Mass General Brigham

Dyspnea associated anxiety: pathophysiology and management

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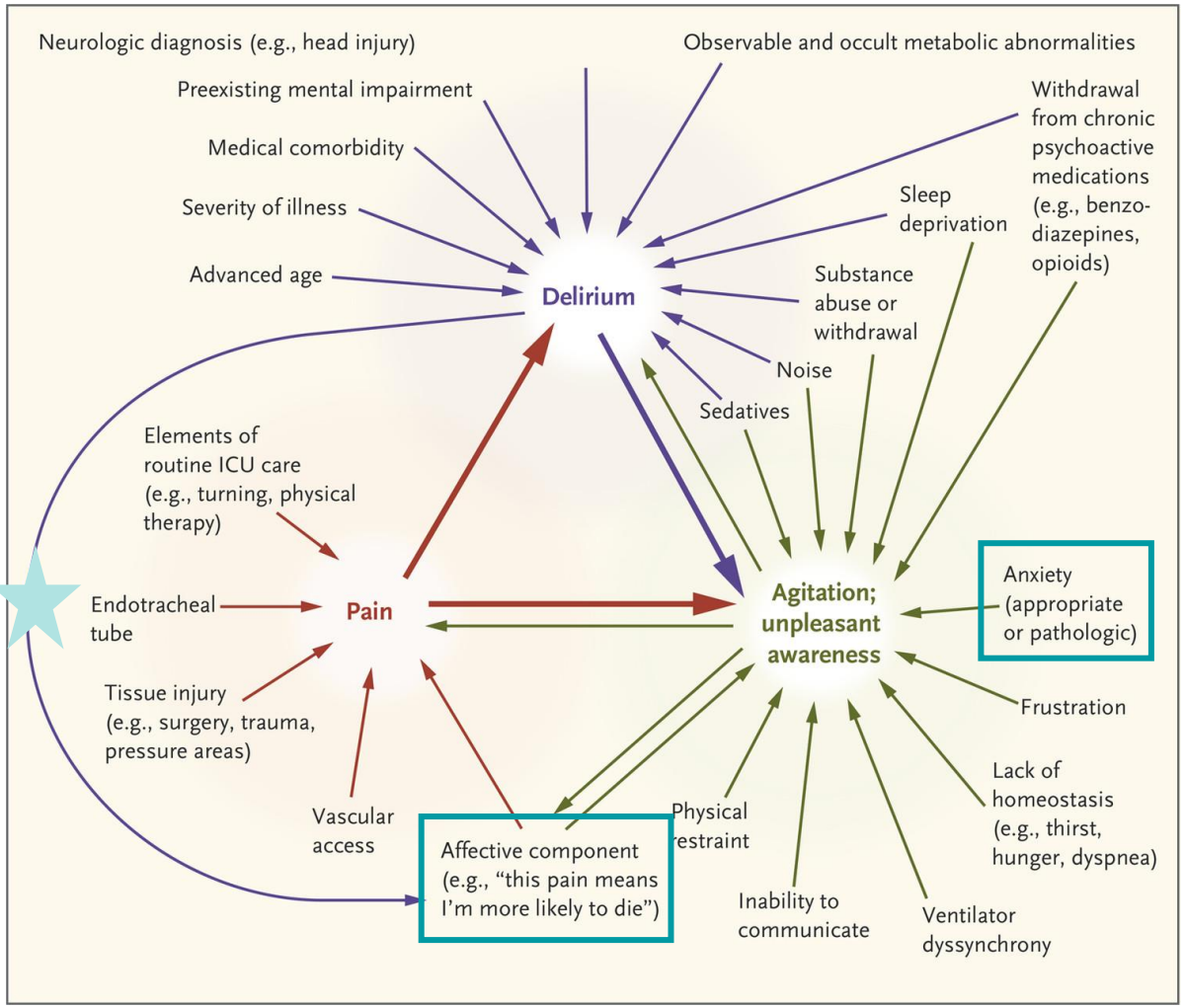
Disclosures

I have no disclosures to report

Anxiety in Critical Illness

- 30-80% of ICU patients experience anxiety [1-3]
- ICU patients associate anxiety with inability to communicate, sleep disturbances, and perceptual disturbances [1]
- Anxiety is significantly correlated to pain levels [4]
- No guidelines for measuring or treating anxiety in the ICU [1]



