Relapse Prevention in Major Depressive Disorder After Successful Acute Electroconvulsive Treatment: a 6-month Double-blind Comparison of Three Fixed Dosages of Escitalopram and a Fixed Dose of Nortriptyline – Lessons from a Failed Randomised Trial of the Danish University Antidepressant Group (DUAG-7)

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Abstract
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Introduction: Electroconvulsive treatment (ECT) is an effective treatment for severe depression but carries a risk of relapse in the following months.
Methods: Major depressive disorder patients in a current episode attaining remission from ECT (17-item Hamilton Depression Rating Scale (HAM-D_{17}) score ≤9) received randomly escitalopram 10 mg, 20 mg, 30 mg or nortriptyline 100 mg as monotherapies and were followed for 6 months in a multicentre double-blind set-up. Primary endpoint was relapse (HAM-D_{17} ≥16).
Results: As inclusion rate was low the study was prematurely stopped with only 47 patients randomised (20% of the planned sample size). No statistically significant between-group differences could be detected. When all patients receiving escitalopram were compared with those receiving nortriptyline, a marginal superiority of nortriptyline was found (p=0.08). One third of patients relapsed during the study period, and one third completed.
Discussion: Due to small sample size, no valid efficacy inferences could be made. The outcome was poor, probably due to tapering off of non-study psychotropic drugs after randomisation; this has implications for future study designs.
ClinicalTrials.gov Identifier: NCT00660062

Introduction
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Clinical practice and several randomised controlled studies have shown that a considerable proportion of patients with severe depression treated with electroconvulsive treatment (ECT) achieve remission after 8–12 treatment sessions over a period of 3–4 weeks [1]. However, the risk of relapse/recurrence is high in the following months. In a recent meta-analysis, the risk of relapse was estimated to be around 40% in a 6 month period after ECT [2]. The evidence on relapse preventing efficacy of antidepressant medication after ECT is sparse regarding choice of drugs and dosage [3].

In a randomised controlled prevention study covering a 25-week period after ECT, patients treated with paroxetine had a significantly lower risk of relapse (10% relapse) than patients treated with imipramine (30% relapse) and placebo (65% relapse) [4].

In a subsequent prevention study it was shown that 84% of subjects in remission after ECT relapsed on placebo drug treatment over a 25-week period, while treatment with nortriptyline and the combination of nortriptyline and lithium reduced the risk of relapse to 60% and 39%, respectively [5].

In the present study we aimed at investigating a potential dose-effect relationship regarding relapse prevention, by comparing daily dosages of escitalopram 10 mg, 20 mg and 30 mg, and additionally we compared these regimens with a daily dosage of 100 mg nortriptyline, which is generally considered an effective target dose in the treatment of acute depression. A dose range was chosen for escitalopram but not for nortriptyline, since escitalopram was the primary focus, whereas nortriptyline was our reference.

Unfortunately, the planned sample size was not achieved, and therefore this report also addresses design issues having an impact on study feasibility, which might be of importance for future research in the field.

Methods
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Organisation
This study was carried out within the Danish University Antidepressant Group (DUAG), [6].

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Ethics and patients

This study was carried out according to the Helsinki Declaration and the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP, 1997) guideline as provided by the European Medicines Agency [7]. The Committee on Biomedical Research Ethics, the Danish Health and Medicines Authority and the Danish Central Data Register approved the study. The study was registered before start at the ClinicalTrials.gov database with identifier NCT00660062 (https://clinicaltrials.gov/ct2/show/NCT00660062). The regional GCP units monitored the study.

Patients were screened and recruited from inpatient wards at participating psychiatric hospitals in Denmark (Hillerød, Gentofte, Rigshospitalet, Frederiksberg, Glostrup, Odense, Horsens, Esbjerg, Aarhus, and Aalborg). The patients received information, both in writing and orally, before written informed consents were obtained.

