

An Overview of Antidepressant Effects on Heart Rate Variability Measurements



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Introduction

Clinicians and researchers who utilize heart rate variability (HRV) may assume that antidepressants (ADs) uniformly increase heart rate (HR) and suppress HRV time- and frequency-domain measurements.

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Introduction

This presentation reviews studies of the effects of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) to describe their respective effects on HRV and the strength of the experimental evidence.

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Introduction

Physicians prescribe antidepressants (ADs) to treat anxiety and clinical depression.

While researchers have raised serious questions regarding their efficacy (compared to placebo) and side effects in mild-to-moderate depression, they appear to be beneficial in severe depression (Advokat et al., 2019; Fournier, 2010).

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Introduction

Tricyclic antidepressants (TCAs) like imipramine (Tofranil) are first-generation drugs that appeared in the late 1950s (Advokat et al., 2019).

TCAs interfere with norepinephrine and serotonin reuptake transporters and blockade postsynaptic acetylcholine and histamine receptors (Advokat et al., 2019).

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Introduction

TCA blockade of postsynaptic muscarinic acetylcholine receptors are responsible for their effects on HR and HRV (van Zyl et al., 2008) and their cardiotoxicity in overdose (Advokat et al., 2019).

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Introduction

Selective serotonin reuptake inhibitors (SSRIs) like fluoxetine (Prozac) first appeared in 1988 (Advokat et al., 2019).

The first six SSRIs primarily block presynaptic serotonin transporters to increase serotonin availability at postsynaptic 5-HT_{1A}-type receptors which are theorized to account for their anxiolytic and antidepressant effects (Advokat et al., 2019).

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Introduction

SSRIs also interfere with norepinephrine reuptake to varying degrees (Advokat et al., 2019).

Unlike TCAs, SSRIs don't produce significant antihistaminic or antimuscarinic side effects. Since they are not cardiotoxic like TCAs, overdose does not cause death (Advokat et al., 2019).

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Introduction

The reviewed studies support a nuanced view of AD effects on HRV. We should not expect all ADs, or all members of a drug class, to increase HR and decrease HRV.

There is consensus that TCAs increase HR and reduce most short-term (~ 5-min) HRV metrics, probably due to their strong antimuscarinic actions (van Zyl et al., 2008).

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Introduction

SSRIs appear to produce weaker effects on HR and HRV than TCAs.

Depending on the study and measurement period length, they have been reported to decrease HR and modestly decrease, increase, or not impact specific HRV metrics (van Zyl et al., 2008).

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Introduction

The reviewed studies include a RCT, meta-analyses, and cross-sectional studies.

Cross-sectional studies suffer from the limited internal validity of quasi-experimental designs. Since participants were not randomly assigned to medications, group differences may have been confounded by participant characteristics.

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Introduction

We counsel caution in drawing conclusions about increased cardiovascular risk from HRV reductions in short-term measurements since only 24-hr measurements (e.g., SDNN and VLF power) have widely-accepted predictive validity.

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McFarlane et al. (2001)

Design

McFarlane et al. (2001) conducted a RCT that compared the SSRI sertraline (Zoloft) with a placebo control.

The authors randomly assigned 38 post-myocardial infarction (MI) patients to these conditions for 6 months. A nondepressed reference group of 11 participants was included.

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McFarlane et al. (2001)

They obtained short-term ECG power spectral measurements (LF/HF ratio and LF nu) in supine and standing conditions, which were supplemented by 24-hr time domain indices (RMSSD and SDNN).

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McFarlane et al. (2001)

Results

SDNN recovery in the sertraline group resembled that of the nondepressed comparison group. In contrast, SDNN declined in the placebo group.

There was no significant effect on RMSSD.

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McFarlane et al. (2001)

There were no significant differences on LF/HF ratio or LF nu between the sertraline and placebo groups.

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McFarlane et al. (2001)

Analysis

Rather than lowering SDNN and LF power, sertraline was associated with SDNN recovery after an MI.

18

van Zyl et al. (2008)

Design

van Zyl et al. (2008) reported a meta-analysis of 14 studies on adults diagnosed with depression using DSM-IV criteria.

The authors noted that sample sizes for reviewed reports regarding TCAs ($n = 6-24$) and SSRIs ($n = 8-104$) were typically small, which may have limited both external validity and statistical power.

