Can self-reported depression be helped by homeopaths?

A pragmatic cohort randomised controlled trial
with qualitative interviews with patients.

Tables, figures and appendixes

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Tables, figures and appendixes accompanying thesis submitted
in partial fulfilment of the degree of Doctor of Philosophy

The University of Sheffield
Faculty of Medicine, Dentistry and Health
School of Health and Related Research

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<td>Interview guide I 120620 rev 121017</td>
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### Table 2. Cochrane reviews of SSRIs in depression

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Condition</th>
<th>Comparator</th>
<th>Trials (n)</th>
<th>Patients (n)</th>
<th>Assessment period</th>
<th>Main results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arroll et al. 2009</td>
<td>Depression</td>
<td>Placebo</td>
<td>4</td>
<td>1,269</td>
<td>6 – 8 weeks</td>
<td>SSRIs effective in primary care; RR 1.28 (95% CI 1.15, 1.43); NNT median 7 (range 7-9); NNH range 20-90; standardised mean difference (SMD) 0.24 (95% CI 0.12, 0.35)</td>
<td>Most studies of short duration (6-8 weeks)</td>
</tr>
<tr>
<td>Cipriani et al. 2012</td>
<td>MDD</td>
<td>Other ADs</td>
<td>37</td>
<td>1,235</td>
<td>1 – 24 weeks</td>
<td>Citalopram (SSRI) more effective than paroxetine (SSRI) and reboxetine (SNRI), less effective than escitalopram (SSRI); more acceptable than tricyclics (TCA), reboxetine and venlafaxine (SNRI)</td>
<td>Risk of overestimation of treatment due to potential bias (sponsorship, publication)</td>
</tr>
<tr>
<td>Cipriani et al. 2010</td>
<td>MDD</td>
<td>Other ADs</td>
<td>59</td>
<td>4,000</td>
<td>1 – 24 weeks</td>
<td>Sertraline (SSRI) more effective than fluoxetine (SSRI); more acceptable/tolerable than amitriptyline and imipramine (TCA), paroxetine (SSRI), and mirtazapine (TeCA), but more likely to cause diarrhoea</td>
<td>Potential reporting bias: Studies did not report on all pre-specified outcomes and outcomes of clear relevance to patients and clinicians were not reported in any trials</td>
</tr>
<tr>
<td>Cipriani et al. 2009</td>
<td>MDD</td>
<td>Other ADs</td>
<td>22</td>
<td>4,000</td>
<td>1 – 24 weeks</td>
<td>Escitalopram (SSRI) more effective than citalopram (SSRI); less withdrawal than duloxetine (SNRI)</td>
<td>Insufficient evidence to compare to other ADs, risk of bias: allocation, blinding, reporting, information about outcomes</td>
</tr>
<tr>
<td>Magni et al. 2013</td>
<td>MDD</td>
<td>Other ADs</td>
<td>171</td>
<td>24,868</td>
<td>4 – 24 weeks</td>
<td>Fluoxetine (SSRI) poorer efficacy profile than sertraline (SSRI) and venlafaxine (SNRI), difference may be clinically meaningful</td>
<td>Insufficient evidence to firmly determine implications, risk of bias in the majority of trials, esp. due to incomplete outcome</td>
</tr>
<tr>
<td>Omori et al. 2010</td>
<td>MDD</td>
<td>Other ADs</td>
<td>54</td>
<td>5,122</td>
<td>2 – 10 weeks</td>
<td>Fluvoxamine (SSRI) more effective than other ADs, but with higher incidence of vomiting and nausea than imipramine, clomipramine and amitriptyline (TCAs)</td>
<td>High risk of reporting bias in most and incomplete data in over half of the trials</td>
</tr>
<tr>
<td>Purgato et al. 2014</td>
<td>MDD</td>
<td>Other ADs</td>
<td>115</td>
<td>26,134</td>
<td>1 – 24 weeks</td>
<td>Paroxetine (SSRI) more effective than reboxetine (SNRI) and less effective than mirtazapine (TeCA) at 1-4 weeks, less effective than citalopram at 6-12 weeks; no evidence of inferiority/superiority to other ADs; paroxetine less adverse events than amitriptyline, imipramine (TCAs) and older ADs, less well tolerated than agomelatin and St John’s Wort</td>
<td>Unclear or high risk of bias in most studies due to poor reporting of allocation concealment and blinding of outcome assessment, incomplete reporting of outcomes; and many studies sponsored by the industry; comparison tolerability with St John’s Wort (n=1)</td>
</tr>
<tr>
<td>Silva de Lima et al. 2005</td>
<td>Dysthymia</td>
<td>Placebo</td>
<td>4</td>
<td>878</td>
<td>4 – 12 weeks</td>
<td>SSRIs effective in treating dysthymia, similar to other ADs (TCAs, MOIs, other ADs); effectiveness over placebo: RR 0.68 (95% CI 0.56, 0.82) (risk of non-response), NNT 5 (95% CI 3.3, 9.0)</td>
<td>Quality of reports were poor with unclear or high risk of bias, with information omitted on study design, allocation concealment, analysis and generalisability</td>
</tr>
<tr>
<td>Silva de Lima et al. 2003</td>
<td>Dysthymia</td>
<td>Other ADs</td>
<td>5</td>
<td>791</td>
<td>4 – 12 weeks</td>
<td>Similar clinical response compared to other ADs, strength of evidence similar to TCAs, better than for other ADs; less side effects of sertraline (SSRI) than imipramine (TCA)</td>
<td>Quality of reporting poor in most studies, including information on allocation concealment only in 1 trial, no ITT-analysis, insufficient information on randomisation in 3 trials, other weaknesses in reporting (baseline data, drop-outs, post-randomisation exclusions, SDs)</td>
</tr>
<tr>
<td>Author, year</td>
<td>Condition</td>
<td>Comparator</td>
<td>Trials (n)</td>
<td>Patients (n)</td>
<td>Assessment period</td>
<td>Main results</td>
<td>Limitations</td>
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<tr>
<td>Bains et al. 2002</td>
<td>Depression in dementia</td>
<td>Other ADs</td>
<td>7</td>
<td>769</td>
<td>6 – 12 weeks</td>
<td>Weak evidence for effectiveness of SSRIs in dementia</td>
<td>Limited number of trials; only 1 trial reported randomisation method and used ITT-analysis, blinding not checked, 3 trials not reported placebo types</td>
</tr>
<tr>
<td>Baumeister et al. 2012</td>
<td>Depression in diabetes mellitus</td>
<td>Placebo &amp; other ADs</td>
<td>5</td>
<td>241</td>
<td>3 – 24 weeks</td>
<td>Moderate and clinically significant effect on depression in diabetes patients at 3-6 months</td>
<td>Limited number of trials, low quality evidence with high/unclear risk of bias, incl. selection, performance, attrition and other bias, each form of bias in at min. half of the trials, heterogeneity of patients and interventions</td>
</tr>
<tr>
<td>Baumeister et al. 2011</td>
<td>Depression in coronary artery disease</td>
<td>Placebo</td>
<td>9</td>
<td>4</td>
<td>4 – 25 weeks</td>
<td>SSRIs had a small effect over placebo</td>
<td>Limited number of trials, low quality evidence with high/unclear risk of bias, incl. selection, performance, attrition and other bias, each form of bias in at min. half of the trials, heterogeneity of patients and interventions</td>
</tr>
<tr>
<td>Hackett et al. 2008</td>
<td>Depression after stroke</td>
<td>Placebo</td>
<td>7</td>
<td>704</td>
<td>6 – 26 weeks</td>
<td>ADs had a small effect over placebo, but also a higher rate of adverse effects. Pooled OR 0.47 (95% CI 0.22, 0.98) for binary outcome measures, OR 0.22 (95% CI 0.09, 0.52) for patients reporting min.50% reduction in mood scores.</td>
<td>Reviewers present results of the review for all medication collectively, incl. TCAs, SSRIs, other ADs, other medication. Unclear/high risk of bias (n=5) due to unclear details of randomisation/allocation concealment (n=4), no/insufficient information on blinding (n=5), unclear/no ITT-analysis (n=3)</td>
</tr>
<tr>
<td>Koch et al. 2011</td>
<td>Depression in multiple sclerosis</td>
<td>Placebo</td>
<td>1</td>
<td>42</td>
<td>12 weeks</td>
<td>Paroxetine (SSRI) non-significantly better than placebo for depression in MS patients, higher incidence of nausea/headache</td>
<td>Insufficient evidence from a single trial (with high attrition rate) to draw any firm conclusions</td>
</tr>
<tr>
<td>Mottram et al. 2006</td>
<td>Depression in elderly</td>
<td>Other ADs</td>
<td>32</td>
<td>4 – 24 weeks</td>
<td>SSRIs &amp; TCAs equally efficacious for depressed elderly people, less withdrawal &amp; side effects in SSRI compared to TCA groups</td>
<td>Risk of bias in most trials due to insufficient information on allocation concealment, “per protocol” analyses, heterogeneity of drugs/patient groups</td>
<td></td>
</tr>
<tr>
<td>Rabindranath et al. 2005</td>
<td>Depression in dialysis patients</td>
<td>Placebo</td>
<td>1</td>
<td>12</td>
<td>8 weeks</td>
<td>No conclusion can be drawn based on a single small trial</td>
<td>Only a single small trial</td>
</tr>
<tr>
<td>Wilkinson &amp; Izmeth 2012</td>
<td>Depression in elderly</td>
<td>Placebo</td>
<td>3</td>
<td>539</td>
<td>6 – 36 weeks</td>
<td>SSRIs superior to placebo at 12 months, no difference at 6, 24 &amp; 36 months</td>
<td>Risk of bias due to insufficient information on allocation concealment (n=1), blinding (n=1), other reasons (n=3). Not clear if ITT-analysis used (n=1), trials were heterogeneous</td>
</tr>
<tr>
<td>Wilson et al. 2001</td>
<td>Depression in elderly</td>
<td>Placebo</td>
<td>2</td>
<td>737</td>
<td>4 – 8 weeks</td>
<td>Some effect of SSRIs over placebo, OR 0.51 (95% CI 0.36, 0.72), NNT 8.45 (95% CI 8.38, 8.53)</td>
<td>Limited evidence from 2 trials, inadequate description of allocation concealment and randomisation procedure</td>
</tr>
</tbody>
</table>
### Table 4. Cochrane reviews of TCAs in depression

