Supplementary methods

Criteria for considering studies for this review

Types of studies or interventions included

Medications considered for inclusion in the treatment analysis were all antidepressants (selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants [TCAs], noradrenergic and specific serotonergic antidepressants, monoamine oxidase inhibitors, norepinephrine reuptake inhibitors, or any other class of antidepressant), antipsychotics (typical and atypical), mood stabilizers (also known as anticonvulsants), and anxiolytics (including benzodiazepines); see below for a list of all medications considered eligible for inclusion. Trials in which medications were used as an augmentation strategy to psychological therapies were also considered. In trials in which flexible doses were used, we assumed that medications were titrated to the ideal dose for the individual patient. Trials that allowed for switching between medications were excluded. As this analysis was not examining efficacy of individual treatments, differences between minimal, maximal and clinically effective doses were not considered here. Studies examining only the effects of a single dose of a psychotropic medication were excluded.

<table>
<thead>
<tr>
<th>Medication type</th>
<th>Medication name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitor (SSRI)</td>
<td>Citalopram, fluoxetine, paroxetine, sertraline, escitalopram, fluvoxamine</td>
</tr>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitor (SNRI):</td>
<td>Venlafaxine, desvenlafaxine, duloxetine, milnacipram, nefazadone</td>
</tr>
<tr>
<td>Tricyclic antidepressant (TCA):</td>
<td>Amitriptyline, clomipramine, imipramine, dosulepin, doxepin, nortriptyline</td>
</tr>
<tr>
<td>Noradrenergic and specific serotonergic antidepressant (NASSA):</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitor (MAOI)</td>
<td>Moclobemide, phenelzine, tranylcypromine</td>
</tr>
<tr>
<td>Norepinephrine reuptake inhibitor (NRI):</td>
<td>Reboxetine</td>
</tr>
<tr>
<td>Melatonergic:</td>
<td>Agomelatine</td>
</tr>
<tr>
<td>Atypical:</td>
<td>Bupropion</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
</tr>
<tr>
<td>Atypical</td>
<td>Amisulpride, aripiprazole, asenapine, blonanserin, clozapine, iloperidone, lurasidone, melperone, olanzapine, paliperidone,quetiapine, risperidone, sertindole, sulpride, ziprasidone, zotepine</td>
</tr>
<tr>
<td>Typical</td>
<td>Benperidol, chlorpromazine, chlorprothixene, flupentixol, haloperidol, levomepromazine, thioridazine</td>
</tr>
<tr>
<td><strong>Mood stabilizers/anticonvulsants</strong></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine, gabapentin, ethosuximide, lacosamide, lamotrigine, levetiracetam, lithium (carbonate), oxcarbazepine, phenobarbital, phenytoin, pregabalin, sodium valproate, tiagabine, topiramate, valproic acid, verapamil, vigabatrin, zonisamide</td>
<td></td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
</tr>
<tr>
<td>Alprazolam, bromazepam, chlordiazepoxide, clobazam, clonazepam, clorazepate, delorazepam, diazepam, flunitrazepam, flurazepam, fluprazepam, loprazolam, lorazepam, lormetazepam, mexazolam, midazolam, nitrazepam, oxazepam, prazepam, temazepam</td>
<td></td>
</tr>
</tbody>
</table>
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Quality assessment

The quality assessment tool (see below) is a partially modified version of a previously published measure, examining heart rate variability (HRV) in functional somatic disorders. Item 2 was modified to assess whether drop-outs were accounted for in treatment studies. Three general domains were covered, including appropriate selection of participants, appropriate quantification of HRV and appropriate control for confounding factors. A maximum score of 18 could be obtained, with a minimum score of 7 required for study inclusion.

Search strategy

Initially, a computerized search of PubMed and EMBASE from January 1961 to May 2014 was conducted. Phrases used for searches included the combination of the following: (depress*, anxi*, schizo*, schizoph*, bipolar*, depend*, panic, obsess*, dysthym*, euthy*) OR (antidepress*, antipsychotic, mood stabilizer, benzo*, anticonvul*) AND (“heart rate variability”, vagal, “autonomic nervous system”). Only studies published in English were selected. In addition to these electronic searches, each article’s citation list and citing articles, identified through Google Scholar, was manually examined for additional studies.

After manuscript submission, a second search was conducted to identify additional studies. Searches were repeated as above but with a publication date restriction of May 2014 to February 2014. Updated numbers of articles retrieved are presented in Fig. S1.

