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 (CO_2) challenge

- Inhalation of 7.5% CO_2 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% CO_2 [2]
- These findings suggest 7.5% CO_2 inhalation is a useful, translational model of human anxiety for treatment development

Duloxetine

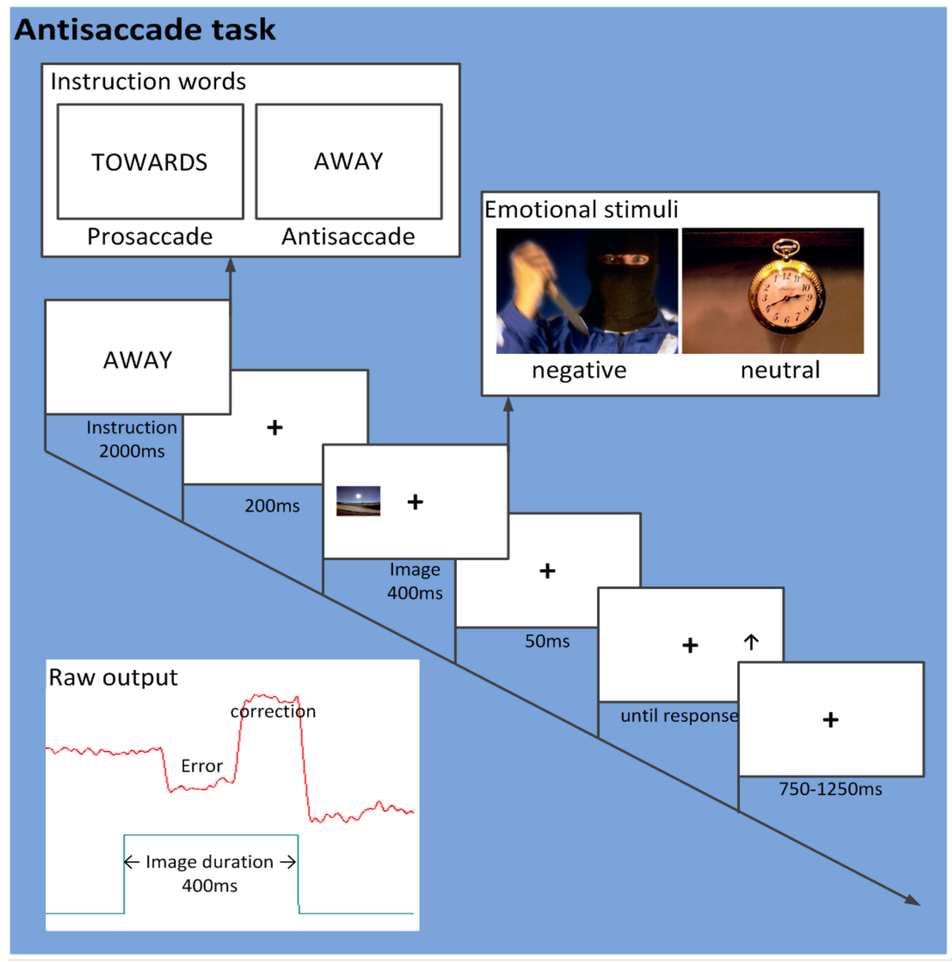
- The SNRI duloxetine has been identified as first for response in the treatment of generalised anxiety disorder [3]
- Short term treatment with duloxetine improves attention and memory in patients with major depression [4]

Aim

- **To examine whether duloxetine can reduce CO_2-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% CO_2 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% CO_2 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 the placebo group at the peak effects of CO_2 ($p = .059$)

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

		Air		7.5% CO_2	
Measure		Baseline	Peak	Baseline	Peak
Subjective	GAD-7	13.34 *(13.54)*	11.30 *(8.77)*	9.26 *(6.97)*	34.62 *(21.44)*
	Positive affect	31.11 *(7.46)*	27.24 *(7.80)*	30.14 *(7.57)*	23.38 *(8.80)*
	Negative affect	12.05 *(2.94)*	11.22 *(2.20)*	11.78 *(2.71)*	19.51 *(8.34)*
Autonomic	Systolic BP	119.73 *(8.96)*	119.41 *(9.34)*	118.62 *(7.94)*	131.65 *(12.88)*
	Diastolic BP	73.47 *(8.11)*	74.22 *(7.68)*	73.43 *(7.46)*	75.65 *(8.04)*
	Heart rate	67.59 *(10.88)*	69.95 *(11.47)*	67.00 *(9.98)*	81.78 *(15.42)*