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Anxiety in Critical Illness: Differential Diagnosis

Anxiety Disorder
- Pre-morbid: Generalized Anxiety Disorder, Panic Disorder
- Adjustment disorder with anxiety
- Anxiety due to another medical condition

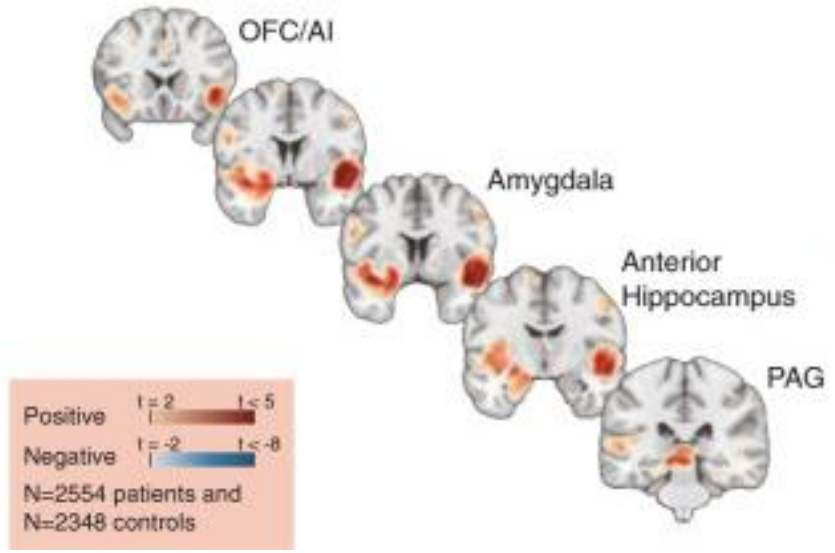
Manifestation of Medical Condition
- Pulmonary Disease: Hypoxia, Hypercapnia, Hyperventilation
- Delirium

Medication side effect
- Steroids, Antibiotics, Beta-Agonists

Substance/medication withdrawal
- Nicotine, GABA-ergic, Alpha-2 agonist withdrawal

Anxiety & Delirium

- Anxiety associated with increased activity in periaqueductal gray, amygdala, thalamus [1]
- Anxiety modulated by the prefrontal cortex (PFC) [1]
- fMRI during delirium: disorganization, less efficient resting-state network during delirium [2]
- Delirium --> decreased ability to attenuate anxiety



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2. Van Montfort et al. NeuroImage: Clinical. 2018.

Pulmonary disease and anxiety

Asthma:

- Adults with asthma have **50% higher** likelihood of having depressive or anxiety disorder compared to healthy population [1]

COPD

- Prevalence of **34% of patients** with COPD [2]
- Pts with COPD are **10x higher** likelihood of having panic disorder [3]

Cystic Fibrosis:

- Symptoms of anxiety in **32% of adults** [4]

Quality of life

- Anxiety associated with higher levels of dyspnea and lower quality of life in pts with COPD [2]
- Untreated anxiety associated with increased emergency healthcare utilization in patients with chronic respiratory disease [2]

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Dyspnea

"subjective experience of breathing discomfort "[1]

- Dyspnea affects half of mechanically ventilated patients [2]
- Described as one of worst ICU-related memories[3]
- Associated with increased risk of PTSD [4]
- Associated with increased length of ICU stay and delayed extubation [4]