Data extraction

Potential articles were reviewed for inclusion using a structured data abstraction form created in Google Forms (see below for questions). Data for analysis from each eligible study was extracted using this form. When a p value was reported as an inequality rather than an exact value, a conservative approach was taken, with the value rounded up (e.g., p < 0.05 was entered as p = 0.05). Where studies reported data as independent subgroups, the following formulas were used to estimate the combined mean and standard deviation for analysis:

\[
\bar{x}_i = \frac{n_{1i} \bar{x}_{1i} + n_{2i} \bar{x}_{2i}}{n_{1i} + n_{2i}} \quad \text{and} \quad s_i = \sqrt{\frac{(n_{1i} - 1)s_{1i}^2 + (n_{2i} - 1)s_{2i}^2 + \frac{n_{1i} n_{2i}}{n_{1i} + n_{2i}} (\bar{x}_{1i} - \bar{x}_{2i})^2}{n_{1i} + n_{2i} - 1}}
\]

where \( \bar{x}_{1i} \) and \( \bar{x}_{2i} \) are the 2 subgroup means; \( s_{1i} \) and \( s_{2i} \) the standard deviations; and \( n_{1i} \) and \( n_{2i} \) the sample sizes of the subgroups 1 and 2. Where subgroups could not be pooled, but a single comparison group was used, the sample size of the control group was divided by the number of subgroups in the paper. Where standard error of the mean was reported without an exact p value, the following formula was applied to estimate standard deviation:

\[
SD = SE \times \sqrt{N}
\]

As pre–post correlations were not widely available for any study included in the treatment analysis, a requirement for paired-sample effect size estimates, a correlation of \( r = 0.660 \) was imputed based on published estimates. Sensitivity analysis was then conducted with various other correlations to ensure that results remained consistent. Finally, for 2 studies in which p values were not reported for nonsignificant findings, the average nonsignificant p value was imputed (p = 0.400).
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Excluded studies

Reasons for study exclusion were did not assess HRV, HRV measure was not included in list of included HRV outcomes, or HRV was not reported in sufficient detail to warrant inclusion (n = 38); HRV was recorded during a task or during sleep only (for ambulatory recordings; n = 20); HRV recording was too short (n = 4); not a case–control design (n = 24); not a pre–post treatment design (n = 15); included duplicated data (n = 10); participants did not meet, or were not assessed to, standardized diagnostic criteria (n = 22); included participants were younger than 18 years (n = 4); presence of other medical conditions were not excluded in participants (n = 13); and raw data were not in an appropriate format for analysis (e.g. data presented graphically or insufficient raw data reported) and corresponding authors either did not provide additional raw data or studies were too old to request further information (n = 28)

Data extraction form template: case–control studies

<table>
<thead>
<tr>
<th>Type of information</th>
<th>Variable name</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study information</td>
<td>Study ID</td>
<td>Enter an ID for the trial. Use the first author’s last name and year e.g. SMITH1992. Use lower case letters to distinguish identical citations e.g. SMITH1992a, SMITH1992b. Use underscores to denote multiple effect sizes for separate extraction (e.g.SMITH2001_1, SMITH2001_2)</td>
</tr>
<tr>
<td>Article title</td>
<td>initials of reviewer</td>
<td>Full article title</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Aim of study</td>
<td>Describe the main aim(s) of the study to ensure it generally meets the objectives of the meta-analysis</td>
</tr>
<tr>
<td>Language</td>
<td>Is the article published in English?</td>
<td></td>
</tr>
<tr>
<td>Age of participants</td>
<td>Are participants aged 18 years or over?</td>
<td></td>
</tr>
<tr>
<td>Date of study</td>
<td>Has the study been conducted in or after 1961</td>
<td></td>
</tr>
<tr>
<td>Inclusion: case–control analysis</td>
<td>Only include studies in which HRV is compared in a psychiatric group to a control group</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>Minimum sample size of 5 per group</td>
<td></td>
</tr>
<tr>
<td>Participant details</td>
<td>Diagnosis of patient group (check box)</td>
<td>Specify diagnostic group (according to study criteria) or describe in other category. Also specify if a non-psychiatric (e.g. relatives) control group</td>
</tr>
<tr>
<td></td>
<td>Comparison group</td>
<td>Specify if matched or unmatched groups (by age, sex, other characteristics)</td>
</tr>
<tr>
<td></td>
<td>If there are more than 2 clinical groups in the article, note here and ensure data are entered separately</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Method of diagnosis</td>
<td>Which diagnostic manual was used to make the above diagnosis? If no formal diagnosis conducted, but referral from a psychiatrist or other specialist, specify if a diagnostic threshold had to be passed for inclusion (e.g. score above/below a threshold on a diagnostic scale). In order to be included, patients must be formal criteria for a psychiatric disorder</td>
</tr>
<tr>
<td></td>
<td>Patient setting</td>
<td>Were patients described as inpatients/outpatients? Other is selected for ‘unknown’ or if nonpsychiatric</td>
</tr>
<tr>
<td></td>
<td>Medication</td>
<td>Were patients medicated at time of physiological recording? If so, provide information about this</td>
</tr>
<tr>
<td></td>
<td>Were physical health conditions excluded?</td>
<td>Specify if physical healthy conditions (e.g. cardiovascular disease) were included or excluded. All other mental health conditions as comorbidities are not considered exclusions</td>
</tr>
<tr>
<td></td>
<td>Other inclusion</td>
<td>Include any other information about the inclusion criteria (for example, duration requirement, comorbidities etc.). Do not duplicate information captured in other fields related to the inclusion/exclusion criteria.</td>
</tr>
<tr>
<td></td>
<td>Number of males in patient group</td>
<td>Specify the number of males and % relative to total sample size of group. Specify if not stated</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Heart rate variability (HRV)</th>
<th>HRV measure (check box)</th>
<th>Check all HRV measures that were obtained in the study: Respiratory sinus arrhythmia (RSA), high frequency absolute (ms²), high frequency normalized (n.u.), RMSSD, SDNN, low frequency absolute (ms²), low frequency normalized (n.u.), LF/HF Ratio, pnn50, mean RR (ms), other nonlinear measure, other.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which HRV for analysis?</td>
<td>Absolute values or log-transformed</td>
<td>Are values log-transformed or absolute values?</td>
</tr>
<tr>
<td>Method of recording</td>
<td></td>
<td>State the method of recording HRV e.g. ECG, Holter, Polar watch, etc.</td>
</tr>
<tr>
<td>Type/length of recording</td>
<td></td>
<td>Specify if long or short term recording; include information about the length of recording in mins/hours</td>
</tr>
<tr>
<td>Recording conditions</td>
<td></td>
<td>Describe conditions of recording, such as whether the participant was lying down, sitting, standing, breathing normally or paced breathing etc. Include information in ‘other’ category if necessary (including whether this information was not reported)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effect size calculations</th>
<th>Patient group Mean</th>
<th>Mean HRV value from the patient group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient group SD</td>
<td>Standard deviation of the mean from the patient group</td>
</tr>
<tr>
<td></td>
<td>Sample size</td>
<td>Sample size of patient group</td>
</tr>
<tr>
<td></td>
<td>Comparison Mean</td>
<td>Mean HRV value from the comparison group</td>
</tr>
<tr>
<td></td>
<td>Comparison Group SD</td>
<td>Standard deviation of the mean from the comparison group</td>
</tr>
<tr>
<td></td>
<td>Comparison Group sample size</td>
<td>Sample size of comparison group</td>
</tr>
<tr>
<td></td>
<td>T or F value</td>
<td>Value of test comparing groups</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td>p value of comparison between groups</td>
</tr>
<tr>
<td></td>
<td>Mean difference</td>
<td>If no separate means reported, then include mean difference and SD of difference</td>
</tr>
<tr>
<td></td>
<td>Appropriate reporting</td>
<td>Are the statistical methods and analyses appropriate for the study design?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inclusion decision</th>
<th>Duplicate publications</th>
<th>Has the study been published or partially published elsewhere? Make a decision here about whether the study is eligible for analysis. If not eligible to be included, provide adequate information as to why</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Check references</th>
<th>Check reference list for any unique references not found in the initial search that may be eligible on the basis of the title.</th>
</tr>
</thead>
</table>
### Data extraction form template: treatment studies

