Pharmacological and psychological treatment in generalized anxiety disorder

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Declaration of interests

Global Association of Mental Illness Advocacy Networks
European Union FP7 Programme – Marie Curie
European College of Neuropsychopharmacology Network Initiative
Medical Research Council - Experimental Medicine
Economic and Social Research Council
NIHR Health Technology Assessment RCT Programme
Department of Health
NHS South & West R & D Directorate
Veterinary Times and BUPA Giving
Wessex Medical Research (States of Jersey Research Fellowship)
University of Southampton Research Management Committee

Bristol-Myers Squibb
Cephalon
Eli Lilly Ltd
Glaxo-SmithKline
Grunenthal
H. Lundbeck A/S
Pierre Fabre
Pfizer Ltd
Roche
Sumitomo
Vernalis Ltd
## Anxiety disorders: 12-month prevalence

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Inter-quartile range (%)</th>
<th>Best estimate (%)</th>
<th>Number affected (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety disorders</td>
<td>Not applicable*</td>
<td>14.0</td>
<td>61.5</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>0.4-2.0</td>
<td>1.8</td>
<td>7.9</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>0.4-2.0</td>
<td>2.0</td>
<td>8.8</td>
</tr>
<tr>
<td>Social phobia</td>
<td>1.1-4.4</td>
<td>2.3</td>
<td>10.1</td>
</tr>
<tr>
<td>Specific phobias</td>
<td>3.4-7.1</td>
<td>6.4</td>
<td>22.7</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>0.6-2.2</td>
<td>1.7-3.4†</td>
<td>8.9</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>0.5-1.1</td>
<td>0.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td>0.7-2.5</td>
<td>1.1-2.9 Böyle</td>
<td>7.7</td>
</tr>
</tbody>
</table>

# According to Eurostat 2010 for the age groups used. * Aggregate data from single study. 95% confidence interval, 13.4-15.6%.
† Age range 14-65 years, 1.7%; age 65+ years, 3.4%.
ϕ Age range 14-34 years, 2.9%; age range 35-65 years, 1.3%; age 66+ years, 1.1%.
Best estimates represent consensus view of experts on most probable estimate from identified range.

Anxiety symptom severity in primary care

### GAD-7 for scoring symptom severity

Over the **last 2 weeks**, how often have you been bothered by the following problem?

<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>

Total score \( \text{___} = \) Add columns \( \text{___} + \text{___} + \text{___} + \text{___} \)

If you checked off any problems, 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?

- Not difficult at all
- Somewhat difficult
- Very difficult
- Extremely difficult

Cut points of 5, 10 and 15 represent mild, moderate and severe anxiety

Spitzer RL et al. Arch Intern Med 2006; 166: 10-17
Symptom remission and severity in GAD

Table 4. Corresponding CGI-S values for mean total scores of the standard scales.

<table>
<thead>
<tr>
<th>CGI-S score</th>
<th>MADRS (MDD)</th>
<th>PAS (PD)</th>
<th>HAMA (GAD)</th>
<th>LSAS (SAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Not at all ill)</td>
<td>5</td>
<td>8</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>2 (Borderline ill)</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>36</td>
</tr>
<tr>
<td>3 (Mildly ill)</td>
<td>19</td>
<td>18</td>
<td>15</td>
<td>59</td>
</tr>
<tr>
<td>4 (Moderately ill)</td>
<td>29</td>
<td>29</td>
<td>24</td>
<td>86</td>
</tr>
</tbody>
</table>

CGI-S, Clinical Global Impression - Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; PAS, Panic and Agoraphobia Scale; HAMA, Hamilton Anxiety Scale; LSAS, Liebowitz Social Anxiety Scale

For CGI-S >4 there were too few patients to be able to equate the CGI-S scores with the standard scale scores (remission is traditionally defined as CGI-S ≤2)
Disability and symptom severity
pooled analysis of escitalopram randomised controlled trial database

Sheehan Disabilities Scale

<table>
<thead>
<tr>
<th>Date of assessment:</th>
<th>Day</th>
<th>Month</th>
<th>Year</th>
</tr>
</thead>
</table>

**Instructions:**
On a scale of 0 - 10, as shown on the diagram below, circle the number that best describes the amount of the patient’s disability or impairment, at this time, in each of the following areas: work, social life and leisure activities, family life and home responsibilities.