Inclusion criteria were: major depressive episode (index episode) within major depressive disorder according to DSM-IVR [8] (based on the use of the Mini International Neuropsychiatric Interview (M.I.N.I.) [9]), a completed ECT treatment, age above 18 years, a post-ECT 17-item Hamilton Depression Rating scale (HAM-D$_{17}$) [10] score of 9 or less being present for at least 7 days, and a written informed consent.

Exclusion criteria were: suicidality corresponding to a score > 3 on the HAM-D$_{17}$ item 3 or uncertainty on the degree of suicidality as judged by the investigator, manic symptoms corresponding to a score of 15 or more on the Bech-Rafaelsen Mania scale (MAS) [10], last ECT given more than 21 days prior to planned randomisation, duration of index episode exceeding 2 years, patient under coercion, dementia or organic brain damage likely to influence the ability to give informed consent or to assess the severity of depression, a history of previous relapse occurring within 2 months after an ECT course (for ethical reasons), schizoaffective disorder, bipolar disorder, ongoing abuse of alcohol or other substances, expected low compliance with study visit-schedule, treatment with fluoxetine less than 6 weeks prior to planned inclusion, current treatment with drugs being incompatible with study drugs, epilepsy, clinically significant liver or heart disease, glaucoma, pregnancy or breastfeeding, and inadequate contraception in fertile females.

A system for recording all screened and potentially eligible patients was set up at each centre.

Study design

Through a central, computerized procedure, eligible patients were randomly and double-blindly allocated to one of 4 treatment groups as described in the following with a block size of 2 [11]. The trial covered a period of 25 weeks with 16 planned data assessment points: baseline, weekly from week 1–5 and then every fortnight until week 25 with an additional safety visit at week 27. At all points patients were rated with the HAM-D$_{17}$, the Hamilton Depression Rating Scale 6-item subscale HAM-D$_6$ [12] and the MAS scale. As self-assessment scales the Major Depression Inventory (MDI) [13] and for quality of life the WHO-5 were applied [14]. Side effects were measured at all visits by the UKU scale [15].

The primary outcome was relapse defined as a HAM-D$_{17}$ scale score of 16 or above present for 14 days.

Criteria for premature study termination were: the patient wishes to withdraw consent, a MAS score higher than 15, side effects interfering with daily activities or deemed unacceptable by investigator, protocol violation, and plasma nortriptyline levels above the chosen safety limit of 700 nmol/l at days 11 or 18.

Rater training

As part of the set-up, investigators performed joint ratings on patients with depression using the Hamilton Depression Rating Scale. This was performed regularly at each centre, and every 4 months at a joint investigator meeting.

Medication and blinding

The dosing schedules of study medication, started after randomisation, were as follows: (Group A) 10 mg escitalopram daily from day one and throughout the study; (Group B) 10 mg escitalopram daily for 7 days, thereafter 20 mg daily throughout the study; (Group C) 10 mg escitalopram daily for 3 days, 20 mg for 4 days and thereafter 30 mg daily throughout the study; (Group D) 50 mg nortriptyline for 7 days and thereafter 100 mg daily throughout the study period. All medication was to be taken at 10 PM in the 4 treatment groups. Medicine packages containing medication for the whole study period in the form of medication packs with 5 tablets (active and placebo tablets of identical appearance) for each day were provided. The active medications were in the form of tablets containing 10 mg escitalopram or 50 mg nortriptyline, respectively. The medication was produced and packaged according to GMP rules [16] by a contract research organisation [11].

All concomitant drugs were tapered off over a maximum period of 8 weeks after randomisation. At the beginning of the study the tapering period was set to 2 weeks but due to observed discontinuation symptoms and many early relapses, we extended the tapering period to 8 weeks after 15 patients had been included. Hypnotics in recommended dosage and benzodiazepines up to a dosage corresponding to a daily dosage of 45 mg oxazepam were allowed throughout the whole study period.

Blood samples for plasma monitoring of escitalopram and nortriptyline were drawn in the morning on days 11 and 18 [17].