<table>
<thead>
<tr>
<th>Type of information</th>
<th>Variable name</th>
<th>Instructions</th>
</tr>
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<tbody>
<tr>
<td>Study information</td>
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<tr>
<td></td>
<td>Article title</td>
<td>Full article title</td>
</tr>
<tr>
<td></td>
<td>Initials of reviewer</td>
<td>Initials of the person completing the form</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Aim of study</td>
<td>Describe the main aim(s) of the study to ensure it generally meets the objectives of the meta-analysis</td>
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<td>Language</td>
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<tr>
<td></td>
<td>Date of study</td>
<td>Has the study been conducted in or after 1961</td>
</tr>
<tr>
<td></td>
<td>Inclusion – treatment analysis</td>
<td>Only include studies in which HRV is compared pre and post a course of administration of a psychotropic drug (cross check against list of psychotropic medications considered for inclusion).</td>
</tr>
<tr>
<td></td>
<td>Sample size</td>
<td>Minimum sample size of 5 per group</td>
</tr>
<tr>
<td>Participant details</td>
<td>Diagnosis of patient Group (check box)</td>
<td>Specify diagnostic group (according to study criteria) or describe in other category. Also specify if a nonpsychiatric (e.g. relatives) control group. Which diagnostic manual was used to make the above diagnosis? If no formal diagnosis conducted, but referral from a psychiatrist or other specialist, specify if a diagnostic threshold had to be passed for inclusion (e.g. score above/below a threshold on a diagnostic scale). In order to be included, patients must be formal criteria for a psychiatric disorder</td>
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<td></td>
<td>Method of diagnosis</td>
<td>Specify if physical healthy conditions (e.g. cardiovascular disease) were included or excluded. All other mental health conditions as comorbidities are not considered exclusions</td>
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<td></td>
<td>Patient setting</td>
<td>Were patients described as inpatients/outpatients? Other is selected for ‘unknown’ or if nonpsychiatric</td>
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<tr>
<td></td>
<td>Medication</td>
<td>Were patients medicated at time of physiological recording? If so, provide information about this</td>
</tr>
<tr>
<td></td>
<td>Were physical health conditions excluded?</td>
<td>Specify if physical healthy conditions (e.g. cardiovascular disease) were included or excluded. All other mental health conditions as comorbidities are not considered exclusions</td>
</tr>
<tr>
<td></td>
<td>Other inclusion</td>
<td>Include any other information about the inclusion criteria (for example, were patients medication free / drug naive prior to starting treatment?). Do not duplicate information captured in other fields related to the inclusion/exclusion criteria.</td>
</tr>
<tr>
<td></td>
<td>Number of males in patient group</td>
<td>Specify the number of males and % relative to total sample size of group. Specify if not stated</td>
</tr>
<tr>
<td></td>
<td>Mean age (SD), range</td>
<td>Specify the mean age reported, with standard deviation and range, if provided</td>
</tr>
<tr>
<td></td>
<td>Other relevant demographic details</td>
<td>Describe any other relevant demographic details</td>
</tr>
<tr>
<td>Medication</td>
<td>Name of medication</td>
<td>Full name specified in article</td>
</tr>
<tr>
<td></td>
<td>Type of medication</td>
<td>Antipsychotic, antidepressant, benzodiazepine, or mood stabilizer</td>
</tr>
<tr>
<td></td>
<td>Class of medication</td>
<td>Specify class of antipsychotic or antidepressant, if relevant. Provide dose of medication in milligrams (if variable dosing, specify below in other information)</td>
</tr>
<tr>
<td></td>
<td>Dose</td>
<td>Specify course of administration in days</td>
</tr>
<tr>
<td></td>
<td>Duration</td>
<td>Provide more specific information here, e.g., if doses were individually titrated</td>
</tr>
<tr>
<td>Heart rate variability</td>
<td>HRV measure (checkbox)</td>
<td>Check all HRV measures that were obtained in the study: Respiratory sinus arrhythmia (RSA), high frequency absolute (ms²), high frequency normalized (n.u.), RMSSD, SDNN, low frequency absolute (ms²), low frequency normalized (n.u.), LF/HF ratio, pnn50, mean RR (ms), other nonlinear measure, other.</td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th>Effect size calculations</th>
<th>Pre-treatment mean</th>
<th>Mean pre-treatment HRV value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment SD</td>
<td>Standard deviation of the pre-treatment mean</td>
<td></td>
</tr>
<tr>
<td>Pre-treatment sample size</td>
<td>Sample size</td>
<td></td>
</tr>
<tr>
<td>Post-treatment mean</td>
<td>Mean post-treatment HRV value</td>
<td></td>
</tr>
<tr>
<td>Post-treatment SD</td>
<td>Standard deviation of the post-treatment mean</td>
<td></td>
</tr>
<tr>
<td>Post-treatment sample size</td>
<td>Sample size after treatment, if attrition occurred and values were not adjusted for missing values</td>
<td></td>
</tr>
<tr>
<td>t or F value</td>
<td>Value of paired test comparing change</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>p value of paired test</td>
<td></td>
</tr>
<tr>
<td>Pre-post correlation</td>
<td>If provided, correlation between pre and post treatment values (r)</td>
<td></td>
</tr>
<tr>
<td>Mean difference and SD of difference</td>
<td>If separate means not reported, then include mean difference and standard deviation of the difference</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inclusion decision</th>
<th>Duplicate publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the study been published or partially published elsewhere?</td>
<td></td>
</tr>
<tr>
<td>Make a decision here about whether the study is eligible for analysis. If not eligible to be included, provide adequate information as to why</td>
<td></td>
</tr>
</tbody>
</table>