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Condition</th>
<th>Comparator</th>
<th>Trials (n)</th>
<th>Patients (n)</th>
<th>Assessment period</th>
<th>Main results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arroll et al. 2009</td>
<td>Depression</td>
<td>Placebo</td>
<td>13</td>
<td>1,233</td>
<td>6 – 8 weeks</td>
<td>TCAs effective in primary care; RR 1.24 (95% CI 1.11, 1.38); NNT median 9 (range 7-16); NNH range 4-30; mean difference HDRS 3.17 (95% CI 2.39, 3.94); standardised mean difference (SMD) 0.49 (95% CI 0.32, 0.67)</td>
<td>Most studies of short duration (6-8 weeks)</td>
</tr>
<tr>
<td>Furukawa et al. 2003</td>
<td>Acute depression</td>
<td>Placebo, different dosage of TCAs vs placebo: 35; TCA vs TCA:6 vs placebo: 2,013, TCA vs TCA:551</td>
<td>41 (TCAs vs placebo: 35; TCA vs TCA:6)</td>
<td>2,564</td>
<td>4 – 8 weeks</td>
<td>Low dosage TCA more likely than placebo to result in improvement: RR 1.65 (95% CI 1.36, 2.00) (4 weeks), RR 1.47 (95% CI 1.12, 1.94) (6-8 weeks). Standard dose TCA not better than low dose TCA, but higher drop-out rate due to side effects</td>
<td>Risk of bias as most trials (n=31) did not provide sufficient information to assess the randomisation procedure (allocation)</td>
</tr>
<tr>
<td>Guaiana et al. 2007</td>
<td>Depression</td>
<td>Other TCAs, SSRIs, other ADs</td>
<td>194</td>
<td>2 weeks – 6 months</td>
<td>Amitriptyline (TCA) at least as efficacious as other TCAs or newer SSRIs, but with more side-effects</td>
<td>The quality of studies was on average assessed as medium to low, with no trial reporting on adequate concealment allocation method</td>
<td></td>
</tr>
<tr>
<td>Leucht et al. 2012</td>
<td>MDD</td>
<td>Other ADs</td>
<td>39</td>
<td>3,509</td>
<td>3 – 12 weeks</td>
<td>Amitriptyline (TCA) more efficacious than placebos (OR 2.67, 95% CI 2.21, 3.23), with more significant effect for severe depression (p=0.02), but with higher rate of side effects resulting in withdrawal (OR 4.15, 95% CI 2.71, 6.35)</td>
<td>Risk of bias due to poorly reported randomisation methods, allocation concealment and blinding, used of “per protocol” analysis in some trials</td>
</tr>
<tr>
<td>Moncrieff et al. 2004</td>
<td>Depression</td>
<td>Active Placebos</td>
<td>9</td>
<td>751</td>
<td>2 – 12 weeks</td>
<td>Small differences in favour of TCAs compared to active placebos (atropine mimicking TCA side effects): mean difference in effect size 0.39 (95% CI 0.24, 0.54), sensitivity analysis omitting a single strongly positive trial: effect size 0.17 (95% CI 0.00, 0.34)</td>
<td>Most studies used “per protocol” analysis</td>
</tr>
<tr>
<td>Silva de Lima et al. 2005</td>
<td>Dysthymia</td>
<td>Placebo</td>
<td>5</td>
<td>600</td>
<td>4 – 12 weeks</td>
<td>TCAs are effective in treating dysthymia, similarly to other ADs (SSRIs, MOIs &amp; other ADs); effectiveness over placebo: RR 0.68 (95% CI 0.59, 0.78) (risk of non-response), NNT 4.3 (95% CI 3.2, 6.5)</td>
<td>Quality of reports were poor, with information omitted on study design, allocation concealment, analysis and generalisability</td>
</tr>
<tr>
<td>Silva de Lima et al. 2003</td>
<td>Dysthymia</td>
<td>Other ADs</td>
<td>7</td>
<td>1,205</td>
<td>4 – 12 weeks</td>
<td>Similar clinical response compared to other ADs, strength of evidence similar to SSRIs and better than for other ADs; more side effects of imipramine (TCA) compared to sertraline (SSRI) and MAOIs</td>
<td>The quality of reporting was poor in most studies, with no information on allocation concealment, no ITT-analysis in five trials, and insufficient information on randomisation in four trials, as well as other weaknesses in reporting (baseline data, exclusions, standard deviations)</td>
</tr>
<tr>
<td>Author, year</td>
<td>Condition</td>
<td>Comparator</td>
<td>Trials (n)</td>
<td>Patients (n)</td>
<td>Assessment period</td>
<td>Main results</td>
<td>Limitations</td>
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<tr>
<td>Baumeister et al. 2011</td>
<td>Depression in coronary artery disease</td>
<td>SSRI</td>
<td>1</td>
<td>81</td>
<td>4 – 25 weeks</td>
<td>Nortriptyline (TCA) comparable to paroxetine (SSRI) at 6 weeks</td>
<td>Single trial, unclear risk of selection bias (allocation concealment) and reporting bias (selective reporting), conflicting interests (funded by manufacturer)</td>
</tr>
<tr>
<td>Hackett et al. 2008</td>
<td>Depression after stroke</td>
<td>Placebo</td>
<td>3</td>
<td>129</td>
<td>6 – 26 weeks</td>
<td>ADs had a small effect over placebo, but also a higher rate of adverse effects</td>
<td>Reviewers present results of the review for all medication collectively, including TCAs, SSRIs, other ADs and other medication. Methodological weaknesses in all TCA trials, unclear or high risk of bias due to unclear details of randomisation (n=2), single blinded (n=2), no use of ITT-analysis (n=1), concealment of allocation unclear in all trials</td>
</tr>
<tr>
<td>Koch et al. 2011</td>
<td>Depression in multiple sclerosis</td>
<td>Placebo</td>
<td>1</td>
<td>28</td>
<td>12 weeks</td>
<td>Desipramine (TCA) non-significantly better than placebo for depression in MS patients, with adverse effects in 86% of desipramine patients</td>
<td>Insufficient evidence from a single trial (with high attrition rate) to draw any firm conclusions</td>
</tr>
<tr>
<td>Mottram et al. 2006</td>
<td>Depression in elderly</td>
<td>Other ADs</td>
<td>32</td>
<td>4 – 24 weeks</td>
<td>TCAs &amp; SSRIs were equally efficacious for depressed elderly people, with more withdrawal and side effects in TCA compared to SSRI groups</td>
<td>Risk of bias in most trials due to insufficient information on allocation concealment, use of “per protocol” analyses, heterogeneity of drugs and patient groups</td>
<td></td>
</tr>
<tr>
<td>Wilkinson &amp; Izmeth 2012</td>
<td>Depression in elderly</td>
<td>Placebo</td>
<td>3</td>
<td>197</td>
<td>6 – 36 weeks</td>
<td>TCA superior to placebo at 24 months (RR 0.70, 95% CI 0.50, 0.99), no difference at 6, 12 &amp; 36 months</td>
<td>Some risk of bias, due to insufficient information on allocation concealment (n=2), blinding (n=1), incomplete outcome data (n=2), selective reporting (n=1), and other reasons (n=3). It was not clear if ITT-analysis had been used, trials were heterogeneous</td>
</tr>
<tr>
<td>Wilson et al. 2001</td>
<td>Depression in elderly</td>
<td>Placebo</td>
<td>7</td>
<td>428</td>
<td>4 – 8 weeks</td>
<td>Some effect of TCAs over placebo, OR 0.32 (95% CI 0.21, 0.47), NNT 3.97 (95% CI 3.88, 4.05)</td>
<td>Risk of bias due to inadequate description of allocation concealment and randomisation procedure</td>
</tr>
<tr>
<td>Author, year</td>
<td>Condition</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Trials (n)</td>
<td>Patients (n)</td>
<td>Assessment period</td>
<td>Main results</td>
</tr>
<tr>
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</tr>
<tr>
<td>Akechi et al. 2008</td>
<td>Depression in incurable cancer patients</td>
<td>Supportive psychotherapy (n=5), hypnosis (n=2), relaxation, CBT, problem solving therapy (each n=1)</td>
<td>Treatment as usual</td>
<td>10 (meta analysis)</td>
<td>780 (meta analysis 51)</td>
<td>4 weeks – 12 months</td>
<td>Significant decrease in depression (SMD -0.44, 95% CI -0.08, -0.80) (6 trials)</td>
</tr>
<tr>
<td>Barbato &amp; D’Avanzo 2006</td>
<td>Depression</td>
<td>Marital therapy</td>
<td>Individual psychotherapy, drug therapy, minimal/no treatment</td>
<td>Varying, depends on comparison</td>
<td>7 weeks – 24 months</td>
<td>Better than no/minimal treatment (SMD 1.28, 95% CI 0.72, 1.85), no significant differences compared to individual psychotherapy (SMD 0.12, 95% CI -0.32, 0.56), lower drop-out rate than drug therapy</td>
<td>Methodological weaknesses in most studies, including small samples, risk of bias esp. resulting from unclear method of allocation concealment and unclear blinding of assessor in most studies, significant heterogeneity among studies, probable use of per protocol analysis (and no ITT-analysis)</td>
</tr>
<tr>
<td>Baumeister et al. 2011</td>
<td>Depression in coronary artery disease</td>
<td>Psychological interventions</td>
<td>Usual care (7 studies) or waitlist (1)</td>
<td>8</td>
<td>3158</td>
<td>4 – 25 weeks</td>
<td>Small but clinically significant effect compared to usual care</td>
</tr>
<tr>
<td>Baumeister et al. 2012</td>
<td>Depression in diabetes mellitus</td>
<td>Psychological interventions</td>
<td>Usual care</td>
<td>8</td>
<td>1122</td>
<td>3 – 24 weeks</td>
<td>Moderate and clinically significant effect compared to usual care</td>
</tr>
<tr>
<td>Churchill et al. 2013</td>
<td>Depression</td>
<td>CBT</td>
<td>Treatment as usual (n=3), attention placebo (n=1)</td>
<td>4</td>
<td>224</td>
<td>2 – 18 weeks</td>
<td>Better than treatment as usual</td>
</tr>
<tr>
<td>Author, year</td>
<td>Condition</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Trials (n)</td>
<td>Patients (n)</td>
<td>Main results</td>
<td>Limitations</td>
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</tr>
<tr>
<td>Dennis et al.</td>
<td>Depression during pregnancy</td>
<td>Interpersonal psychotherapy</td>
<td>Parenting education program</td>
<td>1</td>
<td>38</td>
<td>Reduced risk of depressive symptoms</td>
<td>Methodological weaknesses with risk of bias resulting from insufficient information on random allocation procedure, single trial</td>
</tr>
<tr>
<td>Hackett et al.</td>
<td>Depression after stroke</td>
<td>Psychotherapy: CBT, counselling, motivational interviewing, psycho-education</td>
<td>Usual care</td>
<td>4</td>
<td>448</td>
<td>No evidence of benefit</td>
<td>No blinding of assessors (n=1), details of blinding unclear (n=1), small sample sizes (n=3)</td>
</tr>
<tr>
<td>Henken et al.</td>
<td>Depression</td>
<td>Family therapy</td>
<td>Waitlist</td>
<td>6</td>
<td>519</td>
<td>Better than waitlist control, also in trials with lower risk of bias</td>
<td>Half of the trials were of low methodological quality, with risk of bias resulting from no/unclear allocation concealment, heterogeneous trials reducing generalisability of results</td>
</tr>
<tr>
<td>Hunot et al.</td>
<td>Acute depression</td>
<td>Third wave CBT</td>
<td>CBT</td>
<td>3</td>
<td>144</td>
<td>No difference between approaches</td>
<td>High or unclear risk of bias, esp. no information on allocation of participants (n=2), unclear risk of bias due to attrition (n=1), no pre-published protocol (risk of reporting bias)</td>
</tr>
<tr>
<td>Lane et al.</td>
<td>Depression in congenital heart disease</td>
<td>CBT, psychotherapy, talking/ counselling therapy</td>
<td></td>
<td>0</td>
<td>0</td>
<td>No studies identified</td>
<td></td>
</tr>
<tr>
<td>Lane et al.</td>
<td>Depression in heart failure</td>
<td>Psychological interventions</td>
<td></td>
<td>0</td>
<td>0</td>
<td>No studies identified</td>
<td></td>
</tr>
<tr>
<td>Orgeta et al.</td>
<td>Depression in dementia and mild cognitive impairment</td>
<td>CBT, Interpersonal therapy, counselling</td>
<td>Educational programs, diagnostic feedback, services slightly above usual care</td>
<td>6</td>
<td>439</td>
<td>Positive effect on depression from psychological treatments for dementia. No studies identified for mild cognitive impairment</td>
<td>Unclear or high risk of bias (n=5), esp. due to unclear randomisation, blinding and selective reporting of results</td>
</tr>
<tr>
<td>Author, year</td>
<td>Condition</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Trials (n)</td>
<td>Patients (n)</td>
<td>Assessment Period</td>
<td>Main results</td>
</tr>
<tr>
<td>-------------</td>
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</tr>
<tr>
<td>Rabindranath et al. 2005</td>
<td>Depression in dialysis patients</td>
<td>Psychological interventions</td>
<td>0</td>
<td>0</td>
<td>No studies identified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shinohara et al. 2013</td>
<td>Depression</td>
<td>Behavioural therapies</td>
<td>Other psychological therapies incl. CBT and psycho-dynamic therapies</td>
<td>25</td>
<td>955</td>
<td>5 – 24 weeks</td>
<td>Behavioural therapies not different to other psychological therapies (18 studies, n=690), CBT better than behavioural therapies (15 studies, n=544), behavioural therapies better than psychodynamic therapies (2 studies, n=110)</td>
</tr>
<tr>
<td>Wilkinson &amp; Izmeth 2012</td>
<td>Depression in elderly</td>
<td>Interpersonal therapy</td>
<td>Placebo medication</td>
<td>2</td>
<td>98</td>
<td>6 – 36 weeks</td>
<td>Study 1: No difference between Interpersonal therapy (IT) and placebo medication (1, 2 &amp; 3 years), IT + antidepressant was better than IT alone and placebo alone, no difference between IT and antidepressants Study 2: No difference between psychological therapies + antidepressant compared to antidepressant alone</td>
</tr>
<tr>
<td>Wilson et al. 2008</td>
<td>Depression in elderly</td>
<td>CBT, psychodynamic therapy</td>
<td>Active control interventions, waitlist</td>
<td>9</td>
<td>818</td>
<td>4 – 8 weeks</td>
<td>CBT more effective than waitlist control (5 trials, n=153) and active control interventions (3 studies, n unclear), No difference between CBT and psycho-dynamic therapy (3 studies, n=226)</td>
</tr>
</tbody>
</table>

SMD: Standard mean difference (in outcome measure)
Table 7. Systematic review: Observational uncontrolled studies reporting on outcomes during and after treatment provided by homeopaths for patients suffering from diagnosed or self-reported depression

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>Sample</th>
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<th>Outcome measures</th>
<th>Results</th>
<th>Comments to methods</th>
<th>Model validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adler et al. 2008</td>
<td>Case series, retrospective</td>
<td>All new patients diagnosed with depression (DSM-IV according to SCID) over a 10 month period N=15</td>
<td>Individualised homeopathy for up to 4 consultations: 10 different homeopathic remedies were prescribed</td>
<td>Before to after assessment</td>
<td>MADRS score at first three follow-up consultations</td>
<td>Statistically significant reduction in MADRS scores at 2nd, 3rd and 4th consultation</td>
<td>Strengths: Diagnosed patients assessed with appropriate outcome measures. LOCF for missing data (2nd &amp; 3rd consultation n=3)</td>
<td>High model validity, including rationale for the intervention, intervention used consistently with homeopathy principles, suitability of qualified and experienced practitioner (although only a single homeopath included), appropriate and sufficiently sensitive outcome measures, and a follow-up period sufficient to detect an effect of the intervention.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No other concurrent treatment</td>
<td></td>
<td>Remission rates</td>
<td></td>
<td>Low risk of attrition bias: Sufficient data, incl. co-morbidities (n=8).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Homeopath: 1</td>
<td></td>
<td>Patient-completed outcome measure</td>
<td></td>
<td>Limitations: Small sample. Retrospective. Single practitioner. Unclear risk of reporting bias: No pre-published protocol; same practitioner carried out treatment and assessments. Missing data for 2/3 of participants (n=10) at 4th consultation (one discontinued treatment due to significant improvement, another due to deterioration).</td>
<td></td>
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</table>

SCID: Structured Clinical Interview. IQR: Interquartile range. MADRS: Montgomery & Asberg Depression Rating Scale.
<table>
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<tr>
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<th>Comments to methods</th>
<th>Model validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attena et al. 2000</td>
<td>Uncontrolled observational study, prospective</td>
<td>Diagnosed depression (out of 648 patients diagnosed with sub-acute and chronic conditions) n=24</td>
<td>Pluralist homeopathy (more than one remedy at the time)</td>
<td>Before to after assessment</td>
<td>SF-36, question 2: How do you evaluate your health 1 year after you started treatment? Questionnaire completed over the telephone, called by a researcher (not a practitioner)</td>
<td>Marked improvement: n=13 (54.2%) Moderate improvement: n=8 (33.3%) No improvement/worse: n=3 (12.5%)</td>
<td>Strengths: Follow-up for at least 6 months and assessment after 1 year. Limitations: Small sample. Unclear risk of attrition and reporting bias: No pre-published protocol; limited data for depressed patients. Outcome measure not validated for depression. No information on potential confounding factors.</td>
<td>Low/unclear model validity: Unclear if a significant body of accredited homeopaths would support the rationale for the study, if treatment was consistent with homeopathic principles, and whether practitioners were suitably qualified and experienced. The main outcome was capable of detecting change and the length of the follow-up period was sufficient.</td>
</tr>
<tr>
<td>Clover 2000</td>
<td>Survey, prospective</td>
<td>Diagnosed depression in patients with carcinoma of the breast (from 1000 patients with various complaints) n=14</td>
<td>Individualised homeopathic treatment: Details of treatment unknown (study period 12 months)</td>
<td>Before to after assessment</td>
<td>7-point numerical self-reported rating scale at follow-up consultations Completed by patient with a clinic clerk after follow-up consultation in the absence of a doctor or nurse</td>
<td>7-point NRS at follow-up consultation: +3 n=9 64.3% +2: n=3 21.4% +1: n=1 7.1% 0: n=0 0.0% -1: n=1 7.1% -2/-3/-4: n=0 0.0% + indicates improvement, - indicates deterioration (for further details, see footnote) Participants: Response rate at follow-up consultations (n=2500): 55% (n=1372), no response 45% (n=822) Response rate for depressed patients not reported.</td>
<td>Limitations: Small sample. High risk of attrition bias: Missing data patients (45%), and consultation numbers. Unclear risk of reporting bias: No pre-published protocol. Number of practitioners unclear. Outcome measure not validated for depression. Limited information on potential confounding factors including other treatment (4% of all patients received acupuncture, but not specified for depression).</td>
<td>Insufficient information to assess model validity. Unclear whether outcome measure is sufficiently sensitive to identify changes in depressed patients (not validated for this use).</td>
</tr>
</tbody>
</table>

7-point NRS: 7-point Numerical Rating Scale (Clover 2000): +3 Much better, +2 Better/Moderately better, +1 Slightly better, 0 No change, -1 Slightly worse, -2 Worse/Moderately worse, -3 Much worse.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Dempster 1998</td>
<td>Survey of random selection of patients, retrospective</td>
<td>Diagnosed depression (random selection of 44 patients with various diagnosed mental health problems) n=12</td>
<td>Individualised homeopathic treatment in a single practice, treatment for minimum 1 month Homeopath: 1</td>
<td>Before to after assessment</td>
<td>Self-reported improvement in depression given in percent, assessment 2-36 months after treatment</td>
<td>Improvement in depression: Median 85%, Mode 90% (n=4), Interquartile range 55-90%. Range 10%-100% Improvement in long-standing depression (min.4 yrs) (n=5): 30%, 80%, 80%, 90%, 100% Improvement in recently developed depression (max.4 months) (n=4): 60%, 90%, 90%, 100%</td>
<td>Strengths: Random selection of diagnosed patients. High external validity (similar to ‘real world practice’). Limitations: Small sample. High risk of reporting bias: Not published in peer reviewed journal, no pre-published protocol. Retrospective. Single practitioner. Unclear risk of attrition bias: Patient response rate unclear. Limited information on confounding factors. Assessment period variable. Outcome measure not validated for depression. No information on potential confounding factors.</td>
<td>High model validity including rationale for the intervention provided and intervention used consistently with homeopathy principles, suitability of qualified and experienced practitioner (although only a single homeopath included). Unclear whether outcome measure is sufficiently sensitive to identify changes in depressed patients (not validated for this use).</td>
</tr>
<tr>
<td>Mathie &amp; Robinson 2006</td>
<td>Uncontrolled observational study, prospective</td>
<td>Diagnosed depression (of 961 consecutive patients with various complaints) n=55</td>
<td>Individualised homeopathic treatment Homeopath: 14</td>
<td>Before to after assessment</td>
<td>7-point numerical self-reported rating scale at last follow-up consultation, max. 6 months Patient-completed outcome at consultation with homeopath 7-point NRS at latest follow-up consultation (n=55): Major or moderate improvement (+2 or +3): n=35, 63.6% Data not given for mild improvement (+1), no change/unsure (0) and deterioration (-1/-2/-3)</td>
<td>7-point NRS at latest follow-up consultation (n=55): Major or moderate improvement (+2 or +3): n=35, 63.6% Data not given for mild improvement (+1), no change/unsure (0) and deterioration (-1/-2/-3)</td>
<td>Strengths: High external validity (similar to ‘real world practice’). Limitations: Unclear risk of reporting bias: No pre-published protocol. Unclear risk of attrition bias: Data not reported for depressed patients, incl. drop-out, number of consultations and assessment period. Limited information on potential confounding factors, although plausible alternative explanation for clinical change recorded in 3.7% of all included patients. Outcome measure not validated for depression.</td>
<td>High model validity including rationale for the intervention provided and intervention used consistently with homeopathy principles, practitioners suitable and experienced. Unclear whether outcome measure is sufficiently sensitive to identify changes in depressed patients (not validated for this use). Uncertain if length of follow-up was sufficient.</td>
</tr>
</tbody>
</table>