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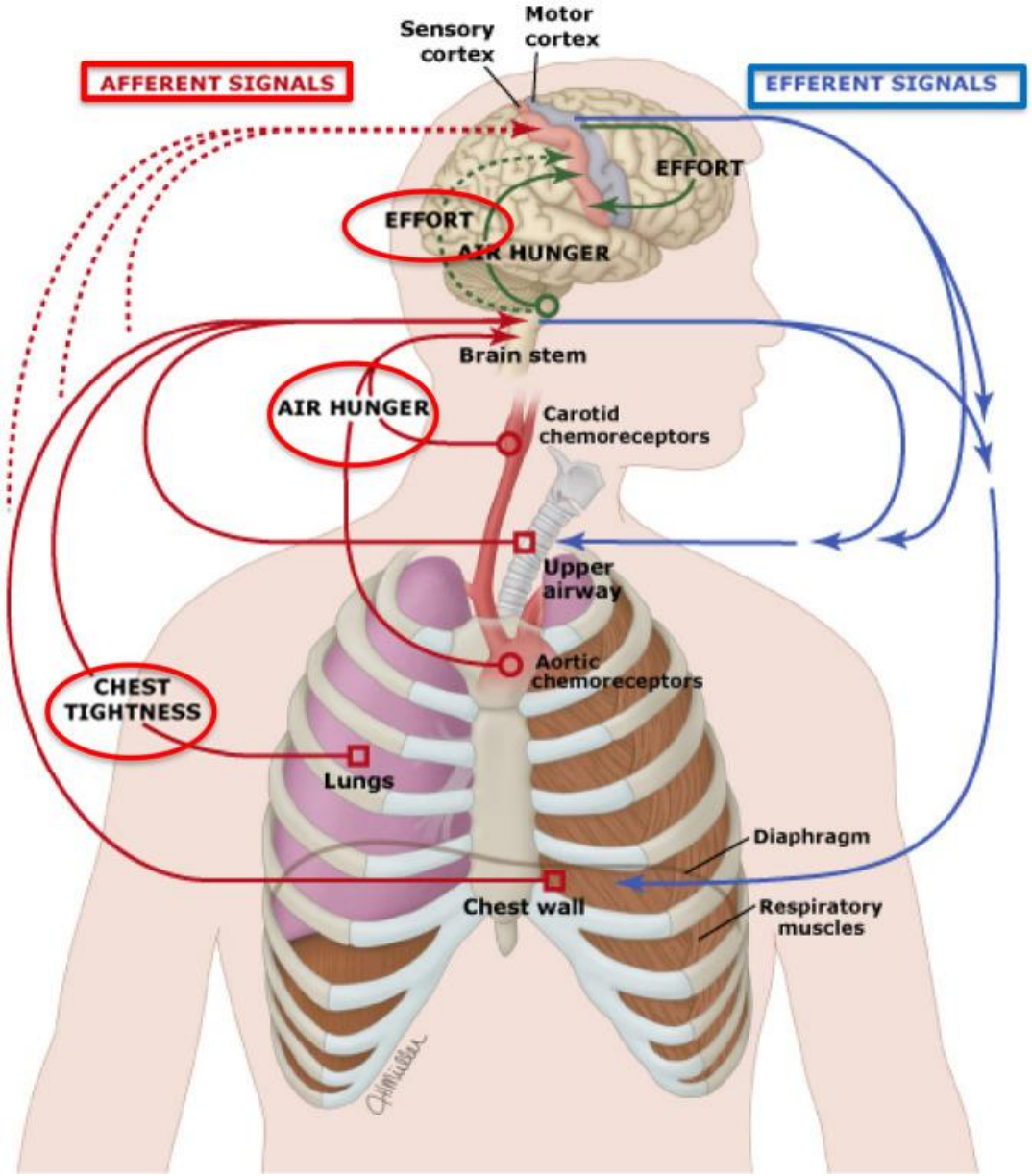
Dyspnea: Mechanisms

- **Work of breathing**
  - Cortico-brainstem-muscle connection
- **Air Hunger**
  - Chemoreceptor sensitivity
- **Chest Tightness**
  - Stretch receptor activation



