Generalized anxiety disorder: new insights into aetiology and treatment

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<table>
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<th>Declaration of interests (1994 onwards)</th>
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<tr>
<td>Department of Health</td>
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<td>Economic and Social Research Council</td>
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<td>European Union FP7 Programme – Marie Curie IRSES</td>
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<td>European College of Neuropsychopharmacology Network Initiative</td>
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<td>Global Association of Mental Illness Advocacy Networks</td>
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<td>Health Education England</td>
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<td>Medical Research Council - Experimental Medicine</td>
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<td>Medical Research Council - Neuroscience and Mental Health</td>
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<td>Medical Research Council - Centenary Award</td>
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<td>NIHR Health Technology Assessment RCT Programme</td>
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<td>NIHR Research for Patient Benefit Programme</td>
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<td>NHS South &amp; West R &amp; D Directorate</td>
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<td>Royal College of Psychiatrists</td>
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<td>University of Southampton Research Management Committee</td>
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<td>University of Southampton MRC Centenary Award</td>
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<td>Veterinary Times and BUPA Giving</td>
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<td>Wellcome Trust</td>
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<td>Wessex Medical Research (States of Jersey Research Fellowship)</td>
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<td>I adhere to no particular ideology about the nature, causes or treatment of mental disorders</td>
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<td>Diagnosis</td>
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<tr>
<td>Anxiety disorders</td>
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<td>Panic disorder</td>
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<td>Agoraphobia</td>
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<td>Social phobia</td>
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<td>Specific phobias</td>
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<td>Generalized anxiety disorder</td>
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<td>Obsessive-compulsive disorder</td>
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<td>Post-traumatic stress disorder</td>
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# 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%.
‡ 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.

Neuropsychobiology of GAD

- **cognitive theoretical models**
  - worrying as maladaptive avoidance of somatic and affective experiences
  - intolerance of uncertainty (worrying as attempt to reduce likelihood of feared outcomes)
  - meta-cognitive theory (worries about worries)
  - emotion dysregulation model (worry as attempt to minimize impact of overwhelming emotions)
  - acceptance based model (development of self-critical beliefs)
  - information processing (preferential attention to ‘threatening’ stimuli)

- **genetic contributions to ‘neuroticism’**

- **adverse life experiences and disordered attachment**

- **disturbances in hypothalamo-pituitary-adrenal axis**

- **disturbances in serotonergic, noradrenergic and GABAergic neurotransmission**

- **alterations in ‘set-point’ of central chemosensors**

GAD: summary of BAP recommendations

- SSRI as first-line drug treatment (SNRI or pregabalin if SSRI unsuitable)
- CBT or applied relaxation as psychological treatment
- need for higher daily doses of pregabalin
- absent onset of effect within 4 weeks indicates treatment response unlikely
- augmentation with pregabalin following partial response to SSRI/SNRI
- combination of CBT and drug treatment after non-response to either alone
- benzodiazepine after non-response to SSRI, SNRI, pregabalin, buspirone
- continue treatment for 18 months after response to acute treatment
- after continuation treatment reduce dosage steadily over three months

Efficacy and tolerability of pregabalin in GAD

- 11 randomised double-blind placebo-controlled trials, and 2 open studies
- efficacy across age, gender, dose range, severity, coexisting depression or insomnia
- somnolence and dizziness are most frequent adverse events
- low potential for withdrawal symptoms

Table 2. Incidence and number needed to harm (NNH) of adverse events: pooled data from six short-term treatment studies.

<table>
<thead>
<tr>
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<th>Pregabalin, 150–600 mg/day (n=1149)</th>
<th>Placebo (n=484)</th>
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<tbody>
<tr>
<td></td>
<td>Incidence (NNH)</td>
<td>Incidence of ‘severe’ (NNH)</td>
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<tr>
<td>Dizziness</td>
<td>31.1% (5)</td>
<td>2.3% (48)</td>
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<tr>
<td>Somnolence</td>
<td>29.2% (6)</td>
<td>2.6% (46)</td>
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<tr>
<td>Headache</td>
<td>16.9% (NA)</td>
<td>1.7% (NA)</td>
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<tr>
<td>Dry mouth</td>
<td>15.1% (12)</td>
<td>0.4% (500)</td>
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<tr>
<td>Infection</td>
<td>10.2% (48)</td>
<td>0.3% (1000)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9.8% (200)</td>
<td>0.6% (500)</td>
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<tr>
<td>Amblyopia</td>
<td>7.5% (19)</td>
<td>0.3% (333)</td>
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<tr>
<td>Incoordination</td>
<td>7.1% (17)</td>
<td>0.3% (333)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6.7% (NA)</td>
<td>0.6% (250)</td>
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<tr>
<td>Constipation</td>
<td>6.2% (33)</td>
<td>0.8% (250)</td>
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<tr>
<td>Thinking abnormal</td>
<td>6.1% (27)</td>
<td>0.8% (500)</td>
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<tr>
<td>Diarrhoea</td>
<td>5.1% (NA)</td>
<td>0.1% (NA)</td>
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NA: not applicable (higher incidence on placebo).
Note: NNH is calculated as the reciprocal of the difference between the incidence of an adverse event on pregabalin versus the incidence of the same adverse event on placebo (Citrome, 2008).
Effects of vortioxetine on anxiety symptoms

