Pharmacological treatment of anxiety disorders – where is the room for improvement?

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Declaration of interests (last 5 years)

- I do not have shares in any pharmaceutical company, nor do family members.
- I do not accept any personal retainer from any pharmaceutical company.
- I have acted as a consultant to a number of companies with an interest in anxiety disorders (Asahi, AstraZeneca, Cephalon, Eli Lilly, GSK, Lundbeck, Organon, Pharmacia, Pierre Fabre, Pfizer, Roche, Servier, Sumitomo, Wyeth).
- I hold or have held research grants (on behalf of my employer) from a number of companies with an interest in anxiety and depressive disorders (Cephalon, Eli Lilly, GSK, Lundbeck, Organon, Pfizer, Pharmacia, Roche, Wyeth).
- I have accepted paid speaking engagements in industry supported satellite symposia at international and national meetings. I do not accept hospitality or travel not related to a speaking engagement.
- I am co-author of the BAP evidence-based guidelines on the treatment of anxiety disorders.
- I am a member of an NHS Trust Medicines Management Committee.
- I am a Medical Patron of Anxiety UK.
Use of licensed medicines for unlicensed applications in psychiatric practice

College Report CR142
January 2007

www.rcpsych.ac.uk

Off-label prescribing in psychiatric practice
David S. Baldwin & Nick Kosky

Abstract: Drug treatment is an essential part of much of psychiatric practice, in patients from a wide age range, across many diagnostic groups and in a variety of settings. Despite the availability of many classes of psychotropic drug, significant numbers of patients remain troubled by distressing and disabling symptoms even after a succession of licensed pharmacoceutical treatments. Psychiatrists may then consider the prescription of a psychotropic outside the narrow terms of its licence, as part of an overall management plan. This article reviews the nature and extent of this aspect of prescribing, outlines when it may be appropriate and makes recommendations for a suggested procedure when prescribing medication ‘off-label’.

Advances in Psychiatric Treatment 2007; 13: 414-422
Properties of the ‘ideal’ anxiolytic drug...

- Effective in all anxiety disorders
- 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 adverse 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 anxiolytic drugs

- 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 is known about management after initial non-response
- discontinuation symptoms can be troublesome

Baldwin DS. Current Pharmaceutical Design 2008; 14: 3482-3491
Where is the room for improvement?

1. identifying patients most likely to benefit from treatment
2. choosing between drug and psychological treatment
3. exerting an earlier onset of clinical effect
4. achieving superior efficacy in reducing symptom severity
5. choosing the right drug for the right patient
6. optimising dosage for maximal effectiveness and tolerability
7. combining treatments to enhance efficacy
8. treating long term to prevent relapse
3. Exerting an earlier onset of clinical effect
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

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 et al. J Psychopharmacol 2009; 23: 867-873
4. Achieving superior efficacy in reducing symptoms
More efficacious and better tolerated antidepressants

- clinically important differences exist between commonly prescribed antidepressants
- sertraline might be the best choice for moderate to severe major depression
- escitalopram might be preferred for more severe end of depression spectrum

2. Nutt DJ. J Psychopharmacol 2009; 23: 865
More efficacious and better tolerated GAD treatments?

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

Baldwin DS et al. B M J 2011; 342: d1199
## Comparative studies of clomipramine and SSRIs in OCD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>N</th>
<th>Efficacy</th>
<th>Tolerability</th>
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</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Piggott et al., 1990</td>
<td>11</td>
<td>CMI = FLX</td>
<td>FLX &gt; CMI</td>
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<tr>
<td></td>
<td>Lopez-Ibor et al., 1996</td>
<td>54</td>
<td>CMI = FLX</td>
<td>FLX = CMI</td>
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<tr>
<td>Fluvoxamine</td>
<td>Smeraldi et al., 1992</td>
<td>10</td>
<td>CMI = FLV</td>
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<tr>
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<td>Freeman et al., 1994</td>
<td>64</td>
<td>CMI = FLV</td>
<td>FLV &gt; CMI</td>
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<tr>
<td></td>
<td>Koran et al., 1996</td>
<td>79</td>
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<td>FLV = CMI</td>
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<tr>
<td></td>
<td>Milanfranchi et al., 1997</td>
<td>26</td>
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<td>FLV = CMI</td>
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<tr>
<td></td>
<td>Rouillon, 1998</td>
<td>217</td>
<td>CMI = FLV</td>
<td>FLV = CMI</td>
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<tr>
<td>Paroxetine</td>
<td>Zohar and Judge, 1996</td>
<td>399</td>
<td>CMI = PAR</td>
<td>PAR &gt; CMI</td>
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<tr>
<td>Sertraline</td>
<td>Bisserbe et al., 1997</td>
<td>168</td>
<td>SER = CMI</td>
<td>SER &gt; CMI</td>
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<tr>
<td>Citalopram</td>
<td>Pidman and Tuma, 1998</td>
<td>24</td>
<td>CIT = CMI</td>
<td>CIT = CMI</td>
</tr>
</tbody>
</table>
Clomipramine and SSRIs: relative efficacy in OCD