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van Zyl et al. (2008)

The 23 comparisons were either within-subjects (pre-post) or between-subjects (AD versus a comparison condition) with random assignment.

The majority of the studies used short-term (5-min) HRV measurements, ranging from 2-8 min.

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van Zyl et al. (2008)

TCAs

The studies examined the effects of amitriptyline (Elavil), imipramine (Tofranil), and doxepin (Silenor).

The short-term studies showed large HR increases and HRV decreases. The ambulatory long-term studies yielded weaker and conflicting results.

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van Zyl et al. (2008)

SSRIs

The studies examined the effects of fluoxetine (Prozac), fluvoxamine (Luvox), and paroxetine (Paxil).

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van Zyl et al. (2008)

The short-term studies showed HR decreases and nonsignificant ($p = 0.07$) SDNN increases.* The ambulatory long-term studies yielded conflicting results.

*HRV measures included time-domain (RMSSD, SDNN, SDANN, pNN50, and CV ratio, which is SDNN/NN) and frequency-domain indices (HF, LF, LnHF, and LF/HF)

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van Zyl et al. (2008)

Conclusions

TCAs increased HR and reduced most HRV metrics. SSRIs exerted more modest cardiac effects than TCAs, decreasing HR and not significantly affecting SDNN or other HRV time- or frequency-domain indices.

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van Zyl et al. (2008)

Analysis

van Zyl et al. (2008) incorrectly labeled the SDNN increase produced by SSRIs “marginally-significant” where ($p = 0.07$) actually represented chance.

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Kemp et al. (2010)

Design

Kemp et al. (2010) reported a meta-analysis of 18 studies that included 673 depressed and 407 healthy participants. Fifteen studies reported short-term and three reported 24-hr ECG measurements of HRV.

26

Kemp et al. (2010)

The authors compared HRV time domain (RMSSD and SDNN), frequency domain (LF, HF, LF/HF ratio), Valsalva test, and nonlinear metrics before and after AD treatment. These indices were not utilized in all studies.

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Kemp et al. (2010)

TCA's

The authors found that HRV decreased after TCA* administration (Hedge's $g = 1.24$), which is a large effect size, and when compared to other treatments.

*TCA's (amitryptiline (Elavil), doxepin (Sinequan), and imipramine (Tofranil))

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Kemp et al. (2010)

SSRIs

The authors found no HRV changes after SSRI* administration, no HRV changes after paroxetine (strong anti-muscarinic AD) therapy, and no differences between the effects of paroxetine and that of other SSRIs.

*SSRIs (escitalopram/Lexapro, mirtazapine/Remeron, nefazodone/Serzone, paroxetine/Paxil, and venlafaxine/Effexor)

29

Kemp et al. (2010)

Analysis

The authors did not break out changes on specific HRV metrics for each drug category. Instead, they reported overall HRV without explaining how they derived this composite measure.

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Kemp et al. (2010)

Conclusion

TCA's reduced HRV and SSRIs did not affect HRV despite an improvement in depressive symptoms.

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Noordam et al. (2015)

Design

Noordam et al. (2015) analyzed repeated 10-s ECGs from 11,729 participants (mean baseline age of 64.6 years) in the longitudinal Rotterdam study.

The authors compared ECGs during AD use and non-use and analyzed the effect of specific drugs on RR interval, SDNN, and RMSSD when there were more than 10 medicated ECGs.

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Noordam et al. (2015)

TCA's

TCA* use was associated with briefer RR intervals (faster HRs) and lower SDNN and RMSSD values than non-use.

* TCA's (imipramine/Tofranil, clomipramine/Anafranil, amitriptyline/Elavil, nortriptyline/Pamelor, and maprotiline/Ludiomil)

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Noordam et al. (2015)

There were differences among TCAs. Clomipramine (Anafranil) and nortriptyline (Pamelor) suppressed HRV the most, while imipramine (Elavil) and maprotiline (Ludiomil) yielded much weaker effects with dosage controlled.

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Noordam et al. (2015)

Consistent TCA use was linked to smaller RR-interval increases compared to non-users, but did not further lower SDNN and RMSSD.