- 5-HT$_3$, 5-HT$_7$ antagonist; 5-HT$_{1B}$ partial agonist; 5-HT$_{1A}$ agonist; inhibits 5-HT transporter: increases 5-HT, NA, DA, acetyl choline and histamine
- no significant difference from placebo in treatment-emergent anxiety ¹
- in meta-analysis of efficacy in patients with MDD and high anxiety (HAMA $>20$), reduces depressive and anxiety symptoms in acute treatment of MDD ²
- pooled analysis of acute treatment studies in GAD indicates significant advantages in reduction in HAMA score and treatment response - more marked in patients with more severe symptoms at baseline ³
- effective in preventing (15% vs. 34%) and delaying (HR 2.71) relapse in randomised, double-blind, placebo-controlled, study in GAD patients ⁴

². Baldwin DS et al. J Affective Disord 2016; 206: 140-150
Where is there room for improvement?

1. identifying patients most likely to benefit from particular treatments
2. addressing common concerns about adverse effects of psychotropic drugs
3. adhering to evidence-based treatment guidelines
4. achieving an earlier onset of clinical effect
5. achieving superior efficacy in reducing symptom severity
6. choosing the right drug for the right patient
7. deciding when response is unlikely
8. improving tolerability to enhance treatment adherence
9. combining treatments to enhance efficacy
10. treating over long periods to prevent relapse

New approaches to treatment development

- much scope for refining animal models of anxiety disorders and ‘anxiolytics’ \(^1\)
- successful development of novel anxiolytics may depend upon a refined biomarker approach combining genetic, cognitive and neuroimaging measures \(^2\)
- confirming potential benefit of novel treatments in necessary large randomised controlled trials is time-consuming and costly and viewed as ‘high risk’ \(^3\)
- ‘repurposing’ existing medicines could offer rapid benefits \(^4\)
- experimental medicine studies in healthy volunteers represent useful ‘proof-of-concept’ approach to determine whether to proceed to pivotal efficacy studies
- may reduce prolonged delay before innovations translate into clinical practice \(^5\)

3. Insel TR. World Psychiatry 2015: 14: 151-153
Repurpose / reposition

• repurpose: application of approved drugs to treat a different condition
  – thalidomide for leprosy and multiple myeloma
  – lamotrigine for bipolar disorder
  – galantamine in smoking cessation

• reposition: further investigation of drugs that failed approval
  – sildenafil (hypertension) for erectile dysfunction
  – zidovudine (eănër) for HIV-related conditions

• ‘low cost generics are an untapped source of therapeutic innovation’

Pantziarka P et al. BMJ 2018; 361: k2701

AMRC. Facilitating adoption of off-patent, repurposed medicines into NHS clinical practice. 2018
Cytokines and anxiety disorders

- bioactive mediators released centrally (microglia, astrocytes) and peripherally (macrophages, monocytes) dependent upon type 1 and type 2 helper cells
- pro-inflammatory cytokines include TNF-α and IFN-γ
- anti-inflammatory cytokines include IL-4 and IL-10
- Th1-Th2 imbalance shifts tryptophan metabolism towards kynurenine and kynurenine metabolism towards (neurotoxic) quinolinic acid
- series of small studies suggest anxiety disorders and PTSD (but not OCD) have variant immunophenotypes

Hou R, Baldwin DS. Hum Psychopharmacol 2013; 29: 67-84
Peripheral inflammatory cytokines in GAD (1)