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>SSRI N Mean (SD)</th>
<th>Clomipramine N Mean (SD)</th>
<th>SMD (fixed) 95% CI</th>
<th>SMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>01 Fluoxetine vs Clomipramine</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Lopez-Porto 1996</td>
<td>24 -0.98 (1.12)</td>
<td>24 -0.98 (1.12)</td>
<td>0.16 [-0.17, 0.70]</td>
<td>0.16 [-0.17, 0.70]</td>
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<tr>
<td>Subtotal (32%) CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>02 Fluvoxamine vs Clomipramine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Khor 1996</td>
<td>39 17.00 (1.70)</td>
<td>39 17.00 (1.55)</td>
<td>0.10 [-0.96, 0.56]</td>
<td>0.10 [-0.96, 0.56]</td>
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<tr>
<td>Milani-Cordi 1997</td>
<td>12 16.40 (9.24)</td>
<td>12 16.40 (9.00)</td>
<td>0.18 [-0.96, 0.97]</td>
<td>0.18 [-0.96, 0.97]</td>
</tr>
<tr>
<td>Munich 2001</td>
<td>61 12.50 (8.00)</td>
<td>61 12.50 (8.00)</td>
<td>0.24 [-1.11, 0.58]</td>
<td>0.24 [-1.11, 0.58]</td>
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<tr>
<td>Schildkraut 1992</td>
<td>5 16.20 (2.50)</td>
<td>5 16.20 (2.40)</td>
<td>0.30 [-0.95, 1.65]</td>
<td>0.30 [-0.95, 1.65]</td>
</tr>
<tr>
<td>Subtotal (35%) CI</td>
<td>117</td>
<td></td>
<td>0.19 [-0.06, 0.48]</td>
<td>0.19 [-0.06, 0.48]</td>
</tr>
<tr>
<td><strong>03 Paroxetine vs Clomipramine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buntin 1993</td>
<td>78 -5.61 (7.42)</td>
<td>78 -5.72 (7.42)</td>
<td>0.28 [-0.03, 0.50]</td>
<td>0.28 [-0.03, 0.50]</td>
</tr>
<tr>
<td>Zohar 1996a</td>
<td>94 -8.00 (8.00)</td>
<td>94 -8.00 (8.20)</td>
<td>0.30 [-0.25, 0.85]</td>
<td>0.30 [-0.25, 0.85]</td>
</tr>
<tr>
<td>Subtotal (35%) CI</td>
<td>272</td>
<td></td>
<td>0.11 [-0.06, 0.36]</td>
<td>0.11 [-0.06, 0.36]</td>
</tr>
<tr>
<td><strong>Total (35%) CI</strong></td>
<td>426</td>
<td>219</td>
<td>0.14 [-0.01, 0.29]</td>
<td>0.14 [-0.01, 0.29]</td>
</tr>
</tbody>
</table>

Favours SSRI        Favours Clomipramine
5. Choosing the right drug for the right patient
SNRI and SSRI in acute treatment of PTSD
12-week multi-centre, randomised, double-blind, placebo-controlled study

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**Graph:**
- Change in CAPS-SX17 from baseline to end-point
- Symptomatic remission CAPS-SX17 20 or less (%) [venlafaxine (37.5-300 mg/day), sertraline (25-200 mg/day), placebo]

* p < 0.05, vs. placebo

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SSRI and mirtazapine in acute treatment of PTSD
6-week single-centre randomised open-label study

* p < 0.05, continuity adjusted chi-square test
Chung MY et al. Hum Psychopharmacol 2004; 19: 489-494
SNRI and SSRI in acute treatment of social phobia

SNRI and SSRI in acute treatment of panic disorder

* p < 0.001 vs. placebo

Escitalopram and citalopram and PANDA domains

*\(p<0.05\); **\(p<0.01\); ***\(p<0.001\); vs. placebo: #\(p<0.05\) escitalopram vs. citalopram

Azapirones in acute treatment of GAD

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

Effect of pregabalin treatment on sleep in GAD
change in MOS sleep score during double-blind treatment

![Graph showing changes in sleep problems index and disturbance with treatments]

- Sleep problems index I
- Sleep problems index 2
- Sleep disturbance

- Placebo (N=125)
- Pregabalin 300-600 mg/day (n=116)
- Venlafaxine 75-225 mg/day (n=125)

*p < 0.05 pregabalin vs. placebo change from baseline

Reduction in depressive symptoms with pregabalin

Patients with more severe depressive symptoms (n=638, mean HAMD 17.4)

Change in Bech melancholia scale score from baseline to endpoint

Overall patient group (n=1555, mean HAMD 13.7)

Stein DJ, Baldwin DS, Baldinetti F et al. Eur Neuropsychopharmacol 2008; 18: 422-430

• p< 0.05, *** p< 0.001, **** p< 0.0001
6. Optimising dosage for maximal effectiveness
Paroxetine in panic disorder: dose-response relationship

Next-step strategies for refractory panic disorder

**Phase 1**
- 20.5%
  - sertraline to 100mg (escitalopram to 15 mg)
  - 6 weeks open
  - N=39

**Phase 2**
- Continued same dosage
  - or
  - ↑sertraline to 200mg
  - (↑escitalopram to 30 mg)
  - 6 weeks double-blind
  - N=24
- - NS -
- 15% 9%

**Phase 3**
- - NS -
- 11% 10%
- Medication optimization
  - or
  - combination with CBT
  - 12 weeks
  - N=19

% remission (no panic attacks and CGI-S of 1 or 2)

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

Baldwin DS et al. Human Psychopharmacology. 2009; 24: 269-275