Antisaccade

- All participants made significantly more antisaccade errors during the inhalation of 7.5% CO_2 compared to air
- However this CO_2-induced impairment was <u>reduced</u> 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

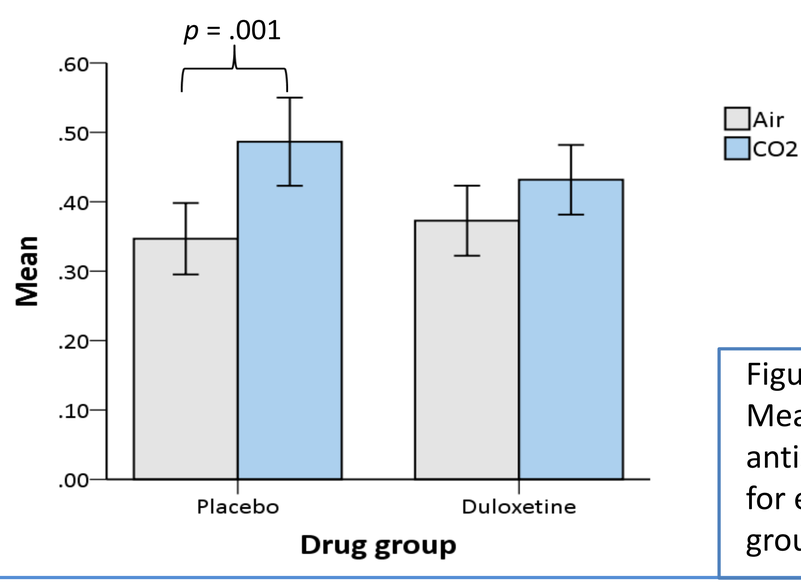


Figure 2.
Mean errors on antisaccade trials for each drug group

Summary and future research

- These findings suggest that prior administration of duloxetine in healthy volunteers can decrease the maladaptive effects of CO_2-challenge on antisaccade performance
- **Notably, the positive effect of duloxetine on attention control in the 7.5% CO_2 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 chemosensor that directly detects increasing CO_2 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

References

[1] Garner, M., Attwood, A., Baldwin, D. S., James, A., Munafo, M. R., 2011. Inhalation of 7.5% carbon dioxide increases threat processing in humans. Neuropsychopharmacol 36, 1557-1562.
[2] Bailey, J. E., Kendrick, A., Diaper, A., Potokar, J. P., Nutt, D. J., 2007. A validation of the 7.5% CO_2 model of GAD using paroxetine and lorazepam in healthy volunteers. J Psychopharmacol 21, 42-49.
[3] Baldwin, D. S., Woods, R., Lawson, R., Taylor, D., 2011. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. Brit Med J 342, d1199.
[4] Herrera-Guzman, I., Gudayol-Ferre, E., Herrera-Guzman, D., Guarida-Olmos, J., Hinojosa-Calvo, E., Herrera-Abarca, J. E., 2009. Effects of selective serotonin reuptake and dual serotonergic-noradrenergic reuptake treatments on memory and mental processing speed in patients with major depressive disorder. J Psychiatr Res 43, 855-863
[5] Van Marle, H. J., Tendolkar, I., Urner, M., Verkes, R. J., Fernandez, G., Van Wingen, G., 2011. Subchronic duloxetine administration alters the extended amygdala circuitry in healthy individuals. Neuroimage 55, 825-831.
[6] Bishop, S. J., 2007. Neurocognitive mechanisms of anxiety: an integrative account. Trends Cogn Sci 11, 307-316.
[7] Ziemann, A. E., Allen, J. E., Dahdaleh, N. S., Drebot, I. I., Coryell, M. W., Wunsch, A. M., …Wemmie, J. A. 2009. The amygdala is a chemosensor that detects carbon dioxide and acidosis to elicit fear behaviour. Cell 139, 1012-21.

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Potential conflicts of interest

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