| Check references | Check reference list for any unique references not found in the initial search that may be eligible on the basis of the title |

References


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Table S1. Individual characteristics of included case-control studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Patient n</th>
<th>Control n</th>
<th>HRV</th>
<th>Recording Length</th>
<th>Diagnostic Criteria</th>
<th>Patient Setting</th>
<th>Medication Status</th>
<th>Male %</th>
<th>Mean Age</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agorastos et al. (2013)</td>
<td>Post-Traumatic Stress Disorder</td>
<td>7</td>
<td>8</td>
<td>RMSSD</td>
<td>5 hours</td>
<td>DSM-IV-TR</td>
<td>Outpatient</td>
<td>Not Medicated</td>
<td>100.00</td>
<td>26.30</td>
<td>12</td>
</tr>
<tr>
<td>Alvarenga et al. (2006)</td>
<td>Panic Disorder</td>
<td>20</td>
<td>20</td>
<td>HF</td>
<td>10 mins</td>
<td>DSM-IV</td>
<td>Outpatient</td>
<td>Both</td>
<td>50.00</td>
<td>35.20</td>
<td>14</td>
</tr>
<tr>
<td>Asmundson &amp; Stein (1994)</td>
<td>Panic Disorder; Social Anxiety Disorder</td>
<td>30</td>
<td>15</td>
<td>RSA</td>
<td>30 mins</td>
<td>DSM-III-R</td>
<td>Outpatient</td>
<td>Both</td>
<td>43.33</td>
<td>36.45</td>
<td>15</td>
</tr>
<tr>
<td>Baumert et al. (2009)</td>
<td>Panic Disorder</td>
<td>7</td>
<td>4*</td>
<td>HF</td>
<td>5 mins</td>
<td>DSM-IV</td>
<td>-</td>
<td>-</td>
<td>28.58</td>
<td>43.00</td>
<td>10</td>
</tr>
<tr>
<td>Blechert et al. (2007)</td>
<td>Post-Traumatic Stress Disorder, Panic Disorder</td>
<td>49</td>
<td>32</td>
<td>RSA</td>
<td>5 mins</td>
<td>DSM-IV</td>
<td>Outpatient</td>
<td>Medicated</td>
<td>28.57</td>
<td>40.52</td>
<td>14</td>
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<tr>
<td>Bornas et al. (2006)</td>
<td>Specific Phobia</td>
<td>61</td>
<td>58</td>
<td>RMSSD</td>
<td>5 mins</td>
<td>DSM-IV</td>
<td>Outpatient</td>
<td>Not Medicated</td>
<td>34.43</td>
<td>36.59</td>
<td>12</td>
</tr>
<tr>
<td>H. A. Chang, Chang et al. (2013b)</td>
<td>Panic Disorder</td>
<td>48</td>
<td>202</td>
<td>HF</td>
<td>5 mins</td>
<td>DSM-IV</td>
<td>Outpatient</td>
<td>Not Medicated</td>
<td>41.67</td>
<td>37.69</td>
<td>14</td>
</tr>
<tr>
<td>H. A. Chang, Chang et al. (2013c)</td>
<td>Post-Traumatic Stress Disorder</td>
<td>32</td>
<td>192</td>
<td>HF</td>
<td>5 mins</td>
<td>DSM-IV</td>
<td>Outpatient</td>
<td>Not Medicated</td>
<td>59.38</td>
<td>35.53</td>
<td>14</td>
</tr>
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**Mood Disorders**