- case-controlled cross-sectional investigation (54 cases, 64 healthy controls)
- DSM-IV-defined patients from primary and secondary care in Southampton
- first demonstration of a Th1/Th2 cytokine imbalance in GAD
- relatively **increased pro-inflammatory response** and **diminished anti-inflammatory response**
- significant differences in serum levels of IL-10, TNF-α, and IFN-γ between GAD and control groups after adjusting for age, gender and BMI
- group differences were independent of the presence or degree of depression
- significantly higher ratios of TNF-α /IL10, TNF-α /IL4, IFN-γ /IL10, and IFN-γ /IL4 in the GAD group compared to the control group

Pro-and anti-inflammatory cytokine ratios

Peripheral inflammatory cytokines in GAD (2)

- case-controlled cross-sectional investigation (48 cases, 48 healthy controls)
- ICD-10 defined patients from secondary care settings in Suzhou, China
- higher serum levels of CRP, IL-1α, IL-2, IL-6, IL-8, IL-12, IFN-γ and GM-CSF
- positive correlations between anxiety and CRP, IL-1α, IL-6, IL-8, IFN-γ, GM-CSF
- replication of elevated levels of IFN-γ (type II interferon)
  - inhibits viral replication; associated with some autoimmune diseases, elevated in depression
- significant reduction in all pro-inflammatory cytokines with SSRI treatment
- treatment response predicted by baseline levels of CRP and Il-6

Tang Z et al. J Affective Disord 2018; 225: 593-598
Hou R et al. Submitted for publication
Experimental medicine models

- safe for participants and investigators, ideally non-invasive
- acceptable to participants, ethics committees, regulatory bodies
- reliable inter-performer and repeat-performer replicability
- valid effects attenuated by clinically effective treatments
- translational from lab to clinic and back again, across species
- feasible ease of performance in practice
- repeatable no attenuation of response if performed again
- subjective measurable psychological effects
- objective measurable physiological effects
- inexpensive can be supported by grant-givers and industry
Experimental medicine models - examples

- obsessive-compulsive disorder  
  no current validated model
- panic disorder  
  CCK-4 administration \(^1\)
- social anxiety disorder  
  Trier Social Stress Test \(^2\)
- post-traumatic stress disorder  
  trauma film paradigm \(^3\)
- generalised anxiety disorder  
  20-minute 7.5% CO\(_2\) inhalation \(^4\)

2. Van Hedger K et al. Psychoneuroendocrinol 2017; 85: 123-133
CCK-4 administration and panic attacks

- 50 μg CCK-4 administration induces panic in 47% controls and 100% patients.
- Symptom cluster is similar in healthy volunteers and panic disorder patients.
- Number and intensity of panic symptoms is dosage-dependent.
- Prior administration of benzodiazepine or beta-blocker attenuates response.

- Prior SSRI administration does not attenuate response.
- CCK-antagonists do not consistently prevent or diminish response.

Acute psychosocial stress models social anxiety

- public speaking task involving intense scrutiny and negative feedback
- induces subjective, autonomic and endocrine changes
- influenced by age, gender, menstrual cycle phase, time, diagnosis, genotype
- benzodiazepines (and gabapentinoids) reduce only subjective anxiety
- propranolol attenuates heart rate and blood pressure (no subjective effects)
- escitalopram and nefazodone (not maprotiline) increase subjective anxiety
- cannabidiol reduces subjective anxiety during/after task

Van Hedger K et al. Psychoneuroendocrinol 2017; 85: 123-133
Trauma film exposure as model of PTSD

- first developed in 1969
- around 100 studies
- series of trauma clips
- induces intrusive memories
- permits interventions

- simple tasks (e.g. ‘Tetris’) up to 4 hrs after film reduces intrusive memories
- positive reappraisal training before/after film reduces psychological distress
- clonidine and yohimbine (but not cortisol) reduce intrusive memories

Carbon dioxide ($\text{CO}_2$) inhalation and anxiety

- brief inhalation of air with 35% CO$_2$ concentration induces acute severe anxiety
- 20-minute inhalation of 7.5% CO$_2$ associated with subjective, autonomic and neurocognitive changes which resemble features of GAD
- uncertain whether anxiety is triggered by relative hypoxia or hypercapnia, or whether both disturbances are needed
- hypercapnia and hypoxia may both be important in driving ‘air hunger’
- patients with panic disorder have increased sensitivity to both conditions
- experimentally induced panic attacks associated with low end-tidal CO$_2$ and high ventilation variance at baseline

1. Baldwin DS et al. CNS Drugs 2017; 31: 307-317
Carbon dioxide (CO$_2$) inhalation and anxiety

- mechanisms underlying provocation of anxiety unclear but probably involve:
  - genetic factors
  - cortisol secretion
  - disturbed respiratory physiology
  - serotonergic neurotransmission
  - noradrenergic neurotransmission
  - acid-sensing ion channels