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Noordam et al. (2015)

SSRIs

SSRI* use did not affect RR interval, but was associated with lower SDNN and RMSSD values with smaller effect sizes than TCAs.

Fluoxetine lowered HRV more than the other SSRIs with dosage controlled.

* SSRIs (fluoxetine/Prozac, citalopram/Celexa, paroxetine/Paxil, sertraline/Zoloft, and fluvoxamine/Luvox)

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Noordam et al. (2015)

Consistent SSRI use did not affect RR interval, SDNN, or RMSSD.

37

Noordam et al. (2015)

Analysis

Limitations of this prospective study were use of 10-s, which could have increased measurement error, instead of ≥ 5 -min ECGs and the cohort's baseline age of 64.6 years, which could have limited the external validity of their findings.

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Noordam et al. (2015)

Conclusions

TCA's were associated with increased RR intervals and reduced SDNN and RMSSD. SSRIs did not affect RR intervals and were associated with smaller HRV reductions.

There were differences in HRV reduction within drug classes. The strongest declines were found for nortriptyline (Pamelor), imipramine (Tofranil), and fluoxetine (Prozac).

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O'Regan et al. (2015)

Design

O'Regan et al. (2015) analyzed 10-min supine ECGs from 4750 participants (≥ 50) in The Irish Longitudinal Study on Ageing (TILDA). Recordings were taken during 5-min spontaneous and 5-min paced (12 bpm) breathing.

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O'Regan et al. (2015)

In this cross-sectional study, the authors compared 3778 controls not taking ADs with 91 who were only taking SSRIs, 34 who were only taking TCAs, and 31 who were only taking SNRIs.

They measured HR, SDNN, and LF and HF power.

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O'Regan et al. (2015)

HR

Mean HRs were higher for participants taking SNRIs and TCAs than controls. SSRI and control HRs were comparable.

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O'Regan et al. (2015)

HRV

ADs were associated with HRV reductions. Those on SNRIs had the lowest HRV and those on SSRIs had the highest HRV.

While participants on SSRIs did not differ from controls on SDNN ($p = .051$), they were significantly lower on LF power.

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O'Regan et al. (2015)

Analysis

The authors did not identify specific ADs within each class and the sample sizes were relatively small.

Since they compared a large control group ($n = 3778$) with smaller AD groups ($n \leq 90$), the variances were unequal. This violated the homogeneity of variance assumption of their t -tests, which could have caused false positives.

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O'Regan et al. (2015)

Conclusion

TCAs were associated with increased mean HR and reduced HRV. SSRIs were linked to smaller declines in LF power compared with TCAs.

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Kemp et al. (2016)

Design

Kemp et al. (2016) conducted a cross-sectional analysis of data from the Brazilian Longitudinal Study of Adult Health, Mood, and Anxiety Disorders.

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Kemp et al. (2016)

They compared 10,466 participants not taking ADs, with those taking escitalopram/ Lexapro ($n = 46$), citalopram/Celexa ($n = 86$), fluoxetine/Prozac ($n = 66$), paroxetine/Paxil ($n = 103$), and sertraline/Zoloft ($n = 139$).

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Kemp et al. (2016)

The authors measured HR and HRV (RMSSD and HF power) using 10-min resting ECGs.

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Kemp et al. (2016)

Results

All the studied SSRIs, with the exception of fluoxetine, were associated with RMSSD and HF decreases compared with controls.

Paroxetine (Paxil) was associated with lower RMSSD than citalopram (Celexa), fluoxetine (Prozac), and sertraline (Zoloft).

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Kemp et al. (2016)

Analysis

This cross-sectional study suffered the limited internal validity of quasi-experimental designs.

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Kemp et al. (2016)

Conclusion

Compared with controls, the SSRIs with the exception of fluoxetine (Prozac) were associated with reduced RMSSD and HF power.

Paroxetine (Paxil) was associated with the lowest RMSSD.

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Conclusions

The reviewed studies support the following conclusions:

- (1) TCAs were associated with increased HR and reduced HRV
- (2) SSRIs were not consistently associated with increased HR
- (3) SSRIs were not consistently associated with reductions in HRV, and when reported, these were less than those linked to TCAs

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Conclusions

(4) Sertraline (Zoloft) was associated with SDNN recovery following a myocardial infarction

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