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*Psychotic Disorders*

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*Substance Dependence Disorders*

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Notes: "Both" in Medication Status indicates inclusion of both medicated and unmedicated patients in patient group. Male % and Mean Age refer to the patient group only. A dash indicates information not reported in the article. * = adjusted sample size, where a common control group was used in a study with multiple patient groups. *Abbreviations: RMSSD = square root of the mean-squared difference between successive R-R intervals; HF = High Frequency (both absolute and normalised values); RSA = respiratory sinus arrhythmia; LLE = largest Lyapunov exponent; PNN50 = proportion of number of pairs of successive beat-to-beat intervals that differ by more than 50 milliseconds; SDNN = standard deviation of all R-R intervals; ApEn = approximate entropy.

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Table S2. Individual characteristics of included treatment studies

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<th>Medication</th>
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<th>HRV</th>
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<th>Patient Setting</th>
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<th>n</th>
<th>Medication</th>
<th>Dose</th>
<th>Duration (days)</th>
<th>HRV</th>
<th>Recording Length</th>
<th>Diagnostic Criteria</th>
<th>Patient Setting</th>
<th>Male %</th>
<th>Mean Age</th>
<th>Study Quality</th>
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<td>Yeragani et al. (1994)</td>
<td>Panic Disorder</td>
<td>13</td>
<td>TCA (Nortriptyline)</td>
<td>82mg</td>
<td>77</td>
<td>HF</td>
<td>260 secs</td>
<td>DSM-III-R</td>
<td>Outpatient</td>
<td>61.54</td>
<td>30.1</td>
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<td>Panic Disorder</td>
<td>16</td>
<td>SSRI (Paroxetine)</td>
<td>19.7mg</td>
<td>105</td>
<td>HF</td>
<td>20 hours</td>
<td>DSM-III-R</td>
<td>-</td>
<td>25</td>
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### Antipsychotics