7-point NRS: 7-point Numerical Rating Scale (Mathie & Robinson 2005): +3 Much better, +2 Better/Moderately better, +1 Slightly better, 0 No change, -1 Slightly worse, -2 Worse/Moderately worse, -3 Much worse.
<table>
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<th>Author, year</th>
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<th>Results</th>
<th>Comments to methods</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Oberai et al. 2013</td>
<td>Uncontrolled observational study, prospective</td>
<td>Diagnosed depression (ICD-10 criteria, min. 2 typical symptoms + 2 common symptoms, excluded if min. 25% improvement in HDRS after 1 week of placebo) n=83</td>
<td>Individualised homeopathic treatment, 6 months Number of homeopaths not specified</td>
<td>Before to during &amp; after assessment</td>
<td>Primary: HDRS at 0, 3, 6 &amp; 12 months Secondary: BDI, CGI-1, CGI-2 at 0, 3, 6 &amp; 12 months Adverse events Outcome measures completed by patients and collected by investigators and consultant psychiatrist</td>
<td>Primary: HDRS baseline: 17.98 (4.9) HDRS 12 months: 5.8 (5.9) (mean, SD) HDRS 0, 3, 6 &amp; 12 months (Repeated Measure ANOVA): p&lt;0.001. Effect size = 0.74 Secondary: BDI baseline: 23.4 (6.9) BDI 12 months: 7.1 (8.7) (mean, SD) BDI 0, 3, 6 &amp; 12 months (Repeated Measure ANOVA): p&lt;0.001. Effect size = 0.72 CGI-1 baseline: 4 (3.2-5) CGI-1 12 months: 1 (1-2) (median, IQR) CGI-1 0, 3, 6 &amp; 12 months (Friedman’s tests) p&lt;0.001. Effect size: 0.82 CGI-2 3 months: 2 (2-3) CGI-2 12 months: 1 (1-1) (median, IQR) CGI-2 3, 6 &amp; 12 months (Friedman’s tests) p&lt;0.001. Effect size: 0.79 Adverse events: None</td>
<td>Strengths: Use of validated outcome measures. Repeated measures (4 time-points). Statistical analyses following ITT principle using LOCF. High external validity (similar to ‘real world practice’). Limitations: Threshold BDI levels for mild, moderate and severe depression not reported. Overlap in categories used to report depression duration at baseline (1-5 years &amp; 5-10 years). Unclear risk of attrition/reporting bias: Minor discrepancies between abstract, text and tables reporting on HDRS threshold levels and types of homeopathic medicines used. No rationale for use of parametric test for HDRS and BDI (unclear if data was normally distributed). Ethical: Patients appear not to have been asked for consent to 1 week run-in placebo treatment.</td>
<td>High model validity including rationale for the intervention provided, intervention used consistently with homeopathy principles, outcome measure reflects main effects expected, outcome measure is capable of detecting change, follow-up period likely to have been sufficient. Unclear: qualification and experience of practitioners, number of practitioners.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>Sample</th>
<th>Intervention</th>
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<th>Outcome measures</th>
<th>Results</th>
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<th>Model validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richards on 2001</td>
<td>Uncontrolled observational survey, prospective</td>
<td>Diagnosed depression (out of 1100 consecutive medically diagnosed patients with various complaints) n=30</td>
<td>Individualised homeopathic treatment, mean 3.7 consultations (minimum 3), study period 1 year Homeopath: 4?</td>
<td>Before to after assessment</td>
<td>GHOS (self-reported) after treatment, after mean 3.7 consultations (min. 3) (study period 1 year) Patient-completed outcome handed to receptionist, clinic doctor completed a separate form recording the outcome score (unclear procedure)</td>
<td>GHOS after treatment (after min. 3 consultations, mean 3.7): +2/3+4: n=15  50.0% +3+/4: n=8  26.7% +2: n=7  23.3% +1/0: n=15  50.0% /-1/-2/3-4: n=0  0.0% + indicates improvement, - indicates deterioration (for further details, see footnote) Participants: Response rate for depressed patients not reported. Only patients with follow-up consultations included. Number of patients with no follow-up consultation not reported.</td>
<td>Strengths: High external validity Limitations: Small sample. Unclear risk of reporting bias: No pre-published protocol. Unclear risk of attrition/confirmation bias: No data for patients with no follow-up sessions, length of follow-up, drop-out rates not reported, unclear outcome recording procedure. No information on potential confounding factors. Outcome measure not validated for depression.</td>
<td>High model validity including rationale for the intervention provided, intervention used consistently with homeopathy principles, qualification and experience of practitioner (although number of practitioners uncertain), follow-up period likely to be sufficient. Unclear whether outcome measure is sufficiently sensitive to identify changes in depressed patients (not validated for this use).</td>
</tr>
<tr>
<td>Sevar 2000</td>
<td>Uncontrolled observational study, prospective</td>
<td>Diagnosed depression (out of 829 consecutive medically diagnosed patients with various complaints) n=64</td>
<td>Individualised homeopathic treatment: First consultation 75 minutes, follow-up 30 minutes Homeopath: 1</td>
<td>Before to after assessment</td>
<td>GHOS (self-reported) after treatment, assessment period 6 months – 7 years Patient-reported outcome, data collected by homeopath</td>
<td>GHOS after treatment (range 6 months – 7 years): +3+/4: n=40  62.5% +2: n=5  7.8% +1/0: n=10  15.6% /-1/-2/3-4: n=0  0.0% Unknown: n=9  14.1% + indicates improvement, - indicates deterioration (for further details, see footnote) The 40 patients who experienced considerable improvement, were able to discontinue antidepressants Participants: Response rate 86% (n=55), No response 14% (n=9)</td>
<td>Strengths: High external validity (similar to 'real world practice'). Limitations: High risk of reporting bias: No pre-published protocol, same person treated + reported outcomes. Unclear risk of attrition bias: Missing data for depressed patients, incl. consultation numbers. No info on potential confounding factors. Outcome measure not validated for depression.</td>
<td>High model validity including rationale for the intervention provided, intervention used consistently with homeopathy principles, suitability of qualified and experienced practitioner (although only a single homeopath included), sufficient follow-up period. Unclear whether outcome measure is sufficiently sensitive to identify changes in depressed patients (not validated for this use).</td>
</tr>
</tbody>
</table>

GHOS: Glasgow Hospital Homeopathic Outcomes Scale, 9-point numerical rating scale including +4 Cured/Back to normal, +3 Major improvement, +2 Moderate improvement, affecting daily living, +1 Slight improvement, no effect on daily living, 0 No change/Unsure, -1 Slight deterioration, no effect on daily living, -2 Moderate deterioration, affecting daily living, -3 Major deterioration, -4 Disastrous deterioration.
<table>
<thead>
<tr>
<th>Author, year</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Sevar 2005</td>
<td>Uncontrolled observational study, prospective</td>
<td>Diagnosed depression (out of 455 consecutive medically diagnosed patients with various complaints) n=27</td>
<td>Individualised homeopathic treatment: First consultation 75 minutes, follow-up 45 minutes (1st) or 30 minutes (other), mean 11 months (min. 6), mean 2.4 consultations (all 455 patients) Homeopaths: 1</td>
<td>Before to after assessment</td>
<td>GHOS after treatment, mean 11 months (minimum 6)</td>
<td>GHOOS after treatment (mean 11 months, min. 6): +4: n=1 3.7% +3: n=16 59.3% +2: n=4 14.8% +1: n=1 3.7% 0: n=5 18.5% 1/-2/3/-4: n=0 0.0% Unknown: n=0 0.0% + indicates improvement, - indicates deterioration for further details, see footnote</td>
<td>Strengths: High external validity (similar to ‘real world practice’). Limitations: Small sample, High risk of reporting bias: No pre-published protocol, same person carried out treatment + reported outcomes Unclear risk of attrition bias: Missing data for depressed patients, incl. consultation numbers. High risk of confirmation bias: Outcome partially based on clinician’s assessment. No information on confounding factors including other treatment, although non-significant difference in entire group (n=455) between ‘homeopathy only’ group (n=375) and combined treatment group (n=80). Outcome measure not validated for depression.</td>
<td>High model validity including rationale for the intervention provided, intervention used consistently with homeopathy principles, suitability of qualified and experienced practitioner (although only a single homeopath included), sufficient follow-up period. Unclear whether outcome measure is sufficiently sensitive to identify changes in depressed patients (not validated for this use).</td>
</tr>
</tbody>
</table>

NHS: National Health Service. GHHOS: Glasgow Hospital Homeopathic Outcomes Scale, 9-point numerical rating scale including +4 Cured/Back to normal, +3 Major Improvement, +2 Moderate improvement, affecting daily living, +1 Slight improvement, no effect on daily living, 0 No change/Unsure, -1 Slight deterioration, no effect on daily living, -2 Moderate deterioration, affecting daily living, -3 Major deterioration, -4 Disastrous deterioration.
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</tr>
</thead>
<tbody>
<tr>
<td>Spence et al. 2005</td>
<td>Uncontrolled observational study, prospective</td>
<td>Diagnosed depression (ICD-10, from 6,888 consecutive diagnosed patients in a university-hospital outpatient clinic) N=201</td>
<td>Individualised homeopathic treatment: First consultation 45 minutes, follow-up 15 minutes, mean total 3.6 consultations (for all patients), study period 6 years</td>
<td>Before to after assessment</td>
<td>7-point numerical self-reported rating scale at follow-up consultations, length not given (study period 6 years)</td>
<td>7-point NRS after mean 3.6 consultations: +3 n=38 18.9%, +2: n=69 34.3%, +1: n=36 17.9%, 0: n=46 22.9%, -1: n=2 1.0%, -2/-3/-4: n=0 0.0%</td>
<td>+ indicates improvement, - indicates deterioration (for further details, see footnote)</td>
<td>High model validity including rationale for the intervention provided, intervention used consistently with homeopathy principles, qualification and experience of practitioners, sufficient follow-up period. It is unclear whether the outcome measure is sufficiently sensitive to identify changes in depressed patients (not validated for this use).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Homeopaths: 12</td>
<td></td>
<td>Patient-reported outcome, data collected by homeopath</td>
<td>Participants: 5% were unable to score (n=8) or the results were influenced by other factors (e.g. other treatment) (n=2)</td>
<td>Strengths: High external validity (similar to ‘real world practice’). Large overall patient sample; several practitioners, treatment more representative of ‘real world practice’. Potential confounding factors mentioned (although not for subgroup of depressed patients). Limitations: Unclear risk of confirmation and reporting bias: Patient-completed outcome, but data collected by practitioner, no pre-published protocol. Unclear risk of attrition bias: Limited data, including length of follow-up for depression patients not reported. Outcome measure not validated for depression.</td>
<td></td>
</tr>
</tbody>
</table>

NHS: National Health Service. 7-point NRS: 7-point Numerical Rating Scale (Spence et al. 2006): +3 Major improvement, +2 Moderate improvement, +1 Mild improvement, 0 No change or unsure, -1 Mild deterioration, -2 Moderate deterioration, -3 Major deterioration.
Table 8. Systematic review: Pragmatic randomised controlled trials reporting on the effectiveness of standardised homeopathic medication for patients with diagnosed or self-reported depression

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
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<th>Control</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Risk of bias assessment, other comments to methods</th>
<th>Model validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wasilewski 2004</td>
<td>Pragmatic RCT</td>
<td>Depression in menopausal women (F32 n=135, F33 n=76) N=211</td>
<td>Homeopathic remedy (H) (same for all participants): Ignatia Homaccord (Heel GmbH) (Ignatia amara &amp; Moschus moschiferus), 3x10 drops daily</td>
<td>Fluvoxamine (F) 50mg 3x daily</td>
<td>HDRS &amp; BDI at 6 weeks</td>
<td>No significant between group differences in HDRS and BDI scores at 6 weeks.</td>
<td>Strengths: Reasonably large sample size of diagnosed participants. Fluvoxamine relevant control modality (similarly effective as other antidepressants). Limitations: No power calculation provided. Unclear risk of selection bias: No information on treatment allocation procedures, consultation length, and practitioner details. Unclear risk of attrition bias: Details of side-effects in homeopathy group not reported. Majority of participants (n=179) had a variety of comorbidities, but unclear how they were divided between treatment arms. Reduced HDRS/BDI scores only reported as percentages, not numbers provided, except for number of participants with min. 50% improvement. High risk of reporting bias: No pre-published protocol found. Authors state differences in tolerability was significant, but no p-value given.</td>
<td>Low/unclear model validity: Substantial number of experienced homeopaths would not support choice of intervention for this group of participants; intervention not based on the ‘like treats like’ principle or on the principle of isopathy; information on qualification and experience of practitioner missing. Outcome measure appropriate and sufficiently sensitive for measuring depression, but uncertain whether 6 weeks is sufficient to assess results.</td>
</tr>
</tbody>
</table>

Table 9. Systematic review: Placebo-controlled double-blinded trials reporting on the efficacy of homeopathic medicinal products used by patients suffering from diagnosed or self-reported depression

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>Sample, condition, recruitment, setting, country</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Risk of bias assessment, other comments to methods</th>
<th>Model validity, other comments to intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adler et al. 2011a</td>
<td>RCT, double-blind, double-dummy, placebo-controlled, non-inferiority trial</td>
<td>Moderate to severe depression (DSM-IV according to SCID + MADRS score min.15) N=91 Homeopathic remedy+placebo for fluoxetine (H) n=48 Fluoxetine+placebo for homeopathic remedy (F) n=43 Referral from MDs within the public health system Depression outpatient clinic, São Paulo, Brazil</td>
<td>Individualised homeopathic remedy (H) (20 different medicines were used, all prescribed in Q-potencies, starting at Q2 + placebo for fluoxetine-hydrochlorine) for 8 weeks Homeopath: 1</td>
<td>Fluoxetine-hydrochlorine (F) 20 mg daily, increased to 40 mg daily after 4 weeks in case of no response + placebo for individualised homeopathic remedy for 8 weeks</td>
<td>Primary: Homeopathy non-inferior to fluoxetine at 4 and 8 weeks</td>
<td>Participants: Randomised Completed</td>
<td>Overall low risk of bias, including random sequence generation, allocation concealment, blinded of participants and personnel, blinding of assessment, completeness of outcome data and reporting. High attrition rates (appr.40%) contribute to potential source of bias. Study well described, including study aim, design, participants, interventions, outcomes, statistics and results. Otherwise well-designed trial.</td>
<td>Overall high model validity, including rationale for intervention, intervention used consistently with homeopathy principles, suitability of qualified and experienced practitioner (although only a single homeopath included), and appropriateness of outcome measures. It is possible that other experienced homeopaths would consider the assessment period to be too short, although a time-effect was found during the study period.</td>
</tr>
</tbody>
</table>