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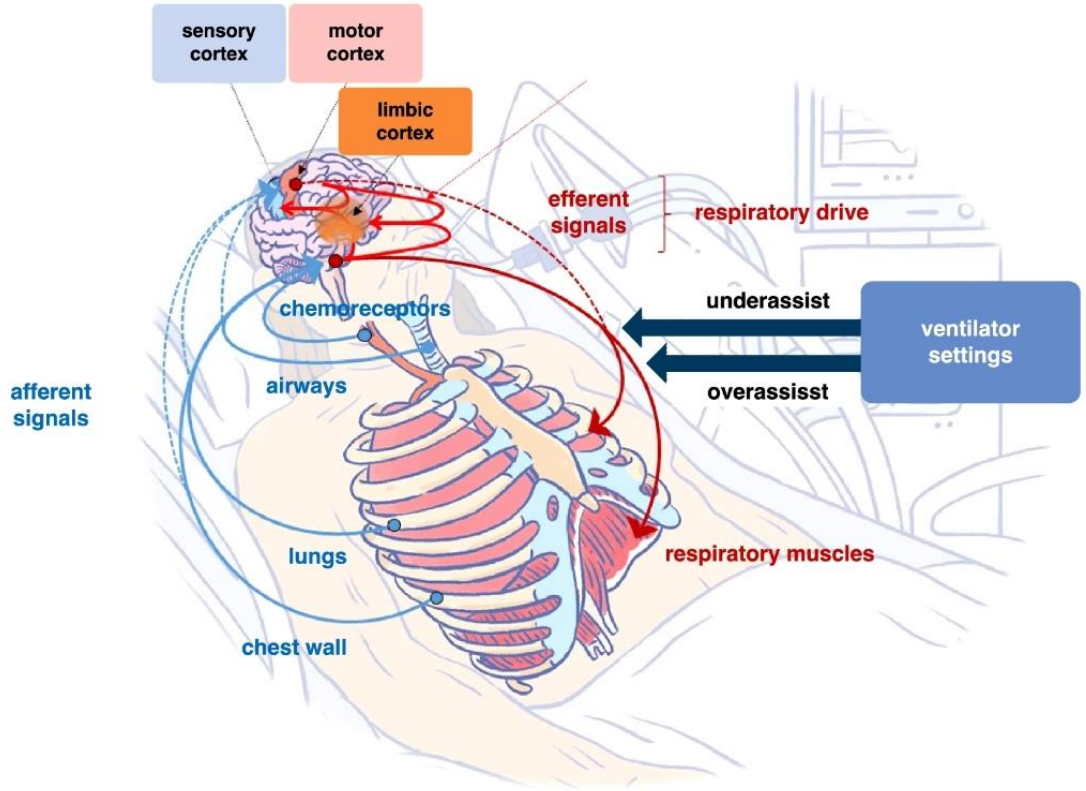
Dyspnea Associated Anxiety

- 47% of ICU patients reported dyspnea on the first day they were able to communicate [1]

- Dyspnea was significantly associated with:
  - Anxiety **(OR: 8.84)**
  - Assist-control ventilation **(OR: 4.77)**



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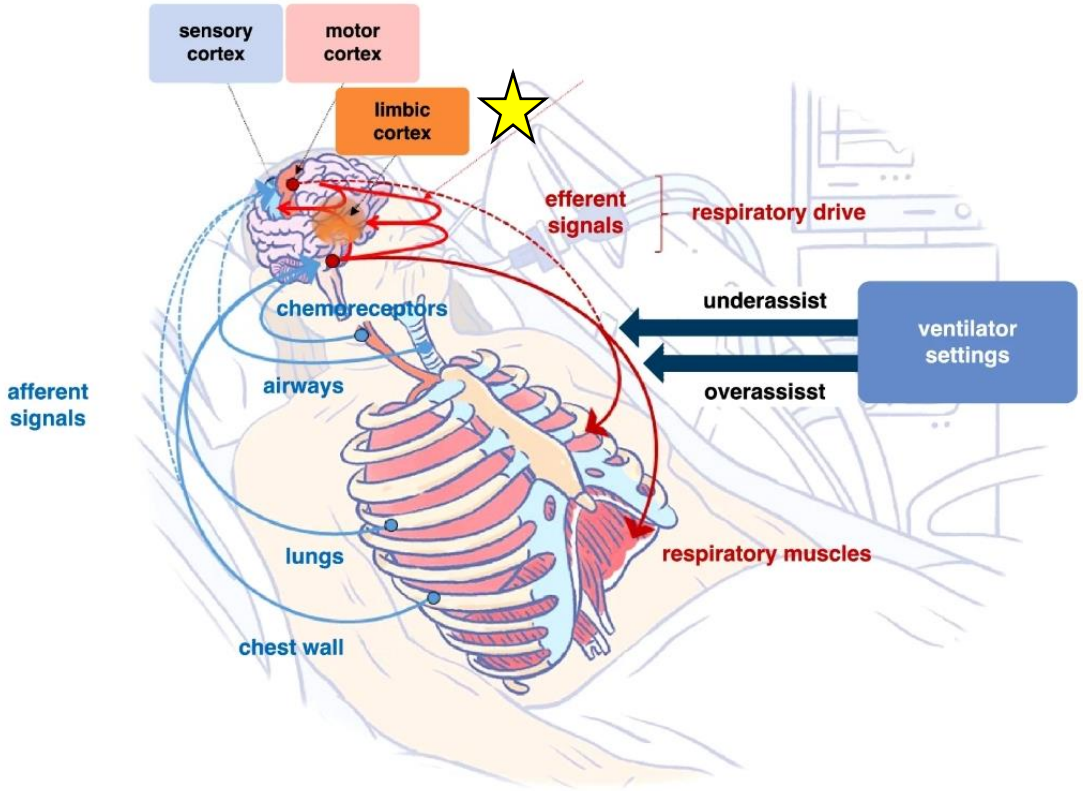
2. Figure: Demoule, A., Decavele, M., Antonelli, M. *et al.* Dyspnoea in acutely ill mechanically ventilated adult patients: an ERS/ESICM statement. *Intensive Care Med* **50**, 159–180 (2024).