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<th>n</th>
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<th>Dose</th>
<th>Duration (days)</th>
<th>HRV</th>
<th>Recording Length</th>
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<td>13</td>
<td>Atypical (Olanzapine)</td>
<td>20mg</td>
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<td>HF</td>
<td>5 mins</td>
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<td>35.3</td>
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<td>35.8</td>
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<td>100mg</td>
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<td>HF</td>
<td>5 mins</td>
<td>DSM-III-R</td>
<td>Inpatient</td>
<td>76.9</td>
<td>32.4</td>
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<td>Agelink, Zeit, et al. (2001)</td>
<td>Schizophrenia</td>
<td>28</td>
<td>Atypical (Sertindole)</td>
<td>4-16mg</td>
<td>21</td>
<td>HF</td>
<td>5 mins</td>
<td>DSM-III-R</td>
<td>Inpatient</td>
<td>66.67</td>
<td>35.6</td>
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<td>Bär et al. (2005)</td>
<td>Schizophrenia</td>
<td>30</td>
<td>Atypical and Typical (Olanzapine, Risperidone, Quetiapine, Ziprasidone, Clozapine, Haloperidol)</td>
<td>various dosages (1-200mg)</td>
<td>2.5</td>
<td>HF</td>
<td>5 mins</td>
<td>DSM-IV</td>
<td>Inpatient</td>
<td>36.67</td>
<td>34.2</td>
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<td>J. S. Chang et al. (2010)</td>
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<td>16</td>
<td>Atypical (Risperidone)</td>
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<td>5 mins</td>
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<td>Inpatient</td>
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<td>Kim, Yi, et al. (2013)</td>
<td>Schizophrenia</td>
<td>40</td>
<td>Atypical (Clozapine)</td>
<td>12.5-25mg</td>
<td>56</td>
<td>ApEn</td>
<td>30 mins</td>
<td>DSM-IV</td>
<td>-</td>
<td>57.5</td>
<td>33</td>
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<td>Malaspina et al. (2002)</td>
<td>Schizophrenia, Schizoaffective Disorder</td>
<td>7</td>
<td>Typical (Haloperidol)</td>
<td>0.3mg/kg</td>
<td>28</td>
<td>PNN50</td>
<td>24 hours</td>
<td>DSM-IV</td>
<td>Inpatient</td>
<td>71.43</td>
<td>30.4</td>
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<td>Rechlin, Claus, et al. (1994b)</td>
<td>Schizophrenia</td>
<td>10</td>
<td>Atypical (Clozapine)</td>
<td>300mg</td>
<td>28</td>
<td>RMSSD</td>
<td>5 mins</td>
<td>DSM-III-R</td>
<td>-</td>
<td>35</td>
<td>30.1</td>
<td>11</td>
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<tr>
<td>J. Wang et al. (2014)</td>
<td>Schizophrenia</td>
<td>83</td>
<td>Atypical (Olanzapine)</td>
<td>5-20mg</td>
<td>28</td>
<td>HF</td>
<td>24 hours</td>
<td>DSM-IV</td>
<td>Inpatient</td>
<td>33.73</td>
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<td>Y. C. Wang et al. (2008)</td>
<td>Schizophrenia</td>
<td>15</td>
<td>Atypical (Amisulpride)</td>
<td>466mg</td>
<td>84</td>
<td>HF</td>
<td>5 mins</td>
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<td>Inpatient</td>
<td>53.33</td>
<td>48.2</td>
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Notes: Male % and Mean Age refer to the patient group only. A dash indicates information not reported in the article. Abbreviations: HF = High Frequency (both absolute and normalised values); RMSSD = square root of the mean-squared difference between successive R-R intervals; RSA = respiratory sinus arrhythmia; SDNN = standard deviation of all R-R intervals; PNN50 = proportion of number of pairs of successive beat-to-beat intervals that differ by more than 50 milliseconds; ApEn = approximate entropy.

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Fig. S1. Study search and data extraction flow diagram
### Table 1: Individual effect sizes of HRV in anxiety disorders compared to controls

<table>
<thead>
<tr>
<th>Study name</th>
<th>Medication</th>
<th>Hedges' g</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-value</th>
<th>Hedges' g and 95% CI</th>
<th>Patient Control</th>
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<tr>
<td>Alvarenga et al. (2006)</td>
<td>Medicated</td>
<td>-0.510</td>
<td>-1.128</td>
<td>0.108</td>
<td>0.106</td>
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<td>Asmundson &amp; Stein (1994)</td>
<td>Medicated</td>
<td>-0.098</td>
<td>-0.708</td>
<td>0.511</td>
<td>0.752</td>
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<tr>
<td>Blechert et al. (2007)</td>
<td>Medicated</td>
<td>-0.363</td>
<td>-0.759</td>
<td>0.333</td>
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<td>Diveday et al. (2011)</td>
<td>Medicated</td>
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<td>0.309</td>
<td>0.802</td>
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<td>Gaebler et al. (2013)</td>
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<td>Keary et al. (2009)</td>
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<td>Moon et al. (2013)</td>
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<td>Gerlach et al. (2003)</td>
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<td>-1.029</td>
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<td>0.107</td>
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<tr>
<td><strong>Overall</strong></td>
<td>Not Medicated</td>
<td>-0.334</td>
<td>-0.510</td>
<td>-0.158</td>
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Fig. S2. Individual effect sizes of HRV in anxiety disorders compared to controls.