SCID: Structured Clinical Interview. MADRS: Montgomery & Åsberg Depression Rating Scale. Homeopathic remedies potentised (diluted & succussed) at following concentrations Q2=2x10^{-16}, Q3=8x10^{-21}, Q4=1.6x10^{-25} (Q4 surpasses Avogadro’s number). Tolerability measured using the side effect rating scale of the Scandinavian Society of Psychopharmacology.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>Sample, condition, recruitment, setting, country</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Risk of bias assessment, other comments to methods</th>
<th>Model validity, other comments to intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adler et al. 2013</td>
<td>RCT, partially double-blinded (for verum vs placebo, but not for extensive vs shorter consultation), placebo-controlled, four-armed trial</td>
<td>Acute major depression (moderate episode) (diagnosed by psychiatrist, degree of depression HAM-D score 17-24 rated by psychologist) N=44 Extensive consultation (first 60-90 min, follow-up 30 min) + homeopathic remedy (H) n=16 Extensive consultation (first 60-90 min, follow-up 30 min) + placebo (P) n=7 Shorter consultation (first 30 min, follow-up 10 min) + homeopathic remedy (H) n=14 Shorter consultation (first 30 min, follow-up 10 min) + placebo (P) n=7 Co-operation with outpatient practices, radio &amp; TV interviews, advertisement in newspapers and underground trains Integrative Medicine outpatient clinic of the Charité – Universitätsmedizin Berlin, Germany</td>
<td>Individualised homeopathic remedy (H) daily (20 different medicines were used, all prescribed in Q-potencies, starting at Q2 + extensive or shorter consultation) Homeopath: 1</td>
<td>Placebo daily</td>
<td>Primary: HAM-D at 6 weeks Secondary: HAM-D at 2 &amp; 4 weeks BDI and SF-12 at 2, 4 &amp; 6 weeks</td>
<td>Data solely analysed descriptively without formal hypothesis testing due to insufficient sample size At 6 weeks: No relevant differences between homeopathic medicines and placebo on HAM-D and BDI Odds ratios: response, remission rates and SF-12 slightly better in shorter compared to extensive consultation group, but large CI</td>
<td>Low risk of bias for comparison of homeopathy and placebo, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of assessment, completeness of outcome data and reporting. High risk of bias for comparison of extensive and short consultation as blinding of practitioners is impossible, although results were in favour of short consultations (opposite of what was expected by the practitioner and researchers) The main weakness of this trial is the fact that it was underpowered due insufficient number of participants (recruited 44 out of 228) Study well described, including study aim, design, participants, interventions, outcomes, statistics and results, although no hypothesis testing was carried out due to small sample size.</td>
<td>Overall high model validity, including rationale for intervention, intervention used consistently with homeopathy principles, suitability of qualified and experienced practitioner (although only a single homeopath included), and appropriateness of outcome measures. It is possible that other experienced homeopaths would consider the assessment period to be too short.</td>
</tr>
</tbody>
</table>

Homeopathic remedies potentised (diluted & succussed) at following concentrations Q2=2x10^{-16}, Q3=8x10^{-21}, Q4=1.6x10^{-25} (Q4 surpasses Avogadro’s number). HAM-D: Hamilton Depression Rating Scale. BDI: Beck Depression Inventory. SF-12: Short Form-12 Health Survey.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>Sample, condition, recruitment, setting, country</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Risk of bias, assessment, other comments to methods</th>
<th>Model validity, other comments to intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macías-Cortés et al. 2015</td>
<td>RCT, double-blinded, double-dummy, placebo-controlled trial</td>
<td>Moderate to severe depression (diagnosed according to DSM-IV, degree of depression HRSD score 14-24) in peri- and post-menopausal women N=133</td>
<td>Homeopathic remedy + placebo for fluoxetine (H) n=44</td>
<td>Fluoxetine + placebo for homeopathic remedy (P) n=46</td>
<td>Placebo for homeopathic remedy + placebo for Fluoxetine (P) n=43</td>
<td>Internet advertisements, community groups, liaison with health professionals, posters at study site, brochures for hospital population Hospital Juárez de México, Ministry of Health</td>
<td>Adverse events at 4 &amp; 6 weeks</td>
<td>Low risk of bias for comparison of homeopathy and placebo, including random sequence generation, allocation concealment, blinding of assessment, completeness of outcome data and reporting. Overall high model validity, including rationale for intervention, intervention used consistently with homeopathy principles, suitability of qualified and experienced practitioner (although only a single homeopath included), and appropriateness of outcome measures. It is possible that other experienced homeopaths would consider the assessment period to be too short.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Individualised homeopathic remedy (H) (all prescribed in liquid C30 or C200 potency, taken 2x daily) Homeopath: 1 Consultation at baseline, 4 &amp; 6 weeks</td>
<td>Control 1: Fluoxetine 20 mg daily + placebo for individualised homeopathic remedy for 6 weeks</td>
<td>Control 2: Placebo for Fluoxetine + placebo for individualised homeopathic remedy for 6 weeks</td>
<td>Primary: HRSD (17-item) at 4 &amp; 6 weeks Clinically significant: min. 3 points Responder: min. 50% decrease Remission: 7 points or less</td>
<td>At 6 weeks:* HDRS: Homeopathy group better than placebo by 5.0 points (p&lt;0.001) Fluoxetine was better than placebo by 3.2 points (p&lt;0.001) Results were also significant using Bonferroni correction (p&lt;0.01) No statistically significant differences between homeopathic medicines or fluoxetine and placebo BDI (ITT-analysis using Bonferroni correction p=0.130) Homeopathy significantly better than placebo and fluoxetine on GS (climacteric scale) (p=0.002) Response 6 weeks (min. 50 % decrease on HRSD): H: 54.4 %, F: 41.3 %, P: 11.6 % (p&lt;0.001) Remission at 6 weeks (min. 7 point reduction on HRSD): H: 15.9 %, F: 15.2 %, P: 4.7 % (p=0.194) Adverse events (AE): Nine different types of AE: Insomnia (n=6, 13.6%), dyspepsia (n=6, 13.6%), nausea (n=5, 11.4%), fatigue (n=5, 11.4%), anxiety (n=4, 9.1%), dizziness (n=4, 9.1%), diarrhoea (n=3, 6.8%), headache (n=3, 6.8%), constipation (n=2, 4.5%). Prevalence similar to fluoxetine and placebo patients (p-values 0.062 to 0.999). No statistically significant differences between fluoxetine and placebo. All AE mild and tolerable with no interruption of medication, except 1 fluoxetine patient with increased anxiety &amp; insomnia. Multiple imputation for missing data.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>* Results were also statistically significant at 4 weeks, but only 6-week results are presented in the table. HRSD: Hamilton Rating Scale for Depression (17-item) Homeopathic remedies potentised (diluted &amp; succussed) at following concentrations C30=1x10(^{-6}), C200=1x10(^{-40}) (both surpass Avogadro’s number). BDI: Beck Depression Inventory. GS: Green Climacteric Scale (vasomotor, somatic and psychological symptoms, and sexual function).</td>
<td></td>
</tr>
</tbody>
</table>
Figures 3, 4 and 5. Histogram, Normal P-Plot of regression Standardized Residual and Scatterplot for Regression Standardized/Residual Regression Standardized Predicted Value

Histogram
Dependent Variable: PHQ-9 score (6 months)

Normal P-P Plot of Regression Standardized Residual
Dependent Variable: PHQ-9 score (6 months)

Scatterplot
Dependent Variable: PHQ-9 score (6 months)
Figures 6, 7 and 8. Histogram, Normal P-Plot of Regression Standardized Residual and Scatterplot for Regression Standardized Residual/Regression Standardized Predicted value

South Yorkshire Cohort

Health data for Clifton Medical Centre, Rotherham and South Yorkshire
South Yorkshire Cohort data of March 2012, analysed June 2012
Viksveen P, Young TA, Relton C, Bissell P.

Introduction and main points

This is an informal report which contains data for Clifton Medical Centre (CMC) collected from the South Yorkshire Cohort (SYC). It includes comparison with other SYC Rotherham and South Yorkshire practices. P-values have been calculated to determine any potential differences between CMC and all Rotherham and all South Yorkshire practices (results considered statistically significant when p<=0.05). Calculations have been adjusted for gender, age group and deprivation score. Results are based on data collected up until March 2012. A more complete overview may be provided by the end of 2012.

Patients invited to participate in SYC: age 16 – 83 years
Results from Health Questionnaire (7 pages) mailed out 10 June & 10 August 2010.
Deprivation score (IMD Score): 30.83 (Rotherham 32.3, England 19.9)

Weight: One out of five CMC patients was obese and 57.5 % were overweight. CMC patients were more overweight (p = 0.0002) and obese (p = 0.0001) than SYC patients overall, but not compared to Rotherham patients overall. The prevalence of obesity in Rotherham was lower compared to 2005 estimates presented by Health Survey England (HSE) (20% versus 28%). Forty-three percent of CMC patients were concerned about their weight, and about half of all patients had increased exercise and tried to eat healthy food, whereas four out of ten controlled their food portion size. Some had joined specific slimming clubs and a limited number used weight loss medication or meal replacements. Weight strategies for CMC patients were not significantly different to Rotherham or SYC patients overall, with the exception of a trend of higher use of weight loss medication other than pills (p = 0.1).

Long-standing illness: About 54% of CMC patients suffered from self-reported long-standing illness. Compared to Rotherham and SYC practices there were no differences in long-standing illness overall or for diabetes, but more CMC patients were anxious (12.0% versus 10.0% / 9.8%) (p = 0.02 / p = 0.05) and depressed (11.0% versus 8.9% / 9.4%) (p < 0.001 / p = 0.64). Three out of ten had moderate or extreme anxiety or depression on the day they completed the Health Questionnaire, which was more compared to Rotherham and SYC practice patients overall (p = 0.01 / 0.008). There was a trend towards a lower frequency of hypertension compared to all Rotherham practices (p = 0.09) and a trend towards higher frequency for heart disease compared to SYC patients overall (p = 0.06).

Long-standing depression: The most typical/average depressed patient (CMC, Rotherham and SYC) was female and between 31 and 44 years. She had a life satisfaction score of about 5 (scale 0-10), which is considerably lower than for other patients, and she had had twice as many consultations with a GP compared to other patients.

For detailed results, see next pages.
### Long-standing illness

<table>
<thead>
<tr>
<th></th>
<th>CMC</th>
<th>Rotherham</th>
<th>South Yorkshire</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-standing illness (all)</td>
<td>54.4%</td>
<td>54.6%</td>
<td>53.3%</td>
<td>0.87 / 0.41</td>
</tr>
<tr>
<td>Anxiety</td>
<td>12.0%</td>
<td>10.0%</td>
<td>9.8%</td>
<td>0.02 / 0.005</td>
</tr>
<tr>
<td>Depression</td>
<td>11.0%</td>
<td>8.9%</td>
<td>9.4%</td>
<td>&lt; 0.0001 / 0.04</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.6%</td>
<td>5.5%</td>
<td>5.4%</td>
<td>0.80 / 0.80</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13.8%</td>
<td>15.6%</td>
<td>14.3%</td>
<td>0.09 / 0.30</td>
</tr>
<tr>
<td>Heart disease</td>
<td>5.3%</td>
<td>4.9%</td>
<td>4.3%</td>
<td>0.46 / 0.06</td>
</tr>
</tbody>
</table>

### Anxiety & depression

<table>
<thead>
<tr>
<th></th>
<th>CMC</th>
<th>Rotherham</th>
<th>South Yorkshire</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate or extreme (EQ-SD)</td>
<td>30.1%</td>
<td>26.7%</td>
<td>26.9%</td>
<td>0.01 / 0.008</td>
</tr>
</tbody>
</table>

(Note: P-values have not been calculated for the following)

### Life satisfaction

**Numerical rating scale (0-10)**

<table>
<thead>
<tr>
<th></th>
<th>CMC</th>
<th>Rotherham</th>
<th>South Yorkshire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed (mean)</td>
<td>4.9</td>
<td>5.0</td>
<td>4.9</td>
</tr>
<tr>
<td>Non-depressed (mean)</td>
<td>7.2</td>
<td>7.4</td>
<td>7.3</td>
</tr>
</tbody>
</table>

### GP consultations

<table>
<thead>
<tr>
<th></th>
<th>CMC</th>
<th>Rotherham</th>
<th>South Yorkshire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed (mean)</td>
<td>2.2</td>
<td>2.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Non-depressed (mean)</td>
<td>1.1</td>
<td>1.1</td>
<td>1.2</td>
</tr>
</tbody>
</table>

(Note: Analysis for non-depressed patients do NOT include all (i.e. also depressed) patients, only non-depressed patients.)

### Long-standing DEPRESSION

<table>
<thead>
<tr>
<th></th>
<th>CMC</th>
<th>Rotherham</th>
<th>South Yorkshire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>54.2%</td>
<td>60.9%</td>
<td>57.2%</td>
</tr>
<tr>
<td>Age groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 24 years</td>
<td>7.2%</td>
<td>7.9%</td>
<td>9.1%</td>
</tr>
<tr>
<td>25-34 years</td>
<td>12.6%</td>
<td>11.2%</td>
<td>14.8%</td>
</tr>
<tr>
<td>35-44 years</td>
<td>21.6%</td>
<td>20.0%</td>
<td>21.1%</td>
</tr>
<tr>
<td>45-54 years</td>
<td>26.3%</td>
<td>22.9%</td>
<td>22.7%</td>
</tr>
<tr>
<td>55-64 years</td>
<td>17.4%</td>
<td>20.0%</td>
<td>17.9%</td>
</tr>
<tr>
<td>65-74 years</td>
<td>8.4%</td>
<td>11.4%</td>
<td>9.9%</td>
</tr>
<tr>
<td>&gt;= 75 years</td>
<td>6.6%</td>
<td>6.7%</td>
<td>4.4%</td>
</tr>
</tbody>
</table>
Results

Clifton Medical Centre (CMC)
Total responses received: 1,547 patients
Female: 60.4%

<table>
<thead>
<tr>
<th>Weight</th>
<th>CMC</th>
<th>Rotherham</th>
<th>South Yorkshire</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum overweight</td>
<td>57.5%</td>
<td>58.1%</td>
<td>52.3%</td>
<td>0.33 / 0.0002</td>
</tr>
<tr>
<td>Minimum obese</td>
<td>20.8%</td>
<td>19.5%</td>
<td>18.2%</td>
<td>0.30 / &lt; 0.0001</td>
</tr>
<tr>
<td>BMI groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.72 / 0.77</td>
</tr>
<tr>
<td>Morbidly obese</td>
<td>2.1%</td>
<td>1.9%</td>
<td>1.8%</td>
<td>0.49 / 0.35</td>
</tr>
<tr>
<td>Obese</td>
<td>18.2%</td>
<td>17.7%</td>
<td>16.2%</td>
<td>0.40 / 0.02</td>
</tr>
<tr>
<td>Overweight</td>
<td>36.6%</td>
<td>36.5%</td>
<td>34.2%</td>
<td>0.95 / 0.07</td>
</tr>
<tr>
<td>Normal</td>
<td>39.5%</td>
<td>41.3%</td>
<td>45.4%</td>
<td>0.12 / &lt; 0.001</td>
</tr>
<tr>
<td>Underweight</td>
<td>3.0%</td>
<td>2.2%</td>
<td>2.3%</td>
<td>0.06 / 0.07</td>
</tr>
</tbody>
</table>

Note: According to Health Survey England (HSE) 2005 the estimated prevalence of obesity for adults in Rotherham was 28.3% (national estimate 24.2%). Ref. NHS Rotherham Local Strategic Need Assessment, July 2011

<table>
<thead>
<tr>
<th>Weight strategies</th>
<th>CMC</th>
<th>Rotherham</th>
<th>South Yorkshire</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight is a concern for me</td>
<td>43.4%</td>
<td>41.7%</td>
<td>41.9%</td>
<td>0.27 / 0.27</td>
</tr>
<tr>
<td>Weight strategies</td>
<td>CMC</td>
<td>Rotherham</td>
<td>South Yorkshire</td>
<td>P-values</td>
</tr>
<tr>
<td>Exercise &amp; food</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increasing exercise</td>
<td>47.5%</td>
<td>46.2%</td>
<td>46.6%</td>
<td>0.36 / 0.20</td>
</tr>
<tr>
<td>Healthy eating</td>
<td>47.2%</td>
<td>47.9%</td>
<td>47.9%</td>
<td>0.63 / 0.58</td>
</tr>
<tr>
<td>Controlling portion size</td>
<td>41.3%</td>
<td>40.5%</td>
<td>40.7%</td>
<td>0.60 / 0.68</td>
</tr>
<tr>
<td>Slimming clubs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slimming world</td>
<td>7.6%</td>
<td>7.8%</td>
<td>8.1%</td>
<td>0.82 / 0.53</td>
</tr>
<tr>
<td>Weight Watchers</td>
<td>12.0%</td>
<td>11.9%</td>
<td>10.8%</td>
<td>1.00 / 0.16</td>
</tr>
<tr>
<td>Rosemary Conley D&amp;F</td>
<td>1.9%</td>
<td>1.7%</td>
<td>1.4%</td>
<td>0.63 / 0.15</td>
</tr>
<tr>
<td>LighterLife</td>
<td>0.5%</td>
<td>0.4%</td>
<td>0.5%</td>
<td>0.70 / 0.97</td>
</tr>
<tr>
<td>OTC weight loss medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alli (Orlistat)</td>
<td>2.7%</td>
<td>2.2%</td>
<td>2.2%</td>
<td>0.26 / 0.19</td>
</tr>
<tr>
<td>Other</td>
<td>2.4%</td>
<td>1.9%</td>
<td>1.8%</td>
<td>0.28 / 0.10</td>
</tr>
<tr>
<td>Meal replacements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LighterLife</td>
<td>0.8%</td>
<td>0.6%</td>
<td>0.8%</td>
<td>0.40 / 0.89</td>
</tr>
<tr>
<td>Other</td>
<td>3.0%</td>
<td>2.9%</td>
<td>2.8%</td>
<td>0.73 / 0.68</td>
</tr>
</tbody>
</table>
Appendix 2. Literature search results for systematic reviews of homeopathy.