Sample size estimation

With a hypothesized risk of relapse over a 25-week study period of 30% for patients treated with 10 mg escitalopram daily, it would require 60 patients in each group (and a total number of 240 patients) to detect a 20% difference between 30 mg escitalopram and 10 mg escitalopram and between 30 mg escitalopram daily and 100 mg nortriptyline daily, at the 5% level of statistical significance with a power of 80%.

Data analysis

This is a Phase IV trial performed to test any difference between the 4 treatment groups with relapse rates as the primary outcome. All randomised patients assessed at one or more post-baseline visits were included in analyses (modified intention to treat population). Based on time to the relapse, a survival analytical approach was used with Kaplan-Meier curves and log rank test. In the survival analyses, observations that were terminated for other reasons than the endpoint in question were censored.

In a post-hoc analysis, all patients receiving escitalopram were compared with those receiving nortriptyline. In another post-

Characteristic	Escitalopram 10 mg n=11	Escitalopram 20 mg n=11	Escitalopram 30 mg n=10	Nortriptyline 100 mg n=14	P
Age, years mean (SD)	54.1 (20.3)	56.5 (10.8)	54.6 (13.5)	55.8 (13.8)	0.99
Female gender, per cent	72.7%	36.4%	40.0%	85.7%	0.03
Numb. episode mean (SD)	3.7 (3.3)	1.1 (1.1)	2.1 (1.8)	3.5 (5.5)	0.29
Dur. depres. illness, years, mean (SD)	22.3 (14.1)	10.4 (11.8)	10.6 (13.8)	9.2 (13.7)	0.10
Duration episode, months, mean (SD)	9.4 (11.7)	10.5 (7.2)	5.5 (4.1)	6.2 (2.9)	0.36
HAM-D$_{17}$ inclusion (SD)	6.5 (2.5)	5.8 (2.5)	4.2 (2.7)	5.6 (2.9)	0.25
HAM-D$_6$ inclusion (SD)	3.7 (1.7)	3.7 (2.2)	2.6 (2.0)	2.9 (2.1)	0.42
MAS inclusion (SD)	0.5 (0.8)	0.5 (1.5)	0.6 (1.0)	0.1 (0.4)	0.68
MDI inclusion (SD)	10.6 (6.0)	16.8 (7.7)	8.9 (8.2)	12.8 (9.1)	0.12
WHO-5 inclusion (SD)	64.4 (16.7)	54.9 (24.6)	61.6 (25.8)	65.4 (28.1)	0.79
SSRI	1	3	1	4	
SNRI	3	6	4	3	
Mirtazapine	4	0	3	4	
Tricyclic	0	2	1	3	
Quetiapine	2	2	3	1	
Olanzapine	0	4	1	2	
Chlorprothixene	0	2	0	1	
Risperidone	0	0	1	0	
Flupentixol	0	0	0	1	
Lithium	0	0	0	0	
Other	0	3	1	3	

Table 1 Baseline characteristics with standard deviations in brackets.

hoc pooled analysis of all patients receiving escitalopram, patients were divided according to the median escitalopram concentration. Survival analysis, using relapse as outcome, was then performed on the group of patients with concentrations respectively above and below the median to investigate any influence of plasma concentration on relapse.

Results
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More than 600 patients were screened for inclusion in the study, but due to the multiple exclusion criteria, patients' disinclination to participate and clinicians' reluctance to refer patients to the trial, recruitment was slow. Therefore the study was prematurely stopped when 47 patients had been randomised, i.e., 20% of the planned sample size. All patients entered the study from September 2009 to November 2012. One patient was withdrawn before drug administration due to early relapse and was not included in the efficacy analysis. Inter-rater reliability for training sessions was very high with an intraclass coefficient (ICC) of 0.93 for HAM-D$_{17}$, and 0.89 for HAM-D$_6$, and 0.91 for MES.
◗ **Table 1** shows sociodemographics, baseline psychometric values, and psychotropic drug use. Gender ratios differed between groups with more females in the escitalopram 10 mg and nortriptyline groups (p=0.03). We analysed the number of completers vs. the number of relapses for females/males and found no statistically significant relation between outcome and gender (p=0.46). No data were available on patients' HAM-D scores prior to their ECT course.
◗ **Table 2** shows patient disposition (endpoint all causes) and number of patients treated with different psychotropic drugs at baseline for each group. Overall, 16 (35%) patients relapsed and 15 (33%) had a successful outcome. 4 patients dropped out due to expiration of medication (administrative) due to delay in deliverance of a new medication batch from the contract research organisation. 2 patients had to be taken out due to serious adverse events (SAE): one patient treated with 10 mg escit-

