Longer term benefits of exercise and escitalopram in the treatment of anxiety in patients with coronary heart disease: Six month follow-up of the UNWIND randomized clinical trial

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Introduction

Anxiety is highly prevalent among patients with coronary heart disease (CHD), and there is growing evidence that high levels of anxiety are associated with worse prognosis[1,2]. However, few studies have evaluated the efficacy of treating anxiety in CHD patients for reducing symptoms and improving clinical outcomes.

Exercise and selective serotonin reuptake inhibitors have been shown to be effective in treating patients with depression[3,4], but have not been studied in cardiac patients with high anxiety.

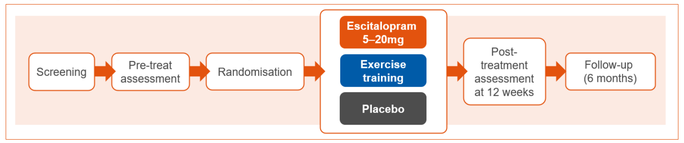
The UNWIND trial aims to evaluate the efficacy of aerobic exercise and escitalopram for improving anxiety symptoms and reducing risk for adverse clinical events in anxious CHD patients[5,6,7].

Methods

Patients were randomized to 12 weeks of escitalopram (up to 20 mg), exercise (3 times/week), or placebo pill. At the conclusion of treatment, participants were followed for 6-months to determine the persistence of benefit on the primary anxiety endpoint assessed by the Hospital Anxiety and Depression Scale-Anxiety scale (HADS-A) (**Diagram 1**). In addition to that, the long term effects of treatment on major adverse cardiac events (MACE) was tracked over a follow-up period of up to 6 years.

Patients with CHD and an anxiety symptom severity score of ≥8 on the anxiety subscale of the HADS-A and/or a DSM-5 primary diagnosis of an anxiety disorder were enrolled in the trial. Exclusion criteria included a primary psychiatric diagnosis other than an anxiety disorder, current treatment for a psychiatric disorder, or participation in any regular exercise > 1 d/wk.

Diagram 1:Summary of UNWIND study design



Results

Effects of Treatment on Anxiety (12-week treatment assessment)

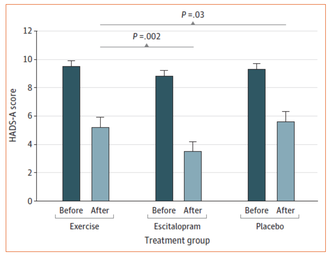
1) HADS-A

- All groups had significantly (p<0.001) reduced anxiety after 12 weeks of treatment with mean reductions in HADS-A score of: exercise (-4.0), escitalopram 5–20 mg (-5.7) and placebo (-3.5)[6]
- **Escitalopram** had **greater reductions in HADS-A scores compared with placebo** in post hoc analysis (p=0.003). Anxiety symptoms (measured by HADS-A) were **significantly lower** for **escitalopram compared to the exercise group**: -1.67 (95% CI -2.68, -0.66; p=0.002) **(Figure1)**[6]

2) STAI-S

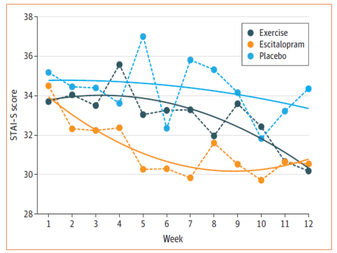
- After 12 weeks, participants in both the exercise and escitalopram conditions had comparable levels of state anxiety (exercise, 30.3; 95%CI, 27.7-32.9; escitalopram, 30.5; 95% CI, 28.0-33.0; P = .95)[6]
- The **escitalopram group** experienced more rapid improvements in anxiety symptoms **early in the treatment course**, however, while reductions in the exercise group occurred primarily in the latter 6 weeks of treatment **(Figure 2)**[6]

Figure 1: Pre-treatment and post-treatment (12-week) HADS-A scores



HADS-A, Hospital Anxiety and Depression Scale-Anxiety; Error bars represent SEs

Figure 2: Pre-treatment and post-treatment (12-week) STAI-S scores



STAI-S, Spielberger State-Trait Anxiety Inventory-State; Plotted lines represent fitted regression estimates using spline interpolation from exploratory analyses demonstrating that the effects of treatment varied over time.

Effects of Treatment on Anxiety (6 months follow-up period)

- Examination of changes in HADS-A scores revealed that the escitalopram group continued to show reduced anxiety relative to the Exercise and Placebo groups. Ancillary measures of anxiety also were examined including the STAI, GAD-7 and HAM-A. Results largely paralleled the primary outcome measure of HADS-A score, though a slightly weaker pattern of group differences were observed in the secondary outcome measures **(Table1)**[7]

Table 1:Six-month follow-up scores on 4 self-report measures of anxiety

Group	HADS-A	STAI-T	GAD-7	HAM-A
Escitalopram	3.9* (3.1, 4.7)	34.3** (32.7, 36.0)	2.2* (1.2, 3.1)	8.9 (7.4, 10.3)
Exercise	5.5 (4.6, 6.3)	35.6 (33.9, 37.3)	3.7 (2.7, 4.7)	10.6 (9.1, 12.1)
Placebo	5.3 (4.1, 6.5)	37.6 (35.1, 40.1)	3.3 (1.8, 4.8)	9.3 (7.1, 11.5)

** P < .05 Escitalopram v Exercise; ** P < .05 Escitalopram v Placebo; * P < .10 Escitalopram v Exercise; GAD 7, Generalized Anxiety Disorder 7 items; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HAM-A, Hamilton Anxiety Scale; STAI-T, Spielberger State-Trait Anxiety Inventory-Trait.*

Major adverse cardiac event (MACE) clinical outcomes (6 year follow-up period)

- Participants were followed for up to 6 years to record the occurrence of clinical events. Over a median follow- up of 3.2 years, 26 participants experienced at least one MACE event including 13 (25%) participants for exercise, 7 (13%) for escitalopram, and 6 (27%) for placebo **(Table 2)**. We found no differences between the 2 active treatment groups or placebo (hazards ratio = 1.01, P = .958), nor between escitalopram and exercise (hazards ratio = 1.16, P = .673)[7].

Table 2: Major adverse cardiac events by treatment group

Event	Escitalopram	Exercise	Placebo
Nonfatal MI	1	2	3
Fatal MI	1	0	0
Revascularization	2	10	1
Stroke	1	1	1
Hospitalization	2	0	1
Total events	7	13	6

MI, myocardial infarction

Conclusions

- Escitalopram is an effective treatment for anxiety in patients with CHD. In the UNWIND trial, 12 weeks of treatment was effective in reducing anxiety, as well as depression and general distress. Moreover, these beneficial effects appeared to persist for 6 months post-treatment, especially for those who continued treatment.
- While patients randomized to the exercise condition had greater functional capacity at 6-month follow-up, and less perceived stress compared to placebo controls, exercise was not effective in reducing symptoms of anxiety and depression.
- Although exercise has a number of health benefits, it should not be considered an effective treatment for anxiety in patients with CHD.
- No treatment-related adverse events were noted, both in the 12-week assessment period and over 1 year follow up

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