Systematic literature search included titles results
Sources searched: Cochrane Library, EMBASE, MEDLINE, PubMed, own archives, reference lists, contact with other researchers.
Date: 20.02.15
Titles: 349 (duplicates removed).
Relevant titles included: 124. Reviews: 123
Note: Cooper & Relton 2010b is not a separate review, but an update of Cooper & Relton 2010a


Coulter MK, Dean ME. Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder. Cochrane Database of Systematic Reviews 2007, 4:CD005648. DOI: 10.1002/14651858.CD005648.pub2.


Fixsen A. Should homeopathy be considered as part of a treatment strategy for otitis media with effusion in children? Homeopathy 2013; 102:145-150.


Heirs M, Dean ME. Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder. Cochrane Database of Systematic Reviews 2007; 4:CD005648. DOI:10.1002/14651858.CD005648.pub2.


Keen D, Hadjikoumi I. ADHD in children and adolescents. BMJ Clin Evid 2011; 02(312). PMCID:PMC3217800


Nuhn T, Ludtke R, Geraedts M. Placebo effect sizes in homeopathic compared to conventional drugs - a systematic review of randomised controlled trials. Homeopathy 2010; 99(1):76-82.


Appendix 3. Databases and other resource website addresses for systematic review.

BHL: British Homeopathic Library [http://hominform.soutron.net/Catalogues/Search.aspx](http://hominform.soutron.net/Catalogues/Search.aspx)
http://www.hlisd.org/LibraryDetail.aspx?libraryid=3106
(BHL has been closed since the literature search was carried out)
BMC CAM: BMC Complementary and Alternative Medicine [www.biomedcentral.com/1472-6882](http://www.biomedcentral.com/1472-6882)
CAMbase: [http://cambase.dmz.uni-wh.de/opencam/index_en.html](http://cambase.dmz.uni-wh.de/opencam/index_en.html)
CAMEOL Database: [http://www.rccm.org.uk/node/115](http://www.rccm.org.uk/node/115)
CCDAN: Cochrane Depression Anxiety and Neurosis Review Group trial register [http://ccdan.cochrane.org/](http://ccdan.cochrane.org/)
CORE-Hom: [https://www.hri-research.org/resources/research-databases/core-hom/](https://www.hri-research.org/resources/research-databases/core-hom/)
DARE: Database of Abstracts of Reviews of Effects: [http://www.crd.york.ac.uk/crdweb/](http://www.crd.york.ac.uk/crdweb/)
EU Clinical Trials Register: [https://www.clinicaltrialsregister.eu/index.html](https://www.clinicaltrialsregister.eu/index.html)
HRI: Homeopathy Research Institute: [http://homeoinst.org/database](http://homeoinst.org/database)
(Database has changed into CORE-Hom since the literature search was carried out)
HTA: Health Technology Assessment database [http://www.crd.york.ac.uk/crdweb/](http://www.crd.york.ac.uk/crdweb/)
Interhomeopathy [www.interhomeopathy.org](http://www.interhomeopathy.org)
NHS EED: NHS Economic Evaluation Database [http://www.crd.york.ac.uk/crdweb/](http://www.crd.york.ac.uk/crdweb/)
Zetoc: Z39.50-compliant access to the British Library's Electronic Table of Contents [http://zetoc.mimas.ac.uk/](http://zetoc.mimas.ac.uk/)
Appendix 4. MEDLINE search result.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present: http://www.proquest.com/en-US/catalogs/databases/detail/medline_ft.shtml

SUMMARY

Best search string: hom*eopat* AND depress*
Nothing added by adding: potentised, dysthymia, other terms or other ways of spelling words
Result: 92
Time limit: 1982 – current
Date: 13.07.12

SEARCH BUILDER

1. exp homeopathy/ 3895
2. homeopathy.mp. 4414
3. 1 OR 2 4414
4. homeopath 62
5. 2 OR 4 4427
6. homeopathic 1805
7. 5 OR 6 4929
8. homeopat* 4971
9. 7 OR 8 4971
10. homoeopathy 359
11. homoeopath 16
12. 8 OR 9 370
13. homoeopathic 317
14. 12 OR 13 619
15. homoeopat* 703
16. 14 OR 15 703
17. homeopat* OR homeopat* 5117
18. hom*eopat* 5117
19. potentised 11
20. potenti?ed 79
21. 19 OR 20 79
22. hom*eopat* OR potenti?ed

Highest search result: hom*eopat* OR potenti?ed 5125

1. exp depression/ 65900
2. depression 244303
3. 1 OR 2 244303
4. depressed 74060
5. 2 OR 4 290118
6. depressive 104477
7. 5 OR 6 323189
8. depress* 351348
9. 7 OR 8 351348
10. depressive disorder 73259
11. 8 OR 10 351348
12. exp dysthymic disorder/ 917
13. dysthymic 1621
14. 12 OR 13 1621
15. dysthymia 1625
16. 13 OR 15 2737
17. dysthym*2776
18. 16 OR 17 2776
21. depress* OR dysthym* 351680

Highest search result: depress* OR dysthym* 351680

Combined search (homeopathy and depression terms)
(hom*eopat* OR potenti?ed) AND (depress* OR dysthym*) 92
(hom*eopat* OR potenti?ed) AND (depress*) 92
(hom*eopat*) AND (depress*) 92
Appendix 5. Letter to patients for screening and baseline data collection.

Date: 17.09.2013

Dear,

You have previously completed and returned the Health Questionnaire we sent to you. You were one of 2,000 people who reported sometimes feeling anxious or depressed. We would like to learn more about your experiences. We would be grateful if you could complete the enclosed Mood and Health Questionnaire. What we learn will help us understand how we can improve the health of people living in South Yorkshire.

It will take about 15 minutes to complete the questionnaire. When you have completed the questionnaire, please put it in the envelope and post it to the researchers at the University of Sheffield. You do not need a stamp.

All your answers will be made anonymous and used only for research purposes. It is completely up to you whether you fill in the questionnaire. You can withdraw from this study at any time in the future.

If you have any queries or require further information about this study please contact Petter Viksveen or Dr. Clare Relton at: ScHARR, University of Sheffield, FREEPOST – SF1314, Sheffield, S1 1AY. Tel: 0114 222 0796. Email: p.viksveen@sheffield.ac.uk

Thank you.

Yours sincerely

Dr. Clare Relton and Petter Viksveen
Researchers at the University of Sheffield
Appendix 6. Mood and Health Questionnaire

Mood and Health Questionnaire
South Yorkshire Cohort

Thank you for completing the previous Health Questionnaire we sent you. You were one of 2,000 people who reported feeling anxious or depressed sometimes. We would like to hear more about your experience and would be grateful if you could complete this questionnaire.

The questionnaire will take about 15 minutes to complete. When you have completed the questionnaire, please put it in the envelope and post it to the researchers at the University of Sheffield. You do not need a stamp.

The information will be treated confidentially and will not be used for any other purpose than for the South Yorkshire Cohort project.

If you have any queries or require further information about this study, please contact Petter Viksveen or Dr Clare Kelton at SCHARR, University of Sheffield, FREEPOST - SF1314, Sheffield, S1 1AY.

Tel: 0114 222 0796
Email: pxviksveen@sheffield.ac.uk
Your health

Here are some simple questions about your health in general. By ticking one answer in each group below, please indicate which statements best describe your own health state TODAY.

**Mobility**
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-care**
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities**
- I have no problems with performing my usual activities (e.g. work, study, housework, family or leisure activities)
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain / Discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety / Depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

**Long standing conditions**
Do you have any long-standing illness, health problem, condition or disability?  Yes  No
If yes, please tick all that apply:

<table>
<thead>
<tr>
<th>Condition</th>
<th>When did this first start?</th>
<th>When did the current episode start?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiredness / Fatigue</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Insomnia</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Anxiety / Nerves</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Depression</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Other: Please describe</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
### Your mood

Over the last 2 weeks, how often have you been bothered by any of the following problems?

Put a circle around the number that corresponds to your answer.

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling nervous, anxious or on edge</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Not being able to stop or control worrying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Worrying too much about different things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Trouble relaxing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Being so restless that it is hard to sit still</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Becoming easily annoyed or irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Feeling afraid as if something awful might happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Over the last 2 weeks, how often have you been bothered by any of the following problems?

Put a circle around the number that corresponds to your answer.

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead, or of hurting yourself.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10. If you checked off any problems (above), how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Your medication

Are you currently taking any medication? (Either prescribed by your doctor, or that you buy yourself).
☐ Yes  ☐ No

Please list all your medication below, including vitamins and mineral supplements, dietary supplements or diet pills, herbal or homeopathic remedies.

<table>
<thead>
<tr>
<th>Name &amp; strength of tablet, medicine, ointment, drops, inhaler or injection</th>
<th>Is this prescribed for you? Please tick:</th>
<th>What is this for?</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Example) Co-codamol 8mg/150mg tablets</td>
<td>☐ Yes  ☐ No</td>
<td>Joint pain</td>
</tr>
<tr>
<td></td>
<td>☐ Yes  ☐ No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ Yes  ☐ No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ Yes  ☐ No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ Yes  ☐ No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ Yes  ☐ No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ Yes  ☐ No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ Yes  ☐ No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ Yes  ☐ No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ Yes  ☐ No</td>
<td></td>
</tr>
</tbody>
</table>

In the past, have you taken any medication or treatment for feelings of depression?  ☐ Yes  ☐ No

<table>
<thead>
<tr>
<th>Name of medicine or treatment</th>
<th>Is this prescribed for you? Please tick:</th>
<th>When did you first take this?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>☐ Yes  ☐ No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ Yes  ☐ No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ Yes  ☐ No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ Yes  ☐ No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ Yes  ☐ No</td>
<td></td>
</tr>
</tbody>
</table>
### About you

In the last 3 MONTHS, how many times have you visited the following:

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Other care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accident and Emergency (A&amp;E)</td>
<td>times</td>
</tr>
<tr>
<td>Hospital - day case</td>
<td>Care worker times</td>
</tr>
<tr>
<td>Hospital - outpatients</td>
<td>Social worker times</td>
</tr>
<tr>
<td>Hospital - in-patients (nights)</td>
<td>Health visitor times</td>
</tr>
<tr>
<td>GP</td>
<td>Community health champion times</td>
</tr>
<tr>
<td>Nurse</td>
<td>Health trainer times</td>
</tr>
<tr>
<td>Physiotherapist</td>
<td></td>
</tr>
<tr>
<td>Dietitian</td>
<td>Acupuncturist times</td>
</tr>
<tr>
<td>Midwife</td>
<td>Chiropractor times</td>
</tr>
<tr>
<td>Mental health worker</td>
<td>Herbalist times</td>
</tr>
<tr>
<td>Psychotherapist</td>
<td>Homeopath times</td>
</tr>
<tr>
<td></td>
<td>Osteopath times</td>
</tr>
<tr>
<td>Other healthcare</td>
<td>Alternative therapist</td>
</tr>
</tbody>
</table>

**Other Please describe**

How many children do you have (under the age of 18)? children

What age is your youngest child? years. Are you currently pregnant?  Yes  No

Your height  feet inches  OR  cm

Your weight  stone lbs  OR  kgs

Are you currently employed?  Yes  No

During the last 3 MONTHS, how many days have you taken off from paid work as a result of ill health?

During the last 3 MONTHS, how many days has your ill health prevented you from carrying out your:

**Alcohol:** How many days in the last WEEK did you drink alcohol? days

How many units of alcohol did you drink in the last WEEK? units

A unit of alcohol is equal to ½ a pint of ordinary beer, lager or cider, 1 single measure of spirits, 1 small glass of wine or 1 measure of fortified wine.

Are you currently involved in another study to do with your health?  Yes  No

If yes, which one / what is it about? ..........................................................
About you

Thank you for your answers. These will be combined with hundreds of others. What we learn will help us understand how we can improve the health of people living in South Yorkshire.

May we contact you again?
☐ Yes  ☐ No

Please fill in your **forename, surname** and **address if different** to those printed to the left:

Forename (print)

Surname (print)

Address

Telephone

Mobile phone*

Email*

*Optional

Signature

Thank you for completing the Health Questionnaire. Please put it in the prepaid envelope and post it to the researchers. NO STAMP NEEDED.

If you have any queries or require further information about this study please contact Petter Viksveen or Dr Clare Relton at: SCHAR, University of Sheffield, FREEPOST - SF1314, Sheffield S1 1AY

Tel: 0114 222 0796  Email: pviksveen@sheffield.ac.uk

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Appendix 7. Mood and Health Questionnaire – follow-up

Mood and Health Questionnaire
Yorkshire Health Study

Thank you for completing the previous Mood and Health Questionnaire we sent you. You were one of 2,000 people who reported feeling anxious or depressed sometimes. We would like to hear more about your experience and would be grateful if you could complete this questionnaire.

The questionnaire will take about 15 minutes to complete. When you have completed the questionnaire, please put it in the envelope and post it to the researchers at the University of Sheffield. You do not need a stamp.

The information will be treated confidentially and will not be used for any other purpose than for the Yorkshire Health Study.

If you have any queries or require further information about the study please contact Petter Viksveen or Dr Clare Pelton at: SCHARR, Regent Court, 30 Regent Street, Sheffield S1 4DA.

Tel: 0114 222 0796
Email: pviksveen@sheffield.ac.uk
Your health

Here are some simple questions about your health in general. By ticking one answer in each group below, please indicate which statements best describe your own health state TODAY.

<table>
<thead>
<tr>
<th>Mobility</th>
<th>Please tick one:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no problems in walking about</td>
<td></td>
</tr>
<tr>
<td>I have some problems in walking about</td>
<td></td>
</tr>
<tr>
<td>I am confined to bed</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Self-care</th>
<th>Please tick one:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no problems with self-care</td>
<td></td>
</tr>
<tr>
<td>I have some problems washing or dressing myself</td>
<td></td>
</tr>
<tr>
<td>I am unable to wash or dress myself</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Usual Activities</th>
<th>Please tick one:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no problems with performing my usual activities (e.g. work, study, housework, family or leisure activities)</td>
<td></td>
</tr>
<tr>
<td>I have some problems with performing my usual activities</td>
<td></td>
</tr>
<tr>
<td>I am unable to perform my usual activities</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain / Discomfort</th>
<th>Please tick one:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have no pain or discomfort</td>
<td></td>
</tr>
<tr>
<td>I have moderate pain or discomfort</td>
<td></td>
</tr>
<tr>
<td>I have extreme pain or discomfort</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anxiety / Depression</th>
<th>Please tick one:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am not anxious or depressed</td>
<td></td>
</tr>
<tr>
<td>I am moderately anxious or depressed</td>
<td></td>
</tr>
<tr>
<td>I am extremely anxious or depressed</td>
<td></td>
</tr>
</tbody>
</table>

Long standing conditions

Do you have any long-standing illness, health problem, condition or disability? Yes □ No □

If yes, please tick all that apply:

<table>
<thead>
<tr>
<th>Tiredness / Fatigue</th>
<th>High blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Heart disease</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Anxiety / Nerves</td>
<td>Stroke</td>
</tr>
<tr>
<td>Depression</td>
<td>Cancer</td>
</tr>
<tr>
<td>Memory problems</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Breathing problems e.g. chronic bronchitis, asthma or emphysema</td>
<td>Other (please state):</td>
</tr>
</tbody>
</table>

□
## Your mood

Over the last 2 weeks, how often have you been bothered by any of the following problems?  
*Put a circle around the number that corresponds to your answer.*

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling nervous, anxious or on edge</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Not being able to stop or control worrying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Worrying too much about different things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Trouble relaxing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Being so restless that it is hard to sit still</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Becoming easily annoyed or irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Feeling afraid as if something awful might happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Over the last 2 weeks, how often have you been bothered by any of the following problems?  
*Put a circle around the number that corresponds to your answer.*

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead, or of hurting yourself</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10. If you checked off any problems (above), how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
## Your medication

Are you currently taking any medication? (Either prescribed by your doctor, or that you buy yourself).

