 (9.9)	14.1 (9.0)
Neuroticism (NEO), Mean (SD)	25.0 (8.4)	22.3 (7.1)

6.Survival curves

Survival curves, estimated from Cox-regression models, for time until ‘relapse of the previous anxiety disorder’, ‘relapse of the previous anxiety disorder or onset of a new anxiety disorder’ or ‘into previous anxiety disorder or onset of a new anxiety disorder or MDD’ (n=87)



CGT = the CGT discontinuation group, ctrl = discontinuation as usual

7. Relapse rates according to discontinuation: never discontinued, lowered dose/stopped but restarted, or stopped*, in completers sample (n=71)

	Never started discontinuation (n=18)	Lowered dose/stopped but restarted (n=27)	Stopped (n=26)	
Relapse of previous anxiety disorder (N=31)	33% (6)	70% (19)	23% (6)	chi2(2)=13.09, p=0.001
Relapse of any anxiety disorder(N=41)	56% (10)	78% (21)	38% (10)	chi2(2)=9.882, p=0.007
Relapse of anxiety disorder or MDD (N=44)	67% (12)	78% (21)	42% (11)	chi2(2)=7.297 p=0.026

***This group discontinued AD completely and this remained so until the last assessment**