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<table>
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<tr>
<th>Study name</th>
<th>Medicated</th>
<th>Hedges' Lower</th>
<th>Hedges' Upper</th>
<th>Hedges' g and 95% CI</th>
<th>Patient Control</th>
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<td></td>
<td>$g$</td>
<td>Limit</td>
<td>Limit</td>
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<td>Ahrens et al. (2008)</td>
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<td>-0.267</td>
<td>-0.885</td>
<td>0.351 0.398</td>
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<td>Bylsma et al. (2014)</td>
<td>Medicated</td>
<td>-0.391</td>
<td>-0.796</td>
<td>0.014 0.058</td>
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<td>Chang, J.S. et al. (2012a)</td>
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<td>-0.759</td>
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<td>-0.953</td>
<td>0.117 0.128</td>
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<td>Clamor et al. (2014)</td>
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<td>Cohen et al. (2003)</td>
<td>Medicated</td>
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<td>Davydov et al. (2007)</td>
<td>Medicated</td>
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<td>Ehrenthal et al. (2010)</td>
<td>Medicated</td>
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<td>-1.156</td>
<td>-0.039 0.036</td>
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<td>Henry et al. (2010)</td>
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<td>-1.289</td>
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<td>Lee et al. (2012)</td>
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<td>Levy (2014)</td>
<td>Medicated</td>
<td>-1.203</td>
<td>-1.792</td>
<td>-0.614 0.000</td>
<td>30 22</td>
</tr>
<tr>
<td>Moon et al. (2013)</td>
<td>Medicated</td>
<td>-1.223</td>
<td>-2.048</td>
<td>-0.397 0.004</td>
<td>41 7</td>
</tr>
<tr>
<td>Moon et al. (2013)</td>
<td>Medicated</td>
<td>-1.251</td>
<td>-2.094</td>
<td>-0.409 0.004</td>
<td>34 7</td>
</tr>
<tr>
<td>Nathshorni et al. (2004)</td>
<td>Medicated</td>
<td>-1.645</td>
<td>-2.827</td>
<td>-0.663 0.001</td>
<td>10 10</td>
</tr>
<tr>
<td>Rechlin et al. (1995)</td>
<td>Medicated</td>
<td>-0.675</td>
<td>-1.015</td>
<td>-0.336 0.000</td>
<td>104 52</td>
</tr>
<tr>
<td>Rottenberg et al. (2007)</td>
<td>Medicated</td>
<td>-0.747</td>
<td>-1.312</td>
<td>-0.182 0.010</td>
<td>25 25</td>
</tr>
<tr>
<td>Vogt et al. (2015)</td>
<td>Medicated</td>
<td>-1.066</td>
<td>-1.440</td>
<td>-0.723 0.000</td>
<td>90 62</td>
</tr>
<tr>
<td>Wang, Y. et al. (2013)</td>
<td>Medicated</td>
<td>-0.382</td>
<td>-0.764</td>
<td>-0.001 0.049</td>
<td>53 53</td>
</tr>
<tr>
<td><strong>Medicated</strong></td>
<td></td>
<td><strong>-0.668</strong></td>
<td><strong>-0.818</strong></td>
<td><strong>-0.517 0.000</strong></td>
<td><strong>731 602</strong></td>
</tr>
</tbody>
</table>

Fig. S3. Individual effect sizes of HRV in mood disorders compared to controls.

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**Study name** | **Medicated** | **Hedges' Lower limit** | **Upper limit** | **p-value** | **Hedges' g and 95% CI** | **Patient Control**
--- | --- | --- | --- | --- | --- | ---
Antonius et al. (2011) | Medicated | -1.844 | -2.611 | -1.077 | 0.000 | 14 | 24
Castro et al. (2008) | Medicated | -0.735 | -1.299 | -0.171 | 0.011 | 25 | 25
Chang, J.S. et al. (2010) | Medicated | -1.805 | -2.613 | -0.998 | 0.000 | 16 | 16
Chang, L.R. et al. (2011) | Medicated | -0.670 | -1.177 | -0.163 | 0.010 | 25 | 40
Chung et al. (2013) | Medicated | -0.923 | -1.278 | -0.568 | 0.000 | 94 | 51
Clamor et al. (2014) | Medicated | -1.089 | -1.817 | -0.361 | 0.003 | 23 | 12
Fujibayashi et al. (2009) | Medicated | -4.443 | -5.122 | -3.764 | 0.000 | 45 | 72
Hamilton et al. (2014) | Medicated | -0.682 | -1.138 | -0.226 | 0.003 | 41 | 36
Hempel et al. (2012) | Medicated | -0.650 | -1.122 | -0.178 | 0.007 | 32 | 40
Henry et al. (2010) | Medicated | -0.328 | -1.081 | 0.424 | 0.392 | 14 | 12
Ieda et al. (2014) | Medicated | -0.800 | -1.368 | -0.233 | 0.006 | 25 | 25
Iwamoto et al. (2012) | Medicated | -0.648 | -0.977 | -0.319 | 0.000 | 211 | 44
Jäuregui et al. (2011) | Medicated | -0.924 | -1.581 | -0.268 | 0.006 | 19 | 19
Kim et al. (2004) | Medicated | -1.937 | -2.410 | -1.465 | 0.000 | 50 | 50
Kim et al. (2009) | Medicated | -0.823 | -1.193 | -0.452 | 0.000 | 61 | 59
Kim et al. (2011) | Medicated | 0.147 | -0.447 | 0.742 | 0.627 | 21 | 21
Kim et al. (2013a) | Medicated | -0.996 | -1.480 | -0.512 | 0.000 | 50 | 28
Moon et al. (2013) | Medicated | -0.571 | -1.377 | 0.234 | 0.165 | 35 | 7
Mueck-Weymann et al. (2002) | Medicated | -1.116 | -1.921 | -0.311 | 0.007 | 18 | 10
Mujica-Parodi et al. (2005) | Medicated | -1.088 | -1.701 | -0.436 | 0.001 | 19 | 24
Scholten et al. (2006) | Medicated | -0.725 | -1.177 | -0.273 | 0.002 | 42 | 37
Agelink et al. (2001c) | Not Medicated | -0.351 | -0.781 | 0.079 | 0.109 | 28 | 80
Akar et al. (2015) | Not Medicated | -1.776 | -2.506 | -1.045 | 0.000 | 19 | 20
Bär et al. (2005) | Not Medicated | -3.768 | -4.607 | -2.929 | 0.000 | 30 | 30
Bär et al. (2006c) | Not Medicated | -1.128 | -1.769 | -0.488 | 0.001 | 21 | 21
Bär et al. (2007b) | Not Medicated | -0.983 | -1.627 | -0.338 | 0.003 | 20 | 20
Bär et al. (2007c) | Not Medicated | -0.772 | -1.338 | -0.206 | 0.006 | 25 | 25
Bär et al. (2008a) | Not Medicated | -0.234 | -0.752 | 0.284 | 0.377 | 28 | 28
Bär et al. (2008b) | Not Medicated | -0.787 | -1.512 | -0.063 | 0.033 | 15 | 15
Bär et al. (2008c) | Not Medicated | -0.429 | -0.833 | -0.024 | 0.038 | 40 | 58
Bär et al. (2012) | Not Medicated | -0.953 | -1.519 | -0.388 | 0.001 | 23 | 30
Berger et al. (2010) | Not Medicated | -1.969 | -2.733 | -1.205 | 0.000 | 19 | 19
Boettger et al. (2006) | Not Medicated | -0.475 | -1.092 | 0.141 | 0.131 | 20 | 20
Chang, H.A. et al. (2013b) | Not Medicated | -0.216 | -0.364 | -0.069 | 0.004 | 314 | 409
Chang, J.S. et al. (2009) | Not Medicated | -0.556 | -1.065 | -0.047 | 0.032 | 30 | 30
Hempel et al. (2009) | Not Medicated | -0.492 | -1.022 | 0.038 | 0.069 | 18 | 57
Peupelmann et al. (2009) | Not Medicated | -0.638 | -1.198 | -0.079 | 0.025 | 25 | 25
Rachow et al. (2011) | Not Medicated | -1.179 | -1.873 | -0.484 | 0.001 | 18 | 18
Voss et al. (2010) | Not Medicated | -0.866 | -1.344 | -0.387 | 0.000 | 36 | 36
Wang et al. (2014) | Not Medicated | -0.599 | -0.964 | -0.233 | 0.001 | 83 | 46
**Not Medicated** | -0.901 | -1.210 | -0.592 | 0.000 | 812 | 987
**Overall** | -0.983 | -1.196 | -0.770 | 0.000 | 1692 | 1639