- [ ] Yes  
- [ ] No

Please list all your medication below, including vitamins and mineral supplements, dietary supplements or diet pills, herbal or homeopathic remedies.

<table>
<thead>
<tr>
<th>Name &amp; strength of tablet, medicine, ointment, drops, inhaler or injection</th>
<th>Is this prescribed for you? Please tick:</th>
<th>What is this for?</th>
</tr>
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<tbody>
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<td>(Example) Co-codamol 30mg/300mg tablets</td>
<td>Yes ☑ No</td>
<td>Joint pain</td>
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<td>Yes ☑ No</td>
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<td>Yes ☑ No</td>
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</table>
# About you

In the last 3 MONTHS, how many times have you visited the following:

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<tr>
<th>Hospital</th>
<th>Other Healthcare</th>
<th>Alternative therapist</th>
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</thead>
<tbody>
<tr>
<td>Accident and Emergency (AGE)</td>
<td>GP</td>
<td>Acupuncturist</td>
</tr>
<tr>
<td>Hospital - day case</td>
<td>Nurse</td>
<td>Chiropractor</td>
</tr>
<tr>
<td>Hospital - outpatients</td>
<td>Physiotherapist</td>
<td>Herbalist</td>
</tr>
<tr>
<td>Hospital - in-patients (nights)</td>
<td>Dietitian</td>
<td>Homeopath</td>
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<tr>
<td></td>
<td>Midwife</td>
<td>Osteopath</td>
</tr>
<tr>
<td></td>
<td>Mental health worker</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psychotherapist</td>
<td></td>
</tr>
</tbody>
</table>

Other Please describe: 

Are you currently employed?  
Yes  No

During the last 3 MONTHS, how many days have you taken off from paid work as a result of ill health?

During the last 3 MONTHS, how many days has your ill health prevented you from carrying out your:  

Household tasks:  Leisure activities:

**Alcohol:** How many days in the last WEEK did you drink alcohol?  

How many units of alcohol did you drink in the last WEEK?  

A unit of alcohol is equal to ½ a pint of ordinary beer, lager or cider, 1 single measure of spirits, 1 small glass of wine or 1 measure of fortified wine.
About you

Thank you for your answers. These will be combined with hundreds of others. What we learn will help us understand how we can improve the health of people living in South Yorkshire.

May we contact you again?
☐ Yes  ☐ No

Please fill in your forename, surname and address if different to those printed to the left:
Forename (print)

Surname (print)

Address

Postcode

Please fill in your preferred contact details below:

Telephone

Mobile phone*

Email*

*Optional

Signature

Thank you for completing the Mood and Health Questionnaire. Please put it in the prepaid envelope and post it to the researchers. NO STAMP NEEDED.

If you have any queries or require further information about this study please contact Petter Viksveen or Dr Clare Reiton at: SCHARR, Regent Court, 30 Regent Street, Sheffield S1 4DA.

Tel: 0114 222 0796  Email: p.viksveen@sheffield.ac.uk

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Appendix 8. Offer group – Treatment offer letter

Offer group – Treatment offer letter (version 8, date 14.07.2012)

Date:

Dear Mr., Mrs., Ms.

You may remember that you recently completed and returned the Mood and Health Questionnaire. Thank you for your help. You reported some degree of anxiety and/or depression. You are one of 162 participants who have been randomly selected to be offered treatment by a homeopath. The treatment is free and we will reimburse your travel costs to consultations.

Homeopathy is a form of complementary and alternative medicine used by many patients. It is used for different conditions, including anxiety and depression. Treatment includes consultations and taking homeopathic medicines. In previous studies some patients reported improvement. Little or no side-effects have been reported by patients. Researchers at the University of Sheffield would like to learn more about your experience with such treatment.

You will be contacted by telephone by a researcher to hear if you want to participate. You can then also ask any questions you may have.

Please read the enclosed Participant Information Sheet for further information.

If you decide to participate then please sign the enclosed Consent Form and return it to us in the enclosed envelope. No stamp is needed.

You may then contact one of the following practitioners to agree the date and time of your first consultation:
Name of practitioner, contact details

If you have any questions or require further information about this study please contact Petter Viksveen or Dr. Clare Relton at: ScHARR, University of Sheffield, FREEPOST – SF1314, Sheffield, S1 1AY. Tel: 0114 222 0796. Email: p.viksveen@sheffield.ac.uk

Thank you.

Yours sincerely

Dr. Clare Relton and Petter Viksveen

Researchers at the University of Sheffield
Appendix 9. Offer group – Participant Information Sheet

Offer group – Participant Information Sheet (version 10, date 25.06.2013)

You have been invited to take part in a study of homeopathic treatment. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. The aim of this study is to find out whether treatment by a homeopath is effective for people who report symptoms of depression.

Why have I been chosen for this study?
You have been chosen because you reported some degree of anxiety and/or depression when you filled in the Mood and Health Questionnaire.

What will I be asked to do?
You are being asked to have a course of homeopathic treatment. This will consist of consultations with a homeopath roughly once every 1-3 months for a maximum period of 9 months. Your homeopath will prescribe homeopathic remedies for you. Homeopathy is a form of complementary and alternative medicine used by many patients. It is used for different conditions, including anxiety and depression. Previous patients have reported little or no side-effects of such treatment. Researchers at the University of Sheffield would like to learn more about your experience with such treatment.

The treatment is free and we will reimburse your travel costs to consultations.

Participating in this study does not affect any other treatment you may be using. You should continue to take any medication or treatment provided by your GP or other health practitioners. Any standard medication you are taking must be continued as prescribed by your GP/specialist. All homeopaths in this study are qualified, registered and experienced practitioners. They have agreed to contact your GP should this become necessary. In such a case they will discuss this with you first. Your GP will be informed if you agree to participate in this project.

Do I have to take part in this research?
No, it is up to you to choose whether you want to take part. If you decide to take part, you will be asked to sign the attached Consent Form. You have the right to withdraw from this study at any given time. This will not affect any other treatment you are receiving. You do not need to give a reason for this (but you may be asked if you are willing to give a reason.)

Will the information I give be kept private?
Yes. All information you provide will be kept strictly confidential. Once we have collected the information, all the data will be made anonymous. As an individual you will not be identifiable in the results of the study. The data will be kept for 5 years or until the end of the South Yorkshire Cohort study.

What will happen to the results of this research?
The results of this research will be published in a health science journal and in a PhD report at the University of Sheffield. If you would like, we will give you a report of the findings of the study.
Who is organising and funding the research?
This study is part of a programme carried out by the principal investigator, Petter Viksveen, at the University of Sheffield. The project has received funding from various sources. The project will pay the homeopaths who provide the treatment and your travel costs.

Who has reviewed the study?
This study has been reviewed by Independent Scientific Reviewers and researchers at the University of Sheffield.

What if I have any concerns or questions or wish to file a complaint?
If you have any concerns, including any experienced negative effects following treatment, if you have any questions or require further information about this study, or wish to file a complaint, please contact Petter Viksveen or Dr. Clare Relton at: ScHARR, University of Sheffield, FREEPOST – SF1314, Sheffield, S1 1AY. Tel: 0114 222 0796. Email: p.viksveen@sheffield.ac.uk Complaints may also be filed directly to the University of Sheffield by contacting Mrs. Kirsty Woodhead at k.woodhead@sheffield.ac.uk

Thank you for reading this.
Appendix 10. Consent form

Consent Form

Centre number: SchARR
Study number: 12/TH/0379
Participant Identification Number:

1. I hereby confirm that I have read and understand the information in the “Offer group – Participant Information Sheet” and have been given the opportunity to ask researchers at the University of Sheffield any questions I may have.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason.

3. I understand that the information I provide will be treated confidentially and will only be looked at by the researchers involved in this project.

4. I understand that any standard medication must be continued as prescribed by my GP/specialist.

_________________________  ________________  __________
Your name (capital letters)  Your signature  Date

Please return the signed consent form to: Petter Viksveen at: SchARR – Regent Court, FREEPOST – SF1314, Sheffield, S1 1AY.
Appendix 11. Adverse Events Assessment Guidelines for the DEPSY project

Adverse Events Assessment Guidelines for the DEPSY project
(version 3, 13.03.2013)

Introduction

This document has been developed for the pragmatic cohort randomized controlled trial of the clinical and cost effectiveness of treatment of depression by homeopaths (DEPSY) at the School of Health and Related Research (ScHARR), University of Sheffield, and which is embedded in the South Yorkshire Cohort (SYC). The aim of the DEPSY project is to assess the acceptability and comparative clinical and cost effectiveness of adjunctive treatment provided by homeopaths in addition to usual care for patients who have self-reported depression (DEPSY). A random selection of patients in the South Yorkshire Cohort (SYC) will be offered treatment by homeopaths. Homeopaths must report adverse events to the research management team. Patients are also informed in the Patient Information Sheet that they may report adverse events directly to the research team.

These Adverse Event (AE) guidelines are mainly based on the Common Terminology Criteria for Adverse Events (CTCAE) (U.S. Department of Health and Human Services 2010, v.4.03), the Standard Operating Procedure developed by the Clinical Trials Research Unit (CTRU) at the University of Sheffield (2012) and existing homeopathy literature. This document supplements the DEPSY risk assessment guidelines (full title: “How to identify and deal with clinical risk issues: Guidelines for homeopaths providing treatment in the DEPSY project.”)

What is an adverse event?

Many definitions of adverse events exist. The CTCAE guidelines define an adverse event (AE) as (p.1): “… any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.”

Different grades of adverse events

Adverse events may be categorised in various ways. The CTCAE guidelines use the following 5 categories (p.1) (semi-colon indicates ‘or’) (definitions are also consistent with European Commission (2011) guidelines):

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only. Intervention not indicated.
Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL (ADL = Activities of Daily Living) (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; resulting in significant disability or incapacity; limiting self-care ADL (ADL = Activities of Daily Living) (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden), or congenital anomaly or birth defect; or events that may require intervention to prevent any of the mentioned consequences.

Grade 4: Life-threatening consequences; urgent intervention indicated. This refers to events where the subject was at risk of death, not where the event hypothetically could have caused death.

Grade 5: Death related to AE.

These grades help us to differentiate between adverse events and serious adverse events.

Adverse events in homeopathy and homeopathic aggravations

Homeopathic remedies are known mostly to be highly diluted products. They are therefore normally considered to be safe (Bornhöft et al. 2006) and not to represent a risk of toxicological effects or interactions with conventional drugs (Woodward 2005). Nevertheless, adverse events following homeopathic treatment have been reported by various authors (e.g. Dantas & Rampes 2000, Grabia & Ernst 2003, Haidvogl et al. 2007). These adverse events have been characterised as transient and mild (Dantas & Rampes 2000) or mild to moderate (Grabia & Ernst 2003). No observational studies or clinical trials have reported serious adverse events (ECCH 2009). Dantas & Rampes (2000) found that adverse events were most commonly: headaches, tiredness, skin eruptions, dizziness, bowel dysfunctions such as diarrhoea or loose stools, and aggravations of patients’ pre-existing symptoms. More recently adverse events after homeopathic medicines have been reported in patients with mental health problems (Pilkington et al. 2005, 2006). However, these adverse events were not serious and did not result in withdrawal from treatment.

Aggravations of patients’ pre-existing symptoms are commonly referred to as ‘homeopathic aggravations’ in the homeopathy literature. They involve a temporary worsening of patients’ already existing symptoms and occur relatively soon after taking a homeopathic medicine (Thompson et al. 2004). These temporary reactions are normally considered favourable and part of patients’ curative process (Endrizzi et al. 2005, Thompson et al. 2004).

What should homeopaths in the DEPSY project do?

The main reason for reporting adverse events in the DEPSY project is to ensure patients’ safety. It is therefore important that homeopaths check for adverse events at each consultation and report any changes in patients which might be considered to be serious adverse reactions (regardless of whether or not the adverse event is viewed by the homeopath as a potentially curative ‘homeopathic
aggravation’). Homeopaths should report any event which would satisfy at least the grade 3 criteria as defined in the CTCAE guidelines. This would include:

- any severe or medically significant reactions, even though they may not be life-threatening
- reactions resulting in hospitalisation or prolongation of hospitalisation
- reactions limiting patients ability for self-care, including daily living activities such as bathing, dressing and undressing, feeding themselves, using the toilet, taking medications

Homeopaths should also report any development into level 3 – Moderate to severe, or more, as defined in the DEPSY Risk Guidelines.

**When in doubt, homeopaths should contact the management team** (see emails below). The DEPSY Management Team will then determine what should be done, including the need to report the event to the Head of the School of Health and Related Research (ScHARR), the sponsor (University of Sheffield), the DEPSY Steering Committee and the and the Regional Ethics Committee; and whether there is a need to contact the patient and/or her/his GP.

Adverse events should be reported using the Adverse Event & Risk form included in the DEPSY Risk Guidelines. The form should be completed within 24 hours of the event and should be emailed to the Chief Investigator, Petter Viksveen at p.viksveen@sheffield.ac.uk and Dr Clare Relton at c.relton@sheffield.ac.uk (PLEASE EMAIL BOTH).

**What should the DEPSY Management Team do?**

The Management Team will receive reports from homeopaths and patients about adverse events. The Management Team will report to the Head of the School of Health and Related Research (ScHARR) at the University of Sheffield within 1-5 days (depending on severity) of the occurrence of the event. They will report serious adverse events (SAE) within 48 hours to the Head of the School of Health and Related Research (ScHARR), the sponsor (University of Sheffield), the DEPSY Steering Committee and the and the Regional Ethics Committee; and when needed the patient and/or her/his GP.

The Management Team will complete the University of Sheffield Adverse Event Report Form and will in line with the Standard Operating Procedure developed by the Clinical Trials Research Unit (CTRU) at the University of Sheffield (2012) include their assessment of the seriousness, frequency and intensity of the Adverse Event; concomitant treatment; the assessed relationship to treatment by homeopath; any actions taken and the outcome. **When in doubt, the Management Team will discuss the issue with the Head of the School of Health and Related Research (ScHARR).**

**Seriousness:** Death; life threatening; inpatient hospitalisation; prolonged hospitalisation; persistent or significant disability/incapacity; congenital abnormality/birth defect.

**Frequency:** Isolated; intermittent; continuous; unknown.

**Intensity:** Mild; moderate; severe.

**Concomitant treatment:** Any treatment other than the treatment provided by the homeopath.

**Assessed relationship to treatment by homeopath:** Definite; probable; possible; unlikely; unrelated; not assessable.
Action taken: None; reduce dose; treatment withdrawn; specific treatment; other.

Outcome: Recovered; improved; unchanged; deterioration; persisted; death.

References


Clinical Trials Research Unit (CTRU), University of Sheffield (2012). CTRU Standard Operating Procedure PM004, Version:3. Adverse events and serious adverse events. 24th August 2012.

Appendix 12. How to identify and deal with clinical risk issues: Guidelines for homeopaths providing treatment in the DEPSY project.

