Effects of antidepressant treatment on heart rate variability in major depression: a quantitative review
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CRD summary
This review concluded that the use of tricyclic antidepressants in patients diagnosed with major depressive disorder lead to changes in heart rate variability that were associated with an increased risk of mortality. The authors' conclusions appeared to reflect the evidence but, given the methodological limitations, these conclusions should be interpreted with caution as they may not be reliable.

Authors' objectives
To investigate the effect of pharmacologic and physical treatments for depression on heart rate variability in otherwise well patients with major depressive disorder.

Searching
Studies were identified through a search of the databases MEDLINE and PsycINFO. The references of retrieved articles were searched for additional studies. Search terms were reported.

Study selection
Studies in adults aged 18 or more with a diagnosis of major depression who were administered an antidepressant (tricyclic antidepressants or selective reuptake inhibitors) or electroconvulsive therapy were eligible for inclusion. Studies were required to assess heart rate variability either pre-drug or post-drug initiation, or between a treated group and an untreated or placebo control group. Studies with two treatment groups were only accepted if patients were randomised. Studies using a variety of drugs were only included if data were presented for each drug separately. Outcome measures included heart rate, time domain measures and frequency domain measures.

Of the included studies, tricyclic antidepressants included amitriptyline, imipramine and doxepin. Selective serotonin reuptake inhibitor medications included fluvoxamine, paroxetine and fluoxetine. Other drugs included bupropion, mirtazapine, nefazodone and reboxetine. Patients were supine (inactive) or ambulatory (active). Most studies included controlled breathing. Electroconvulsive therapy was administered two or three times per week up to 12 treatments. Time recordings were short (two to eight minutes) or long (24 hours) and treatment duration ranged from one to eight weeks.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Heart rate, time domain measures and frequency domain measures were extracted. Heart rate variables were extracted to calculate effect sizes (Cohen's d). Where estimates of correlation between repeated measures could not be estimated from data reported, the median of test-re-test correlations for the heart rate variability measure in the literature was employed. In studies reporting pre-post data for a treatment and control group, only the pre-post data were used.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
The studies were combined using a narrative synthesis

Values were grouped by treatment type and length of electrocardiogram (ECG) recording (short versus 24 hour). In
short recordings, only data from patients in the supine position were included. Differences in mean values were calculated using one sample t tests, or between group t tests.

Results of the review
Fourteen studies, including 23 comparisons, were included in the review. The total number of patients included in the review was not reported. This could not be calculated from the tables, as it was unclear whether some studies assessing a number of treatment comparisons had used the same patients. Four comparisons were treatment versus control. The remaining 19 comparisons were pre-post design. Sample sizes ranged from five to 104 participants in each comparison.

Tricyclic antidepressants:
Ten comparisons were available for investigating tricyclic antidepressants. In the short recording studies (eight comparisons), tricyclic antidepressants led to decrease in all measures of heart rate variability reported and a significant (20.8%) increase in heart rate (p<0.001). Mean effect sizes ranged from 2.40 to 9.32. In the long recording studies (two comparisons), changes were small and inconsistent.

Selective serotonin reuptake inhibitors:
Seven comparisons were available for investigating selective serotonin reuptake inhibitors. In the short recording studies (five comparisons), selective serotonin reuptake inhibitors led to a significant decrease (-2%) in heart rate (p=0.01) in all five studies. The only change in heart rate variability was a marginally significant increase in the standard deviation of all NN intervals (p=0.07). In the long recording studies (two comparisons), results were contradictory.

Other treatments
A decrease in heart rate were seen using nefazodone (one comparison, -5.9% change, p<0.05) and an increase using mirtazapine (one comparison, 15.29% change, p<0.05). Decreases in all reported measures of heart rate variability were seen with bupropion and mirtazapine (both included one comparison). No significant effects were seen using electroconvulsive therapy or reboxetine.

Authors' conclusions
Tricyclic antidepressants are associated with a large decrease in heart rate variability and increase heart rate. However, data for selective serotonin reuptake inhibitors is not clear. Although the effect of selective serotonin reuptake inhibitors on heart rate variability is weaker than for tricyclic antidepressants, evidence shows that selective serotonin reuptake inhibitors are associated with a small decrease in heart rate and an increase in one measure of heart rate variability. The use of tricyclic antidepressants in depression leads to changes in heart rate variability that are associated with increased risk of mortality.

CRD commentary
This review addressed a clear question in terms of inclusion criteria and outcomes of interest. It did not address participant characteristics or study design, which may have led to subjective decisions regarding inclusion. Two relevant medical databases were searched and search terms were reported, but there did not appear to be any efforts to identify unpublished studies. This means that potentially relevant studies may have been missed. Search dates were not reported and it is unclear whether language restrictions were applied. Publication bias was not considered in the report. The review process for study selection and data extraction were not reported, so reviewer error and bias cannot be ruled out. Some outcome measures seem to have been decided post-hoc, as the justification for some measures was that the outcome was common to most studies. Quality was not assessed in the report, which may mean that the results of primary studies, and any synthesis of them, may not be reliable.

The decision to use a narrative analysis was appropriate, given the diversity in the measures reported and the different recording times in the included studies. Many included only one comparison. All but one study included less than 30 participants. There is a discrepancy in the reported results; the text reports significant increases in heart rate with nefazodone, yet this is reported in the table as a -5.9% change.
The authors recognise some of the methodological difficulties with the review, specifically: small sample sizes; variety of methods of measuring and assessing heart rate variability; differing recording times; and differences in medication between studies. The authors’ conclusions appear to reflect the evidence, but given the limitations, these conclusions should be interpreted with caution as they may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implication for practice.

**Research:** The authors stated that further studies on the effect of specific selective serotonin reuptake inhibitors on heart rate variability using consistent methodology are needed. The authors also suggested that studies clarifying whether causes of variability between studies of selective serotonin reuptake inhibitors are due to differences in measurement or differences in medication are necessary.

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