Table 2 Patient disposition (endpoint all causes).

Outcome	Escitalopram 10 mg	Escitalopram 20 mg	Escitalopram 30 mg	Nortriptyline 100 mg	Total
Completer	3	5	1	6	15
Relapse	5	4	5	2	16
Left due to side effect	0	0	1	0	1
Left due to high plasma conc.	0	0	0	3	3
Wanted to end study	2	1	2	1	6
Protocol violation	1	0	0	0	1
Administrative	0	1	1	2	4
Total	11	11	10	14	46

alopram was re-admitted due to insomnia, probably caused by tapering-off of usual medication, and one patient treated with 30 mg escitalopram was readmitted to hospital due to prolongation of the ECG QTc interval above recommended value. 3 patients had to be taken out due to plasma nortriptyline concentrations above the stated safety limit of 700 nmol/l (one patient with 801 nmol/l at day 11, one patient with 1 182 nmol/l at day 18, and one patient with 1 090 nmol/l at day 18). Only one patient had plasma concentration below the recommended efficacy limit of 230 nmol/l on both days.
◗ **Fig. 1** shows Kaplan-Meier curves, based on relapse, for all 4 groups. No overall statistically significant difference could be detected (log-rank test, p=0.10).
When all patients treated with escitalopram were compared with the nortriptyline treated patients, numerically, the nortriptyline group performed better and this approached statistical significance (log-rank test, p=0.08) (◗ **Fig. 2**). No associations between escitalopram plasma concentration and risk of relapse were found (p=0.83).

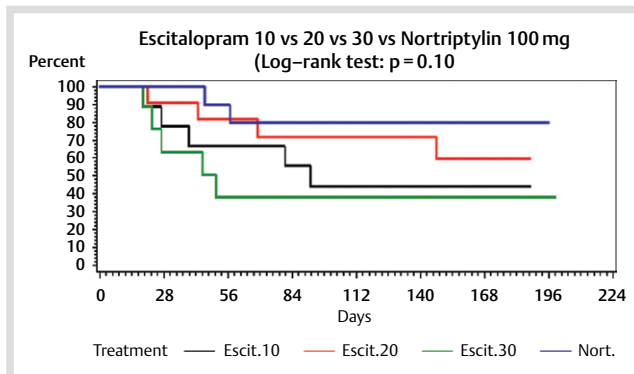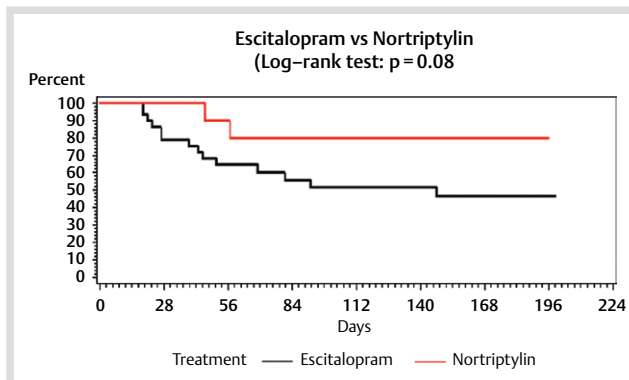**Fig. 1** Kaplan-Meier curves for the 4 treatment groups based on relapse.

Fig. 2 Kaplan-Meier curves for all patients receiving escitalopram (10 mg or 20 mg or 30 mg) and the nortriptyline group based on relapse.