How to identify and deal with clinical risk issues: Guidelines for homeopaths providing treatment in the DEPSY project (version 7, 16.02.2013)

Introduction

This document has been developed for homeopaths who treat patients included in the pragmatic cohort randomized controlled trial of the clinical and cost effectiveness of treatment of depression by homeopaths (DEPSY) project at the School of Health and Related Research (ScHARR), University of Sheffield, and which is embedded in the South Yorkshire Cohort (SYC). The aim of the project is to assess the acceptability and comparative clinical and cost effectiveness of adjunctive treatment provided by homeopaths in addition to usual care for patients who have self-reported depression (DEPSY). A random selection of patients in the South Yorkshire Cohort (SYC) will be offered treatment by homeopaths.

This document is mainly based on the clinical risk protocol developed by Sheffield Mind (2011, undated), and supplemented by the guidelines for management of depression developed by the National Collaborating Centre for Mental Health (NCCMH 2006). It includes issues that have been considered particularly important for homeopaths in the DEPSY project. Practitioners are encouraged to read the full Sheffield Mind and NCCMH guidelines. These documents will be provided by the Chief Investigator.

A special thanks to Sheffield Mind for permission to use their documents for this project.

Confidentiality

- Take the patient’s wishes into consideration, but make aware that if the concern is serious enough it may be necessary to breach confidentiality
- Discuss limits of confidentiality at the start of treatment and again when dealing with a risk issue
- Make decisions regarding breaching confidentiality after discussion with your supervisor and/or the Chief Investigator of the research project

Your competency

- Work within the limits of your competency
- Work according to a recognised and enforceable code of ethics developed by your professional organisation
- Make sure you have regular supervision, depending on your need and level of experience
Monitoring and measuring the level and urgency of risk

Ask patients directly about their mental health, in order to identify any potential risk factors. When communicating with patients, make sure you use everyday language so that your patients understand.

When a risk issue is identified or there is a perceived change in the level of a known risk:
- Engage with the patient and explore risk with the patient
- Be willing to explore the patient’s feelings and introduce the idea that positive change is possible
- Know where to find information that will help you and the patient make decisions about risk
- Share anonymised information with your supervisor and/or the project Chief Investigator
- Record fully and accurately the issue and action taken, using a clinical risk assessment form (Appendix A) with dates, times, people involved, actions taken, and outcomes of actions
- Provide regular reports to the Chief Investigator, who will forward it to the Steering Committee and the Project Team to monitor levels and frequency of risk situations and plan accordingly

What is clinical risk?

Clinical risk is the possibility of something negative happening as a direct result of the behaviour of a patient or people in their surroundings. It includes information received from or about a person that may have a negative impact on the patient or anyone the patient is in contact with.

Risk means situations and circumstances that could result in:
- Suicide
- Significant self-harm
- A person being harmed by others
- A person causing harm to others
- A significant deterioration in a person’s mental health

Harm can be physical or emotional/psychological.

Warning signs

The following may be possible indications of risk:
- Suicidal ideation
- Evidence of starting to self-harm or increase in existing self-harming behaviour
- Patients reporting violence or threats of violence from others
- Patients reporting that they want to or do cause harm to others
- Situations disclosed that suggest children or vulnerable adults may be at risk
- Sudden changes in behaviour (especially in response to life challenges or therapy)
- Beginning or increasing substance misuse (including alcohol and tobacco)
- Erratic attendance for treatment
- Increase in negative behaviours
- Changes in sleeping/eating patterns
- Becoming increasingly isolated
- Patients on the edge of collapse/at risk to self
- Patients who are unresponsive in therapy
- Patients stopping prescribed medication
- Unexpected improvement, sudden or spontaneous recovery of depressed mood
- Failure to improve
Patients at risk and factors that may increase the level of risk

Consider patients’ individual histories, including any medical, family and psychosocial issues. Assess:
- The presence or absence of any protective factors
- What the patient is saying and how this fits with known risk factors
- Expressed or documented concerns from significant others, and your supervisor’s or the project Chief Investigator’s assessment

Even when patients are not known to be high risk, situations can occur and/or develop which increase the level of risk.

Patient risk factors

- Suicidal ideation or previous suicide attempts
- Self-harm or history of self-harming
- History of violence and/or aggression from or towards others
- Psychiatric diagnosis and symptoms, severe enduring mental health problems (e.g. depression, eating disorders) and long term physical ill health
- Depth of depressive feelings, inability to resist negative thoughts
- Hopelessness about the present and future, sense of helplessness in a crisis
- Lack of confidence and low self-esteem
- Isolation, self-neglect
- Lack of coping/problem solving skills
- Inability to resist attempts at exploitation
- Impulsiveness, past and/or current high risk behaviours
- Unsettled and/or chaotic lifestyles
- Increase in aggressive behaviour/anger management problems
- Difficulties in establishing and maintaining meaningful relationships with others
- Misuse of drugs and/or alcohol

Contextual factors

- Family history
- Being in a high risk group (i.e. demographics, age, gender, occupation)
- Vulnerable adults
- History of difficult relationships with a vulnerable adult or child
- History of violence and/or aggression from others or towards others
- Moving into an abusive/exploitative relationship
- Lack of social support or the unwillingness/inability to use support networks
- Lack of stability in personal circumstances (family, job, accommodation)
- Changes in circumstance (relationship crisis, loss of job/home/role/a loved one, recent discharge from hospital or release from prison)
- Increases in external pressures (stress, bullying, debt, work pressures)
Clinical assessment tool

Level 1: Mild

Assessment criteria:
- Reactive depression with no past history
- Possible use of anti-depressants
- Relationship breakdown with no significant history
- Coming to term with life changes
- Symptoms might be amenable to cognitive work

Risk: No significant risk issues.

Level 2: Mild, moderate to severe

Assessment criteria:
Any criteria from level 1 plus:
- Likely use of anti-depressants
- Current relationship difficulties
- Recent life change that is causing fundamental review of life direction
- Family difficulties in the past, but patient currently has some supportive relationships

Risk: Possible risk issues in the past but no longer current.

Level 3: Moderate to severe

Assessment criteria:
Any criteria from level 1 & 2 plus:
- Moderate levels of risk requiring active monitoring and management
- Longer term mental health difficulties such as depression, anxiety, panic disorder
- Likely to have had previous hospital admissions
- History of sexual abuse or family violence
- Current serious relationship problems
- Relational difficulties with self/others due to early experience, but some support in community
- Possible eating difficulties
- Likely involvement of other agencies
- Aged under 19

Risk: Possible self-harm/suicide ideation but engaged with sense of containment. **Suggest patient could also be seen by her/his General Practitioner (GP).**

Level 4: Severe

Assessment criteria:
Any criteria from previous levels plus:
- Likely suicide ideation and previous attempts on life
- Likely history of self-harm
- Long term severe mental illness
- Serious health problems of possible psychosomatic origin
- Some psychosis if stabilised and managed
- More serious neglect or abuse in childhood
- Less support within and/or poor functioning in the community
- Possible child protection issues
- Other agencies involved but poor engagement likely

Risk: Possible self-harm/suicide ideation but willing to address this with the practitioner. **The patient should also be seen by her/his General Practitioner (GP) and/or a mental health specialist.**
Level 5: Severe – possible inpatient/crisis team

Assessment criteria:
Any of the previous criteria plus:
- Significant risk issues
- Serious suicide attempts
- Long term self-harm
- Dissociation
- Complex eating disorder
- Possible diagnosis of personality disorder
- Serious attachment difficulties
- Several hospitalisations

Risk: Urgent concern about risk of self-harm/suicide or harm to others. The patient should be seen by her/his General Practitioner (GP) and/or a mental health specialist, and possibly be treated by a crisis team.

Procedures for managing clinical risk

Consider if patients in risk have adequate social support and whether they know who to contact in case their condition deteriorates. Contact patients who do not attend follow-up consultations. Respect patients’ decision in case they choose to withdraw from the study, but make an effort to check if their mental state of health has deteriorated and, if necessary, recommend them to contact their General Practitioner (GP) and/or Mental Health Team.

Severe and/or urgent risk

Risk issues in one-to-one consultations rarely need immediate action. However, if during a consultation patients attempt to harm themselves or the therapist:
- Press the panic button (if there is one in the room, check this beforehand)
- Stay calm and reassuring
- Express concern clearly and use the time to gather as much information as possible
- Determine the urgency of the situation and discuss how to proceed
- Involve another practitioner if needed
- Make a judgement, together with the patient if possible, about whether they are safe to leave
- Make referral to another service such as the GP or Community Mental Health Team if needed
- If the patient is not safe to leave the building alone, seek permission from her/him to contact a relative, friend and/or the appropriate agency
- If all other avenues have been explored, call an ambulance
- If in doubt, dissuade the patient from leaving the building alone
- If the patient insists on leaving and there is sufficient concern about their safety, contact the police
- If the event takes place over email or telephone: Obtain as much detail as possible, in particular name and contact details, where the person is at that moment, contact persons, GP/healthcare practitioner details; and offer to talk to them or recommend someone who they may contact

To learn more about emergencies, become familiar with http://www.sheffieldmentalhealth.org.uk
High level of risk, but less urgent

- Gather as much information about the situation as possible
- Monitor all ongoing risk issues regularly and carefully
- Consider involving other agencies, GP, etc.
- Pay attention to the patient’s wishes, the confidentiality and information sharing policies
- Inform the Chief Investigator of all ongoing risk issues
- Share information with relevant others when appropriate, and with the patient’s permission

Who you may contact

For any issues that arise during and outside consultations, consider discussing these with your personal supervisor. You should make arrangements for supervision according to your own needs throughout the project. You have the responsibility to organise and finance this yourself. Treatment of patients should only start once such an arrangement has been made. Please inform the Chief Investigator once you have identified a supervisor.

General questions on safety or other questions related to the research project: Contact the Chief Investigator: Petter Viksveen, at p.viksveen@sheffield.ac.uk or tel. 0114 222 0796 or +47 51 11 32 15.

Clinical risk issues

- **If not urgent:** Contact the Chief Investigator, who will either answer your question or recommend an appropriate person you may contact: Petter Viksveen, at p.viksveen@sheffield.ac.uk or tel. 0114 222 0796 or +47 51 11 32 15.

- **In case of severe risk or urgent matters:** Contact the Manager or another person at the clinic where consultations are being carried out AND the Chief Investigator (CI) of the project: Petter Viksveen, at p.viksveen@sheffield.ac.uk or +47 51 11 32 15 **AND** Dr Clare Relton c.relton@sheffield.ac.uk or tel. 0114 222 0796. (For further details on reporting of adverse events and risks, see Appendix A). In case you are unable to reach Petter Viksveen or Dr Clare Relton, contact the administrator at ScHARR (same phone number 0114 222 0796).

- **In case immediate help is needed:** Call another practitioner or person at the clinic for assistance and/or call emergency/ambulance services and/or police at 999 or 112, as appropriate.

References


**Appendix A: Adverse Event & Risk form for DEPSY**

An adverse event is an unfavourable event that includes, but is broader than, unintended errors and mistakes which arise as a result of research activity and result in one or more research participants having symptoms or being cause physical or psychological harm or serious distress. For further information – refer to the DEPSY Adverse Events Guidelines.

Please complete this form within 24 hours of the event occurring and email it to Chief Investigator Petter Viksveen at p.viksveen@sheffield.ac.uk AND to Dr Clare Relton at c.relton@sheffield.ac.uk They need to report it to the Head of the School of Health and Related Research (ScHARR) at the University of Sheffield within 1-5 days (depending on severity) of the occurrence of the event. They will report serious adverse events (SAE) within 48 hours to the sponsor (Head of Operations Section, University of Sheffield), the Chair of the Steering Committee of the DEPSY project and the Regional Ethics Committee (REC). They will also report SAE to the patient’s GP.

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<td><strong>Homeopath’s name and contact details:</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient’s name, date of birth and contact details:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Patient’s GP name and contact details:</th>
</tr>
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<table>
<thead>
<tr>
<th>Details:</th>
</tr>
</thead>
<tbody>
<tr>
<td>When did the event take place?</td>
</tr>
<tr>
<td>Where did the event take place?</td>
</tr>
</tbody>
</table>

What happened and what was the impact of the event?

<table>
<thead>
<tr>
<th>Do you have any thoughts on why the event occurred?</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Action taken:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Follow up required (incl. any action(s) taken or planned to limit the risk of an event re-occurring):</th>
</tr>
</thead>
</table>
Appendix 13. Interview guide I 120620 rev 121017

Project title (abbreviated): Depression in South Yorkshire (DEPSY)
Principal investigator: Petter Viksveen, Postgraduate Research Student, ScHARR, University of Sheffield. p.viksveen@sheffield.ac.uk
Aim: To explore the positive and negative experiences with homeopathic treatment in patients who have taken or who are taking antidepressant drugs.
Qualitative interview method: Semi-structured face-to-face interviews after 1st consultation + after a minimum of 2 follow-up consultations and 6 months.
Time: 2012 – 2013

INTERVIEW GUIDE I (1st interview) (version 2, date 20.06.2012)

Introduction: This is the guide for the first out of two interviews to be carried out as part of this project. The first interview will be carried out after patients have had their first consultation with a homeopath. Interviews will aim at lasting 30-60 minutes, including time for welcoming and closing the interview, but timeframes will be flexible. The length of the interview will be audio-recorded.

Introduction of interview to participants:
- Welcome participant and explain the purpose of the interview, which is to learn from the participant’s experience with homeopathic treatment.
- Explain to the participant why and how she/he was chosen.
- Explain the procedure of the interview, including the use of audio-recording equipment.
- Inform the participant of ethical issues, including anonymity and confidentiality (who will have access to data and assure that the final results will not contain any information that may identify the participant), and the right to withdraw from the project at any given time, until the data have been analysed.
- Ask the participant if she/he has any questions, before the start of the interview.
- PI introduces himself, including his name, University affiliation and role in project.
- Check the participant’s name and contact details.
- Ask the participant to sign the consent form.

Semi-structured interview:
- Invite the participant to tell about her/his experience (in general). Stay open to issues she/he may raise (e.g. general experiences of her/his depression), let her/him ‘tell her/his story’.
- As much as possible pose open-ended questions (as opposed to closed and leading questions), include ‘what’ and ‘how’ questions, and avoid ‘why’ questions.
- Probe arising issues to understand them in depth.
- Actively listen by confirming understanding of the participants’ responses, incl. feeding back the interviewer’s understanding to allow the participant to confirm, adjust or correct.
- As much as possible use participants’ own words and give time and room to reflect to allow for her/him to make ‘new discoveries’.
- Pay attention to arising conflicting issues and aim to clarify and sort them out.
- Redirect the interview in case responses are not relevant.
- Interviewer should stay friendly, interested and neutral (no approval or disapproval).
- Questions posed to participants during the first interview may include:
  - What was your experience during and after the first consultation?
  - In which way was this similar or different to other treatment you have previously received?
What was your experience when you took the homeopathic medicine?
- In which way was this similar or different to when you take antidepressant drugs?

Follow-up questions will be kept as open as possible, such as:
- Can you tell me more about …?
- Can you give a more detailed description of …?
- Do you have any examples of …?

Closing of interview:
- As the end of the interview approaches, the interviewer will ask
  - If there are any other issues the participant would like to mention.
  - If the participant has any question with regards to the interview.
  - If they have any comments with regards to the experience of the interview.

The participant’s travel expenses will be reimbursed, based on average public transportation costs. Participants sign for reimbursed expenses.

Questions posed to participants during the second interview may include:
- How has your health developed over the past months?
- What was your experience with homeopathic treatment?
- In which way was this similar or different to your experiences with other forms of treatment that you have received?
- What was your experience when taking homeopathic medicines?
- In which way was this similar or different to when you take antidepressant drugs?
- How do you evaluate whether your homeopathic treatment is working?
- How do you think it’s working? Extend this section. How do they hold different views of depression and treatment in their head?
- Views of risks of treatment, conventional and homeopathic
- Ask which drugs they were on, what treatment have they had
- How do people reflect on how they choose treatment?
- Open with general question about their depression
- Questions on consultation
- What do they know about homeopathy? How do they assess existing ‘evidence’… The debate about homeopathy … There is a lot of debate these days about whether homeopathy works or not. What do you think about this? Did you check any information/sources before you went for treatment?