Fig. S4. Individual effect sizes of HRV in psychotic disorders compared to controls.

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<table>
<thead>
<tr>
<th>Study name</th>
<th>Medicated</th>
<th>Hedges' $g$</th>
<th>Lower limit</th>
<th>Upper p-value limit</th>
<th>Hedges' $g$ and 95% CI</th>
<th>Patient Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bär et al. (2006a)</td>
<td>Medicated</td>
<td>-1.105</td>
<td>-1.759</td>
<td>-0.451</td>
<td>0.001</td>
<td>±</td>
</tr>
<tr>
<td>Bär et al. (2006b)</td>
<td>Medicated</td>
<td>-0.884</td>
<td>-1.521</td>
<td>-0.246</td>
<td>0.007</td>
<td>±</td>
</tr>
<tr>
<td>Chang, R.L. et al. (2012)</td>
<td>Medicated</td>
<td>-0.727</td>
<td>-1.206</td>
<td>-0.248</td>
<td>0.003</td>
<td>±</td>
</tr>
<tr>
<td>Herbsleb et al. (2013)</td>
<td>Medicated</td>
<td>-1.048</td>
<td>-1.668</td>
<td>-0.427</td>
<td>0.001</td>
<td>±</td>
</tr>
<tr>
<td>Rechlin et al. (1996)</td>
<td>Medicated</td>
<td>-0.475</td>
<td>-0.836</td>
<td>-0.114</td>
<td>0.010</td>
<td>±</td>
</tr>
<tr>
<td>Agelink et al. (1998b)</td>
<td>Not Medicated</td>
<td>-0.254</td>
<td>-0.759</td>
<td>0.250</td>
<td>0.323</td>
<td>±</td>
</tr>
<tr>
<td>Dolezal et al. (2014)</td>
<td>Not Medicated</td>
<td>-0.983</td>
<td>-1.565</td>
<td>-0.401</td>
<td>0.001</td>
<td>±</td>
</tr>
<tr>
<td>Henry et al. (2012)</td>
<td>Not Medicated</td>
<td>-0.869</td>
<td>-1.524</td>
<td>-0.213</td>
<td>0.009</td>
<td>±</td>
</tr>
<tr>
<td>Sucharita et al. (2012)</td>
<td>Not Medicated</td>
<td>-0.424</td>
<td>-0.956</td>
<td>0.107</td>
<td>0.118</td>
<td>±</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>Not Medicated</td>
<td>-0.694</td>
<td>-0.897</td>
<td>-0.491</td>
<td>0.000</td>
<td>±</td>
</tr>
</tbody>
</table>

Fig. S5. Individual effect sizes of HRV in substance dependence disorders compared to controls.

References


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