**Work:**
At this time, how much is your work impaired because of your problems?

<table>
<thead>
<tr>
<th>Not at all impaired</th>
<th>Mildly impaired</th>
<th>Moderately impaired</th>
<th>Markedly impaired</th>
<th>Very severely impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**Social life and leisure activities:**
At this time, how much is your social life and leisure activities impaired because of your problem?

<table>
<thead>
<tr>
<th>Not at all impaired</th>
<th>Mildly impaired</th>
<th>Moderately impaired</th>
<th>Markedly impaired</th>
<th>Very severely impaired</th>
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<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**Family life and home responsibilities:**
At this time, how much is your family life and home responsibilities impaired because of your problem?

<table>
<thead>
<tr>
<th>Not at all impaired</th>
<th>Mildly impaired</th>
<th>Moderately impaired</th>
<th>Markedly impaired</th>
<th>Very severely impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Date ____________________________
Rater’s signature ____________________________

Correlation with symptom severity

- Work (correlation 0.64; p<0.001)
- Social (correlation 0.65; p<0.001)
- Family (correlation 0.70; p<0.001)

Evidence-based guidelines for treating GAD

Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology


BAP, 2005

Issue date: January 2011

Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults

Management in primary, secondary and community care

This updates and replaces NICE clinical guideline 22

NICE, 2011

Guidelines

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders – First Revision

WFSBP, 2008

Evidence-based pharmacological treatment of generalized anxiety disorder

David S. Baldwin, Sarah Waldman and Christer Allgulander

CINP, 2011
NICE guideline: Step 1
identification and assessment

- Identify and communicate the diagnosis of GAD as early as possible to help people understand the disorder and start effective treatment promptly.

- Consider the diagnosis of GAD in people presenting with anxiety or significant worry, and in people who attend primary care frequently who:
  - have a chronic physical health problem or
  - do not have a physical health problem but are seeking reassurance about somatic symptoms (particularly older people and people from minority ethnic groups) or
  - are repeatedly worrying about a wide range of different issues.

- Conduct a comprehensive assessment that does not rely solely on the number, severity and duration of symptoms, but also considers the degree of distress and functional impairment.

People with GAD and a comorbid depressive or other anxiety disorder

- Treat the primary disorder first (that is, the one that is more severe and in which it is more likely that treatment will improve overall functioning) (see ‘Related NICE guidance’, page 23).
NICE guideline: Step 2
low intensity psychological intervention

<table>
<thead>
<tr>
<th>Type of intervention</th>
<th>Intervention should:</th>
</tr>
</thead>
</table>
| Individual non-facilitated self-help | - Include written or electronic materials of a suitable reading age (or alternative media).  
- Be based on the treatment principles of cognitive behavioural therapy (CBT).  
- Include instructions for the person to work systematically through the materials over a period of at least 6 weeks.  
- Usually involve minimal therapist contact, for example an occasional telephone call of no more than 5 minutes. |
| Individual guided self-help         | - Include written or electronic materials of a suitable reading age (or alternative media).  
- Be supported by a trained practitioner, who facilitates the self-help programme and reviews progress and outcome.  
- Usually consist of five to seven weekly or fortnightly face-to-face or telephone sessions, each lasting 20–30 minutes. |
| Psychoeducational groups            | - Be based on CBT principles, have an interactive design and encourage observational learning.  
- Include presentations and self-help manuals.  
- Be conducted by trained practitioners.  
- Have a ratio of one therapist to about 12 participants.  
- Usually consist of six weekly sessions, each lasting 2 hours. |
Psychological treatments in GAD

- cognitive-behaviour therapy (CBT): individual or computerised
- applied relaxation
- psychodynamic therapy
- mindfulness-based stress reduction
- mindfulness-based cognitive therapy
- acceptance-based behaviour therapy
- interpersonal emotional processing therapy
- emotional well-being therapy

Bolognesi F, Ruini C, Baldwin DS. In preparation
Cognitive behaviour therapy in GAD
systematic review and meta-analysis

- 12 RCTs (n=659) comparing CBT vs. waiting list controls
- 8 RCTs (n=439) comparing CBT vs. applied relaxation
- 6 RCTs n=600) comparing CBT vs. other psychotherapies

- CBT superior to waiting list control
- CBT not significantly different to applied relaxation
- CBT superior to psychodynamic therapies