Patients’ responses may be followed up by additional probing questions, as considered appropriate by the interviewer, in order to obtain as clear and detailed understanding of patients’ thoughts, views, feelings and experiences, as possible. Follow-up questions will be kept as open as possible and will therefore primarily be along the following lines:
- Can you tell me more about …?
- Can you give a more detailed description of …?
- Do you have any examples of …?
Appendix 14. Interview guide II 120620

**Project title** (abbreviated): Depression in South Yorkshire (DEPSY)

**Principal investigator:** Petter Viksveen, Postgraduate Research Student, ScHARR, University of Sheffield. [p.viksveen@sheffield.ac.uk](mailto:p.viksveen@sheffield.ac.uk)

**Aim:** To explore the positive and negative experiences with homeopathic treatment in patients who have taken or who are taking antidepressant drugs.

**Qualitative interview method:** Semi-structured face-to-face interviews after 1st consultation + after a minimum of 2 follow-up consultations and 6 months.

**Time:** 2012 – 2013

**INTERVIEW GUIDE II (2nd interview) (version 2, date 20.06.2012)**

**Introduction:** This is the guide for the second out of two interviews to be carried out as part of this project. The second interview will be carried out after patients have had a minimum of two follow-up consultations with a homeopath, a minimum of 6 months after their first consultation. Interviews will aim at lasting 30-60 minutes, including time for welcoming and closing the interview, but timeframes will be flexible. The length of the interview will be audio-recorded.

**Introduction of interview to participants:**
- Welcome participant and explain the purpose of the interview, which is to learn from the participant’s long-term experience with homeopathic treatment.
- Explain to the participant why and how she/he was chosen.
- Explain the procedure of the interview, including the use of audio-recording equipment.
- Inform the participant of ethical issues, including anonymity and confidentiality (who will have access to data and assure that the final results will not contain any information that may identify the participant), and the right to withdraw from the project at any given time, until the data have been analysed.
- Ask the participant if she/he has any questions, before the start of the interview.
- PI introduces himself, including his name, University affiliation and role in project.
- Check the participant’s name and contact details.
- Ask the participant to sign the consent form.

**Semi-structured interview:**
- Invite the participant to tell about her/his experience (in general). Stay open to issues she/he may raise (e.g. general experiences of her/his depression), let her/him ‘tell her/his story’.
- As much as possible pose open-ended questions (as opposed to closed and leading questions), include ‘what’ and ‘how’ questions, and avoid ‘why’ questions.
- Probe arising issues to understand them in depth.
- Actively listen by confirming understanding of the participants’ responses, incl. feeding back the interviewer’s understanding to allow the participant to confirm, adjust or correct.
- As much as possible use participants’ own words and give time and room to reflect to allow for her/him to make ‘new discoveries’.
- Pay attention to arising conflicting issues and aim to clarify and sort them out.
- Redirect the interview in case responses are not relevant.
- Interviewer should stay friendly, interested and neutral (no approval or disapproval).
- Questions posed to participants during the second interview may include:
  - How has your health developed over the past months?
  - How has your mood been?
- What is your experience with homeopathic treatment?
- In which way was this similar or different to your experiences with other forms of treatment that you have received?
- What is your experience with the homeopathic consultation?
- In which way was this similar or different to other treatment you’ve received?
- What is your experience with taking homeopathic medicines?
- In which way was this similar or different to when you take antidepressant drugs?
- If you have experienced any changes, how do you think it works?
- In which way do you think this is similar or different to how antidepressant drugs work?
- Do you see any risks involved with homeopathic treatment?
- Do you see any risks involved with antidepressant treatment?
- What kind of antidepressant drugs have you been taking?

Follow-up questions will be kept as open as possible, such as:
- Can you tell me more about …?
- Can you give a more detailed description of …?
- Do you have any examples of …?

**Closing of interview:**
- As the end of the interview approaches, the interviewer will ask
  - If there are any other issues the participant would like to mention.
  - If the participant has any question with regards to the interview.
  - If they have any comments with regards to the experience of the interview.

The participant’s travel expenses will be reimbursed, based on average public transportation costs. Participants sign for reimbursed expenses.
Appendix 15. Letter to patients – Invitation for qualitative interviews

Letter to patients – Invitation for qualitative interviews (version 9, date 03.07.2012)

Date:

Dear Mr., Mrs., Ms.

You are one of over a hundred people who received treatment by a homeopath. We would be interested in learning more about your experiences. We are therefore inviting you to participate in an interview with a researcher at the University of Sheffield. What we learn will help us understand how we can improve the health of people living in South Yorkshire. It is up to you to choose whether you want to take part in this interview. Before you decide, please take time to read the following information carefully.

During the interview we will particularly focus on your health and your experiences with homeopathic treatment. You will be free to choose how to respond to questions. The interview will last from 30 to 60 minutes and will be audio-recorded. All information you provide will be kept strictly confidential and your answers will be made anonymous. It will only be used for research purposes. The data will be kept for 5 years or until the end of the South Yorkshire Cohort study. You can withdraw from this study at any time in the future. The results of this research will be published in a health science journal and in a PhD report at the University of Sheffield. If you would like, we will give you a report of the findings of the study.

Your transportation expenses will be refunded.

If you choose to accept the offer, then please sign the attached consent form. You will be contacted by telephone by a researcher to hear if you want to participate. You can then also ask any questions you may have.

If you have any queries or require further information about this study please contact Petter Viksveen or Dr. Clare Relton at: ScHARR, University of Sheffield, FREEPOST – SF1314, Sheffield, S1 1AY. Tel: 0114 222 0796. Email: p.viksveen@sheffield.ac.uk

Thank you.

Yours sincerely

Dr. Clare Relton and Petter Viksveen
Researchers at the University of Sheffield
Appendix 16. Consent form

Consent Form (version 1, date 26.06.2012)

Centre number: (to be filled in by researcher)
Study number: (to be filled in by researcher)
Participant Identification Number: (to be filled in by researcher)

1. I hereby confirm that I have read and understand the information in the "Letter to patients – Invitation for qualitative interviews" and have been given the opportunity to ask researchers at the University of Sheffield any questions I may have.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason.

3. I understand that the information I provide will be treated confidentially and will only be looked at by the researchers involved in this project.

_________________________________  ____________________________  ____________
Your name (capital letters)  Your signature  Date

Please return the signed consent form to: Petter Viksveen at: ScHARR, University of Sheffield, FREEPOST – SF1314, Sheffield, S1 1AY.
Appendix 17. Health & Human-Interventional Studies Research Governance Committee, Report on the visit to ScHARR to discuss the DEPSY clinical trial

Health & Human-Interventional Studies Research Governance Committee

Report on the visit to ScHARR to discuss the DEPSY clinical trial
(16th January 2015)

To:
Mr Petter Viksveen (Principal Investigator)
Dr Clare Relton (1st Supervisor)
Professor Jen Nicholl (Head of Department and 2nd Supervisor)
cc:
Dr Cindy Cooper, Chair of the University’s Health & Human-Interventional Studies Research Governance Committee
Professor Martin Thornhill, member of the University’s Health & Human-Interventional Studies Research Governance Committee

1. Preliminary statement

On 16th January 2015, Dr Cooper and Professor Thornhill from the University’s Health & Human-Interventional Studies Research Governance Committee and the Committee’s Secretary (Miss Nicola Donkin) (referred to as the QA (quality assurance) team), met with Mr Petter Viksveen, Dr Relton and Professor Jon Nicholl (present for the summarising section only) in order to discuss ‘A pragmatic cohort randomized controlled trial of the clinical and cost effectiveness of treatment of depression by homoeopathy (DEPSY)’. The DEPSY trial has been classed as potentially medium risk according to its risk assessment.

The meeting aimed to quality assure DEPSY’s quality control systems in order that the University can be reasonably confident that DEPSY will comply with its protocol and will safeguard the dignity, rights, safety and well-being of the participants.

2. Format of the visit

The QA team asked the DEPSY team a series of questions relating to the following seven areas:

a) Governance arrangements (strategic)
b) Appropriately qualified staff and researchers
c) Day-to-day management arrangements (operational)
d) Protocol compliance
e) Dignity, rights, safety and well-being of the participants
f) Data integrity and record-keeping
g) Procedure in place should a participant make a complaint about the trial

A summary of the discussion relating to each of the areas is outlined below, followed by a list of the recommendations made by the QA team for the DEPSY clinical trial.

a) Governance arrangements (strategic)

It was confirmed that the trial had a Steering Committee (SC) consisting of: Professor Simon Gilbody (Chair), Professor Paul Butson, Professor Stephen Walters, Dr Clare Relton, Bridget Strong (Sheffield Mind), user representative Mrs Carmen Calvo-Rodriguez and Peter Viksveen (PI). The QA team noted that this was satisfactory but that they must ensure that the Steering Committee remains independent and cannot be outnumbered by the Management Group members. There must be a minimum of three independent people on the SC, including at least one lay member and two academics. It was confirmed that the SC had not yet met but that a meeting will now take place. The QA team noted that the SC must satisfy the protocol at its first meeting, and in advance of any
participant recruitment taking place. Formal Terms of Reference for the SC should also be agreed at its first meeting.

The Management Committee consists of Dr. Clare Ralston (1st supervisor), Professor Paul Bisell (advisor) and Mr. Petter Viksveen (PI). They have not met formally but have been taking notes of the supervision meetings. The QA team recommended that more formal minutes are taken of such meetings. It was confirmed that Professor Jon Nicholl (Head of ScheRE) had recently taken on the role of 2nd supervisor.

The protocol states (p. 12) that research governance approval will be sought from Sheffield PCT. The DEPSY team confirmed that it will now be sought from Barnsley PCT. Mr. Viksveen is currently in the process of obtaining an NHS Research Passport.

The DEPSY team confirmed that there is a £125K budget for the research project which includes funding the PI’s study costs. The European Central Council of Homeopath (ECCH) has agreed that their Treasurer will monitor the budget (ECCH only made a small donation to the project funds). The DEPSY team confirmed that homeopath would be paid according to the number of participants that they treat; the payment is coming from the trial’s funds rather than a central university account so there are no university contracts involved. Agreement regarding payment is set out in the letter between the PI and the homeopath. The QA team queried whether the letter would be legally binding if any disputes arose. The DEPSY team stated that if homeopath did not deliver then they would not be paid and that they did have a back-up list of homeopath to contact.

b) Appropriately qualified staff and researchers
The QA team reviewed the Delegation of Duties Log. It was recommended that there is clarification regarding to whom the particular roles may be delegated, and that this is approved by the supervisory team. As the project is recruiting via the South Yorkshire Cohort (SYC) the level of involvement with the Clinical Trials Research Unit must also be agreed.

The DEPSY team confirmed that all homeopathy consultations will take place in GP Practices; to date, four GP Practices have agreed to participate and the DEPSY team now plan to ask all 40 SYC GP Practices. Participants will be able to choose which Practice to attend and GPs will be kept informed of their patient’s participation.

The homeopath will be providing the package of care and will therefore be responsible for reporting adverse events (not the GP). The DEPSY team confirmed that all homeopath would be attending a half-day training session run by Sheffield Mind which would provide information on the protocol and guidance on reporting adverse events. Each homeopath will also be provided with an adverse event reporting form. The QA team recommended that the definition of an ‘adverse event’ be considered as it currently states events are ‘unexpected’ but in reality some may be anticipated. It is very important that it is made clear to homeopath in the training exactly what should be reported, and that this is included in written guidelines; to ensure clarity. There must then be a clear procedure for deciding which adverse events are serious and potentially linked to the intervention, and how these are dealt with. There should be two named people on the adverse event form in case of absence of the PI. The QA team recommended that homeopath check at each consultation if there have been any adverse events and that this check is documented. All homeopath should receive the training on the protocol and guidance on risk/adverse events before participating in the project.

The DEPSY team confirmed that the practice of homeopathy is not controlled by any statutory regulation but that they have checked that all participating homeopaths are registered with The Society of Homeopaths. The QA team recommended that their registration be checked annually.

c) Day-to-day management arrangements (operational)
The DEPSY team confirmed that key decisions (such as protocol changes) would be recorded in the minutes of supervisory meetings and in reports to the Steering Committee. It was confirmed that Dr Relton would act on anything requiring attention in Mr Viksveen’s absence.

Regular meetings will be held in order to ensure that homeopaths understand their responsibilities and remain up-to-date with the project. The QA team noted that these would be very useful for monitoring and an opportunity to remind the homeopaths of any changes to protocol. The QA team agreed with Dr Relton’s suggestion that the homeopaths be paid a nominal fee (in the region of £10–20) for attending these meetings to ensure commitment.

d) Protocol compliance
The DEPSY team confirmed that any substantial amendments would be submitted to the NHS REC; it would be up to the sponsor to decide if the amendment was minor or substantial. Any amendments to the protocol will be circulated to the homeopaths by email; the QA team recommended that confirmation of receipt and understanding of the changes be received in writing.

If any deviation is made from the protocol then this will be recorded by the homeopath. Due to the methodology of the project, if a participant withdraws from care then they are not withdrawing from the trial, they will still receive the questionnaire as these are not provided by the homeopaths.

e) Dignity, rights, safety and well-being of the participant
The DEPSY team will send an initial questionnaire and use the responses to decide if participants are eligible based upon inclusion/exclusion criteria. The DEPSY team will also review SYC patient notes to provide an extra check in case participants don’t report certain conditions on their questionnaire. The risk assessment which will be provided by homeopaths will provide an additional checkpoint. If a participant does give cause for concern, either via questionnaire responses or interactions with the homeopath, there must be clear procedures for managing the risk (e.g. referral to/ alerting the GP).

Mr Viksveen confirmed that he has a great deal of experience of interacting with mental health patients so is confident in dealing with any issues that may arise during the qualitative interviews.

The DEPSY team will keep copies of all informed consent documentation to ensure this has been provided by every participant.

f) Data integrity and record-keeping
To ensure patient confidentiality all records will be kept on a university password-protected computer or within a locked filing cabinet. The homeopaths are bound by the confidentiality and data protection policy of The Society of Homeopaths; the QA team recommended that they are reminded of this policy.

e) Procedure in place should a participant make a complaint about the trial
The information on the procedure for a participant to make a complaint about the trial is not currently on the participant information sheet; the QA team stressed that this must be added. It should also be made clear that adverse events can be reported directly to the DEPSY team.

List of recommendations
i. The Steering Committee must always include at least three independent members who consist of at least two academic members and at least one lay member.
ii. The Steering Committee must meet before participant recruitment begins. At the meeting the protocol must be ratified and formal Terms of Reference agreed.
iii. Formal minutes of all supervision meetings should be made, as these are essentially meetings of the Management Committee.
iv. The protocol should be kept up-to-date to ensure it reflects all changes made to the project.
v. It should be agreed with the supervisory team to whom the duties listed on the Delegation of Duties Log may be delegated.
vi. The management of data relating to South Yorkshire Cohort participants must be agreed with the Clinical Trials Research Unit.

vii. All homeopaths must be provided with clear guidance on the protocol to ensure that they adhere to it.

viii. The training for homeopaths must clearly outline adverse event reporting, and there must be two named contacts for reporting in case of absence. Homeopaths should check at each consultation if there have been any adverse events and should document this check.

ix. There must also be clear procedures for deciding what constitutes a serious adverse event and for dealing with such events. This should be added to the protocol.

x. The registration of participating homeopaths to The Society of Homeopaths should be checked annually.

xi. Records of key decisions must always be made.

xii. The team should consider whether to pay homeopaths a nominal fee for attending regular 'catch-up' meetings.

xiii. Confirmation of receipt and understanding of protocol amendments should be obtained from the homeopath in writing.

xiv. Homeopaths should be reminded of the need to abide by the confidentiality and data protection policy of The Society of Homeopaths.

xv. The procedure for a participant to make a complaint about the clinical trial must be added to the participant information sheet. It should also be noted how participants can directly report adverse events.

xvi. If a participant does give cause for concern, either via the questionnaire or through interaction with the homeopath, there must be a clear procedure for managing the risk (e.g. referral to alerting the GP).

xvii. The above-noted procedures should be set up as Standard Operating Procedures which are separate to the protocol.

It was agreed that the above recommendations will be implemented before participant recruitment begins. The responsibility for ensuring these are undertaken before participant recruitment is delegated to Professor Jon Nicholl, as Head of School.