Chemosensory mechanisms and anxiety

- pH chemosensory areas within brain stem, amygdala, hypothalamus and PAG
- ‘circumventricular organs’ (CVO): chemosensory areas e.g. sub-fornical organ, area postrema and lamina terminalis (lack BBB)
- acid-sensing ion channel 1 (ASICa) in amygdala, dentate gyrus, cortex, striatum
- lactate-sensitive orexin-expressing neurones in hypothalamus
- pH-sensitive serotonergic neurones (and neurones expressing NK-1) in raphe
- acid-sensing T-cell death-associated gene-8 receptor (TDAG8) in sensory CVOs
- hypoxia-sensitive neurones in dorsal PAG

PAG: periaqueductal gray
Acid-sensing ion channels

- pH-sensitive ion channels, activated by extracellular acidosis
- ASIC1A involved in cued and contextual fear conditioning
- ASIC1A in amygdala may help to prevent suffocation by inducing active defence responses
- NSAIDs reduce ASIC1A and ASIC3 currents: amiloride reduces currents in all subtypes

7.5% CO$_2$ inhalation model of GAD

- healthy participants
- 20 minutes inhalation of air ‘enriched’ with CO2 or normal air
- inhalation order blind and counterbalanced
- assessed at baseline, before and after each inhalation
- subjective experience (rating scales, questionnaires)
- autonomic measures
- performance on computerised cognitive tasks
Effects of 7.5% CO2 challenge on self-report anxiety

Effects of 7.5% CO2 challenge on autonomic arousal

7.5% CO₂ challenge – the ‘lived experience’

“Dry mouth...
Felt my heart beating a bit faster
I was like sweating a bit as well
And a bit shaky”

ICD-10 F41.1 B 1-4

I felt quite breathless
I felt sick a bit
I think I felt nauseous
I started to breathe rapidly

ICD-10 F41.1 B 5-8

I felt a bit disconnected
Disoriented
I felt quite - probably random in the head

ICD-10 F41.1 B 9-12

Makes me feel very nervous
Sort of apprehensive
When is this going to stop so I can go back to normal

ICD-10 F41.1 A

Other effects like numbness….and tingling
Slight tingling in feet
Felt my cheeks burn-up

ICD-10 F41.1 B 13-14

I think it was more…..the restlessness
Everything was a bit intense, at the same time
I couldn’t keep still

ICD-10 F41.1 B 15-18

I was trying hard to concentrate.
...was like quite a struggle to keep concentrating.
I was not doing as I was supposed to
I knew I was struggling

ICD-10 F41.1 B 19-22
CO₂ challenge and negative thought intrusions

n = 24 (within-subjects)
7.5% CO$_2$ inhalation and attention to threat

Garner MJ et al. Neuropsychopharmacology 2011; 36: 1557-1562
Placebo-controlled studies: panic attacks

- administration of SSRIs, venlafaxine, TCAs, or MAOI toloxatone can attenuate panic response to CO$_2$ challenge $^1$

- administration of SSRI escitalopram prior to 3 minutes 5% CO$_2$ in individuals ‘at high risk of panic disorder’ had no effect on subjective or autonomic anxiety $^2$

- in patients with established panic disorder 12 weeks of SSRI or SNRI treatment reduced subjective anxiety following 5% and 7% CO$_2$ challenge, when compared to the effects of baseline inhalation, before treatment $^3$

- SSRIs often take 4 weeks to exert sustained therapeutic effects in patients with anxiety disorders, so prolonged drug administration may be needed to generate valid findings in experimental medicine studies involving healthy subjects

Placebo-controlled studies: anxiolytics

- benzodiazepine administration attenuates CO₂-provoked subjective, but not autonomic, anxiety ¹, ², ³, ⁴ (though not all evidence is consistent ⁵)
- zolpidem administration attenuates subjective anxiety ⁴
- pregabalin had limited effect on subjective and autonomic anxiety ⁶
- beta-blocker (propranolol) or anti-histamine (hydroxyzine) had no effect on self-report anxiety ⁷
- model employed to assess potential anxiolytic efficacy of novel compounds:
  - CRF₁ receptor antagonist R317573 ²
  - NK₁ receptor antagonists vestipitant and vofopitant ⁸