Results on all-cause endpoints were similar to the above results (data not shown).

Regarding the UKU side-effect scale, the sum scores (last observation carried forward) were low and without statistically significant differences between groups.

Discussion
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The most important finding from this study is that one third of patients relapsed over the 6-month study period across all 4 treatment arms, and only one third had a successful outcome. This poor overall outcome is comparable with that of Sackeim et al [5]. Our study outcome might have been more favourable if patients had been started on pharmacotherapy before or at the same time as commencement of ECT as discussed below.

In this study we could not demonstrate statistically significant differences in risk of relapse between the 4 interventions. The lack of discrimination between risks of relapse in the 4 groups might obviously be ascribed to the small sample size (type II error). It could also be a true negative finding relating to the discontinuation of non-study drugs in all treatment groups. Relapse due to per-protocol tapering-off of non-study medication was also observed in a recently published long-term study from the DUAG [18]. However, it is worthwhile noting that patients treated with nortriptyline had a lower risk of relapse than the pooled group of patients treated with escitalopram, on an 8% statistical significance level. The nortriptyline dosage seemed to

be adequate as only one patient had a level below the recommended plasma concentration efficacy level (Danish Medicines Agency). Even though the marginal superiority of nortriptyline obviously might be related to the inclusion of patients dosed relatively low in the pooled escitalopram group, i.e., 10 mg, nortriptyline arm performance was numerically superior to each of the escitalopram arms (○ **Table 2**). We found no association between escitalopram plasma concentrations and the risk of relapse, although a recent study indicated a relationship between plasma citalopram and antidepressant efficacy [19]. Our negative finding on that aspect might be ascribed to the small sample size.

The results from the WHO-5 well-being scale confirm previous results showing that patients in remission, as defined by the HAM-D$_{17}$ scale, do still have some degree of poor well-being [20], below the Danish population mean of 68.7 [21] which emphasises the need for a broader concept of remission that includes patient perspective and side effects.

Our experience from this multicentre study is that it was difficult to recruit patients to a relapse prevention study when using mono-therapy after ECT. During the study period it became clear that the majority of patients had received one or more medications during ECT, and that the tapering-off of such ongoing non-study medications after randomisation caused distress and probably in itself increased risk of relapse. Accordingly, and based on impressions from regular consultations with centres, clinicians were reluctant to refer these severely ill hospitalised patients to a post-ECT trial using only mono-therapy study drugs. Unfortunately, the planned registration of all screened patients was incomplete, resulting in that no valid data on the distribution of eligible patients on various reasons for non-randomisation were available. Besides potentially reducing the power of a trial, non-randomisation of eligible patients, whether due to patients' or due to clinicians' resistance will most likely lead to limitations in generalisability of the study results [22].

Future studies should take the issues outlined above into consideration by allowing co-medication after randomisation. Another approach would be to start study medication prior to ECT, thereby maybe reducing the risk of early relapse and making the design more acceptable for patients and clinicians. This is supported by the study by Yildiz et al. [23] who found a significant reduction in relapse when trial medication was started early compared to later in the ECT course but not by the study by Prudic et al. [24], who found no difference in relapse rates when pharmacotherapy was started before or after ECT. However, if patients are randomised before remission has been obtained, the outcome of the post-randomisation acute treatment needs to be taken into account.

Overall, one third of patients relapsed over the 6-month study period, and only one third had a successful outcome. This calls for more research in this area.

The primary limitation was the small sample size with only 20% reached, in spite of allocation of patients for a prolonged period at 10 centres.

The main lesson to be learned is that allocating patients to study drugs given as monotherapy after remission is not feasible, and that pilot studies carefully revealing the reasons for non-inclusion of eligible patients are necessary [25].

Conflict of Interest
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Klaus Martiny and Else Refsgaard had part of their salary paid from a Lundbeck grant. Investigators received a grant for the inclusion of patients. This grant was solely to be used for research purposes and research education. No authors indicated any other conflicts of interest regarding the submitted paper.

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