### NICE guideline: Step 3

**High intensity psychological intervention or SSRI**

<table>
<thead>
<tr>
<th>Type of intervention</th>
<th>Intervention should:</th>
</tr>
</thead>
</table>
| CBT                  | - Be based on the treatment manuals used in the clinical trials of CBT for GAD.  
                         - Be delivered by trained and competent practitioners.  
                         - Usually consist of 12–15 weekly sessions (fewer if the person recovers sooner; more if clinically required), each lasting 1 hour. |
| Applied relaxation    | - Be based on the treatment manuals used in the clinical trials of applied relaxation for GAD.  
                         - Be delivered by trained and competent practitioners.  
                         - Usually consist of 12–15 weekly sessions (fewer if the person recovers sooner; more if clinically required), each lasting 1 hour. |

- If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI). Consider offering sertraline first because it is the most cost-effective drug, but note that at the time of publication (January 2011) sertraline did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented. Monitor the person carefully for adverse reactions.
NICE guideline: step 4

Treatment

- Inform people with GAD who have not been offered or have refused the interventions in steps 1–3 about the potential benefits of these interventions, and offer them any they have not tried.

- Consider offering combinations of psychological and drug treatments, combinations of antidepressants or augmentation of antidepressants with other drugs, but exercise caution and be aware that:
  - evidence for the effectiveness of combination treatments is lacking **and**
  - side effects and interactions are more likely when combining and augmenting antidepressants.

- Combination treatments should be undertaken only by practitioners with expertise in the psychological and drug treatment of complex, treatment-refractory anxiety disorders and after full discussion with the person about the likely advantages and disadvantages of the treatments suggested.

- When treating people with complex and treatment-refractory GAD, inform them of relevant clinical research in which they may wish to participate, working within local and national ethical guidelines at all times.
Properties of the ‘ideal’ drug treatment

- Effective in all patients
- Effective across all symptom domains
- Effective across spectrum of severity
- Effective in achieving remission
- Effective in preventing relapse
- Effective in comorbid depression
- Rapid onset of anxiolytic action
- Cost-effective
- Once-daily dosage
- Minimal side effects
- Minimal interference with everyday life
- No development of tolerance
- No discontinuation symptoms
- Suitable in physically ill patients
- Free from interactions
- Safe in overdose

Baldwin DS, Ajel KI. Neuropsychiatric Dis Treat 2007; 3: 185-191
...but there are no ideal drug treatments

- response rates to initial treatment can be disappointing
- not possible to reliably predict likelihood of response
- substantial proportion experience unwanted effects
- many patients relapse despite treatment adherence
- little known about management after non-response
- discontinuation symptoms can be troublesome

Baldwin DS. Current Pharmaceutical Design 2008; 14: 3482-3491
Baldwin DS. Human Psychopharmacol 2011; 26: 1-3
BAP guidelines for drug treatment in GAD

- choose an evidence-based treatment
- consider an SSRI for first-line treatment
- higher doses may be associated with greater response rates
- periods of up to 12 weeks may be needed to assess efficacy
- continue treatment for a further 6 months after response
- use an agent known to be effective in preventing relapse
- monitor efficacy and tolerability regularly
- routine combination with psychotherapy is not recommended
- switch to another evidence-based treatment after non-response
- consider benzodiazepines after non-response to SSRI and SNRI

Reduction in symptom severity in GAD

p < 0.05, ** p < 0.01, *** p < 0.001, versus placebo; # p < 0.05 versus paroxetine
mean HAMA scores at baseline placebo 27.1, ESC 5 27.1, ESC 10 26.0, ESC 20 27.7, PAR 27.3

SNRI in treatment of GAD

Mean Baseline HAMA Total Score: ~25-26

Fixed dose quetiapine in treatment of GAD
reduction in mean HAMA score

Dose-response relationships with pregabalin in GAD pooled analysis of clinical trial database

Montgomery SA. Exp Opin Pharmacother 2006; 7: 2139-2154

* p < 0.05, ** p < 0.01, *** p < 0.001, vs. placebo
Anxiolytic effects within hours?

- 89 patients with ‘dental anxiety’
- no DSM-IV anxiety disorder diagnoses
- randomised placebo-controlled trial
- pregabalin 150 mg, alprazolam 0.5 mg

- onset of effect by 2.5 hrs for alprazolam
- onset at 3.0 hrs for pregabalin
- sedative effects at 3.0 hrs with both drugs
- provides model for onset-of-effect studies

Nutt DJ et al. J Psychopharmacol 2009; 23: 867-873
Agomelatine in acute treatment of GAD

Overall response rates (≥50% reduction in HAMA): agomelatine 66.7%, placebo 46.6%

Mean baseline HAMA scores: placebo 28.6, agomelatine 29.0

SSRI in acute treatment of GAD
proportion of patients entering symptomatic remission

* p < 0.05, ** p < 0.01, *** p < 0.001, vs. placebo; # p < 0.05 vs. paroxetine

Efficacy vs. effectiveness of benzodiazepines
systematic review and meta-analysis of RCTs

Withdrawals due to lack of efficacy

Withdrawals for any reason

NICE and BNF guidance on benzodiazepines

1. Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling or causing the patient unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness.