Placebo-controlled studies: antidepressants

- limited and inconsistent evidence

- placebo-controlled administration of SSRI paroxetine for 21 days (10 mg titrated to 20 mg after day 8) reduced subjective anxiety \(^1\)

- placebo-controlled investigation of 3-week administration of either venlafaxine (150 mg) or pregabalin (200 mg) found no significant effect on ratings of subjective anxiety or autonomic response in either group \(^2\)

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Effects of duloxetine in 7.5% CO₂ model

- healthy volunteers, double-blind design
- 14 days of duloxetine (30mg mane then 60 mg mane)
- CO₂ challenge on day 14

* p < 0.01

Duloxetine reduced subjective anxiety

Independent of effects on autonomic function

Pinkney V et al. J Psychopharmacol 2014; 28 (suppl.): A62
Effects of duloxetine on attention and worry

Attenuates anti-saccade errors  * p < 0.01

Less increase in negative thought intrusions in worry task

Pinkney V et al. J Psychopharmacol 2014; 28 (suppl.): A62
Memantine improves attention in CO₂ challenge

- 37 healthy volunteers
- 3 non-adherent, 4 did not finish inhalation
- 14 day memantine: 5 mg increased to 10 mg on Day 7
- CO₂ increased HR, systolic BP and subjective anxiety
- no significant effect of memantine on subjective anxiety
- CO₂ reduced attention control (increased errors)
- memantine group made fewer eye-movement antisaccade errors vs. placebo, particularly during CO₂ (p=0.055)

Pinkney V et al. J Psychopharmacol 2015; 29 (suppl.): A116
Anxiolytic effects of quetiapine in 7.5% CO\textsubscript{2} model

- 27 healthy volunteers
- 2 non-adherent
- 14 day quetiapine: 25 mg increased to 50 mg on Day 3
- no effect on autonomic measures
- quetiapine reduced CO\textsubscript{2} anxiety on some measures
- no effect on neurocognitive measures

_Woolley J et al. J Psychopharmacol 2015; 29 (suppl.): A115_
Effects of mindfulness in 7.5% CO$_2$ model

- controlled study of focused attention (FA) and open monitoring (OM)
- FA and OM reduced anxiety during CO$_2$ compared to relaxation control group
- groups did not differ in autonomic response

Effect of 20 min prefrontal tDCS in 7.5% CO$_2$ model

- 36 healthy volunteers randomised to:
  i. 2mA prefrontal tDCS for 20mins
  ii. sham (double-blind, anode = left)
- no effect on autonomic measures
- no effect on subjective anxiety
- tDCS group made fewer erroneous eye-movements to threat
- tDCS group were slower to orient towards threat than sham group (175 msec vs. 159 msec)

Anxiolytic effects of ibuprofen in 7.5% CO$_2$ model

- ibuprofen (NSAID) inhibits inflammation-induced expression of ASIC1
- 27 healthy volunteers randomised to ibuprofen (400 mg) or placebo
- 7.5% CO$_2$ inhalation 90 minutes after single dose administration
- ibuprofen significantly attenuated subjective anxiety response
- no significant differences in autonomic response or attention control

*Barnes JW et al. J Psychopharmacol 2017; 31 (8 suppl.): A28*
Amiloride (non-specific ASIC blocker)

- single-dose placebo-controlled amiloride (20mg) administration study
- 60 healthy volunteers, 51 completed study
- baseline 20-minute air and 7.5% CO$_2$ inhalation
- second CO$_2$ inhalation following drug administration
- no effect of placebo on CO$_2$ inhalation
- trend for reduction in subjective anxiety after amiloride (p=0.083)

Parker R et al. J Psychopharmacol 2018; 32 (8 suppl.): A127-8
7.5% CO₂ inhalation model of generalized anxiety

• fulfills criteria for an experimental medicine model

• replicable effects across a range of outcome measures:
  – self-report anxiety
  – autonomic response
  – pathognomonic symptoms
  – negative thought intrusions
  – selective attention to threat
  – cognitive control

• measurable effects of range of manipulations:
  – duloxetine
  – memantine
  – quetiapine
  – mindfulness
  – tDCS
  – ibuprofen

• scope for further exploration with drugs affecting acid-base balance:
  – carbonic anhydrase inhibitor
  – GABA-A sub-type selective ligands
  – acetazolamide
  – TPA 023B

*Baldwin DS et al. CNS Drugs 2017; 31: 307-3017*
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- MRC Neuroscience and Mental Health
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- Dr Daniel Meron
- Dr Verity Pinkney
- Dr Johanna Miler
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- Robert Parker