The effects of duloxetine on subjective, autonomic and neurocognitive response to 7.5% carbon dioxide challenge

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Background
7.5% carbon dioxide (CO₂) challenge
• Inhalation of 7.5% CO₂ for 20 minutes increases subjective and physiological symptoms of anxiety and impairs attention control in healthy humans [1]
• Some anxiolytics (such as lorazepam and paroxetine) can reduce the subjective anxiety response to 7.5% CO₂ [2]
• These findings suggest 7.5% CO₂ inhalation is a useful, translational model of human anxiety for treatment development

Duloxetine
• The SNRI duloxetine has been identified as first for response in clinical trials for anxiety [3]
• Short term treatment with duloxetine improves attention and emotion processing [4]

Aim
• To examine whether duloxetine can reduce CO₂-induced anxiety and deficits in attention and emotion processing

Method
• 40 healthy volunteers were randomised to receive a 2 week course of duloxetine (30-60mg titrated after 3 days) or matched placebo (groups balanced by gender, double-blind)
• Participants completed an emotional antisaccade task in which they looked toward (prosaccade) or away (antisaccade) from negative and neutral images during 7.5% CO₂ or air (order counterbalanced across gender and group)
• Subjective ratings of state anxiety (GAD-7) were taken before and after each inhalation
• Autonomic arousal (blood pressure, heart rate and respiration rate) was assessed throughout both inhalations

Results
Subjective mood and Autonomic Arousal
Mixed model analysis of variance (ANOVA) revealed:
• 7.5% CO₂ significantly increased post-inhalation levels of state anxiety, heart rate, respiration rate and systolic blood pressure (p < .001 for all comparisons), irrespective of drug group
• Means suggest a smaller increase in anxiety in the duloxetine compared to placebo group at the peak effects of CO₂ (p = .059)

Table 1.
Effects of 7.5% CO₂ on mean (SD) anxiety, mood and autonomic arousal

<table>
<thead>
<tr>
<th>Measure</th>
<th>Air Baseline</th>
<th>Peak Baseline</th>
<th></th>
<th>CO₂ Baseline</th>
<th>Peak Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p = .001</td>
</tr>
<tr>
<td>GAD-7</td>
<td>13.34 (13.54)</td>
<td>11.30 (8.77)</td>
<td>9.26 (6.97)</td>
<td>34.62 (21.44)</td>
<td></td>
</tr>
<tr>
<td>Positive affect</td>
<td>31.11 (7.46)</td>
<td>27.24 (7.80)</td>
<td>30.14 (7.57)</td>
<td>23.38 (8.80)</td>
<td></td>
</tr>
<tr>
<td>Negative affect</td>
<td>12.05 (2.94)</td>
<td>11.22 (2.20)</td>
<td>11.78 (2.71)</td>
<td>19.51 (8.34)</td>
<td></td>
</tr>
<tr>
<td>Autonomic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>119.73 (8.96)</td>
<td>119.41 (9.34)</td>
<td>118.62 (7.94)</td>
<td>131.65 (12.88)</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>73.47 (8.11)</td>
<td>74.22 (7.68)</td>
<td>73.43 (7.46)</td>
<td>75.65 (8.04)</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>67.59 (10.88)</td>
<td>69.95 (11.47)</td>
<td>67.00 (9.98)</td>
<td>81.78 (15.42)</td>
<td></td>
</tr>
</tbody>
</table>

Summary and future research
• These findings suggest that prior administration of duloxetine in healthy volunteers can decrease the maladaptive effects of CO₂ challenge on antisaccade performance
• Notably, the positive effect of duloxetine on attention control in the 7.5% CO₂ model of anxiety occurred in the absence of a clear effect of duloxetine on subjective mood and autonomic arousal
• Our findings converge with:
  1. Recent evidence that duloxetine can reduce activity in the amygdala and associated networks during emotion processing [5]
  2. Human neurocognitive models of anxiety which implicate this network in a range of cognitive and emotional biases that characterise anxiety [6]
  3. Research in rodents that identified the amygdala as a chemo sensor that directly detects increasing CO₂ concentrations to provoke fear behaviours [7]
• We plan to examine whether duloxetine can modulate attention in clinically anxious patients
• We also plan to examine whether compounds reported to reduce anxiety (such as the off-label use of memantine) produce similar results

Antisaccade
• All participants made significantly more antisaccade errors during the inhalation of 7.5% CO₂ compared to air
• However this CO₂-induced impairment was reduced after 2 week administration of duloxetine
• Contrary to previous literature [1], no effects of image valence were identified, with similar errors made on neutral and negative trials

Potential conflicts of interest
VLP is funded by an ESRF PhD-studentship. This research was funded by a Medical Research Council grant [MR/J011754/1] awarded to MG, MRM and DSB.

References

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