2. The use of benzodiazepines to treat short-term ‘mild’ anxiety is inappropriate.

3. Benzodiazepines should be used to treat insomnia only when it is severe, disabling or causing the patient extreme distress.

Benzodiazepine prescribing in Europe

- 501 psychiatrists, questionnaire survey, management of GAD
- 81.4% patients received benzodiazepines before referral
- a first-line treatment in 26% of patients
- treatment duration less than 6 weeks in 78.9% respondents

Azapirones in acute treatment of GAD

- efficacious in acute treatment especially if benzodiazepine-naïve
- less well tolerated than benzodiazepines

Reducing depressive symptoms with pregabalin

** HAM-D

<table>
<thead>
<tr>
<th>Pregabalin dose (mg/day)</th>
<th>Placebo (n=424)</th>
<th>150 (n=195)</th>
<th>300-450 (n=416)</th>
<th>600 (n=368)</th>
</tr>
</thead>
</table>

Mean change from baseline:

** p<0.01, *** p<0.001 vs. placebo

Baseline mean ~13.7

---

** Bech melancholia factor

<table>
<thead>
<tr>
<th>Pregabalin dose (mg/day)</th>
<th>Placebo (n=422)</th>
<th>150 (n=210)</th>
<th>300-450 (n=416)</th>
<th>600 (n=367)</th>
</tr>
</thead>
</table>

Mean change from baseline:

* p<0.05, *** p≤0.001 vs. placebo

Baseline mean ~6.1

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Stein DJ, Baldwin DS, Baldinetti F et al. Eur Neuropsychopharmacol 2008; 18: 422-430
Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis

David Baldwin, professor of psychiatry and honorary consultant psychiatrist;^1^ Robert Woods, senior research executive;^2^ Richard Lawson, statistician;^2^ David Taylor, professor of psychopharmacology^3^

Across all treatments:

- first meta-analysis to rank treatments for response, remission, and withdrawals
- fluoxetine ranked first in terms of response and remission
- sertraline ranked first in terms of withdrawals due to adverse events

Across treatments with a licence for GAD:

- duloxetine ranked first in terms of response
- escitalopram ranked first in terms of remission
- pregabalin ranked first in terms of withdrawals due to adverse events
Relapse prevention studies in GAD

Onset of effect and later overall response analysis of the escitalopram clinical trial database

Response rates based on onset at Wk 2

Chance of responding if no onset

Baldwin DS et al. Human Psychopharmacology. 2009; 24: 269-275
Prediction of response in GAD treatment

- post-hoc analysis of pooled pregabalin clinical trial database (4 studies, n=960)
- response defined as ≥50% reduction in HAMA score from baseline to endpoint

Pregabalin augmentation of SSRI/SNRI in GAD
HAMA at endpoint, responder and remission status

Initial partial or non-response to SSRI/SNRI: (HAMA $\geq 16$ and <50% decrease in HAMA from baseline
Mean pregabalin daily dosage at Week 8: 496 mg

Combining CBT and drug treatment

- due to lack of data, not currently possible to draw conclusions
- continuing need for large RCT of CBT vs SSRI vs [CBT+SSRI]

A multimodal serotonergic psychotropic drug LuAA21004 in major depression and GAD

- 5-HT₃ and 5-HT₇ antagonist
- 5-HT₁B partial agonist
- 5-HT₁A agonist
- inhibits 5-HT transporter
- enhances NA and DA

Summary of potential BAP guidelines for GAD

- choose an evidence-based treatment
- consider an SSRI for first-line treatment
- treatments vary in their dose-response relationships
- periods of up to 6 weeks may be needed to assess efficacy
- continue treatment for a further 12 months after response
- use an agent known to be effective in preventing relapse
- monitor efficacy and tolerability regularly
- routine combination with psychotherapy is not recommended
- augment with pregabalin after non-response to SSRI or SNRI
- consider benzodiazepines after non-response to SSRI, SNRI, pregabalin