Dyspnea and Anxiety Interplay

Physically Sensitive:

- ↑ CO2 and ↓ pH (respiratory acidosis) leads to activation of the locus coeruleus, hypothalamus, ventrolateral medulla (limbic system) involved in both ventilatory control and in panic [1]



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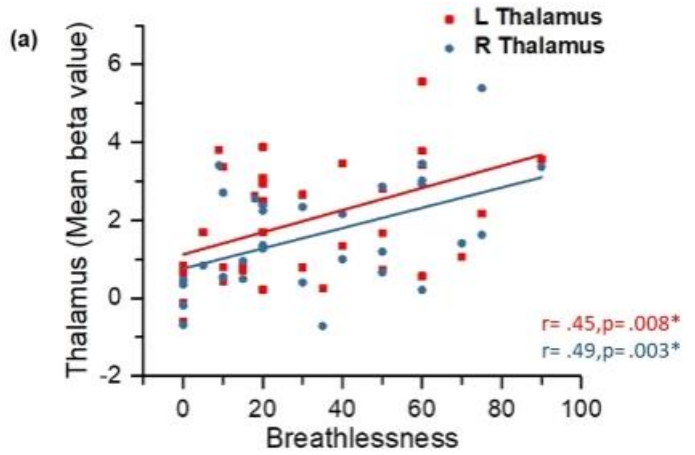
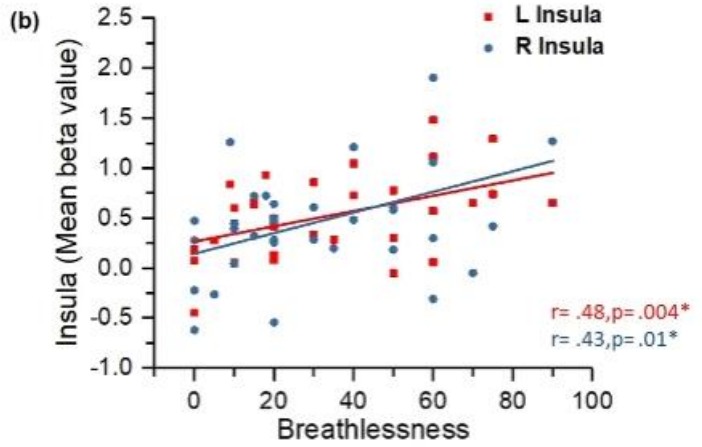
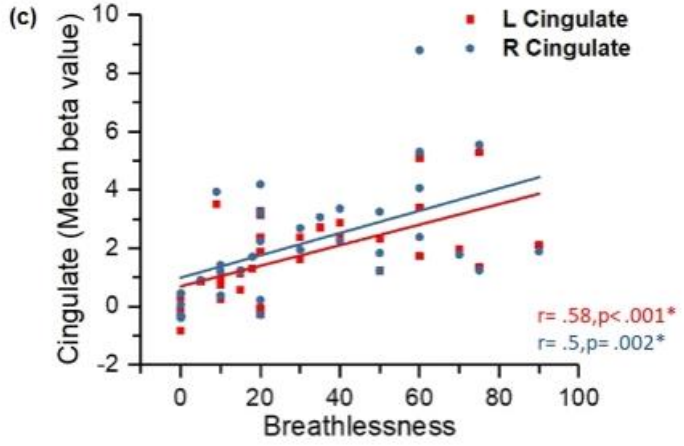
Dyspnea and Anxiety Interplay

Physically Sensitive:

- fMRI during inspiratory mechanical occlusion compared between high and low anxiety individuals found:
  - breathlessness significantly associated with activation of bilateral thalamus, bilateral insula and bilateral cingulate gyrus (emotion-related areas)
  - Increased activation in high-anxiety individuals







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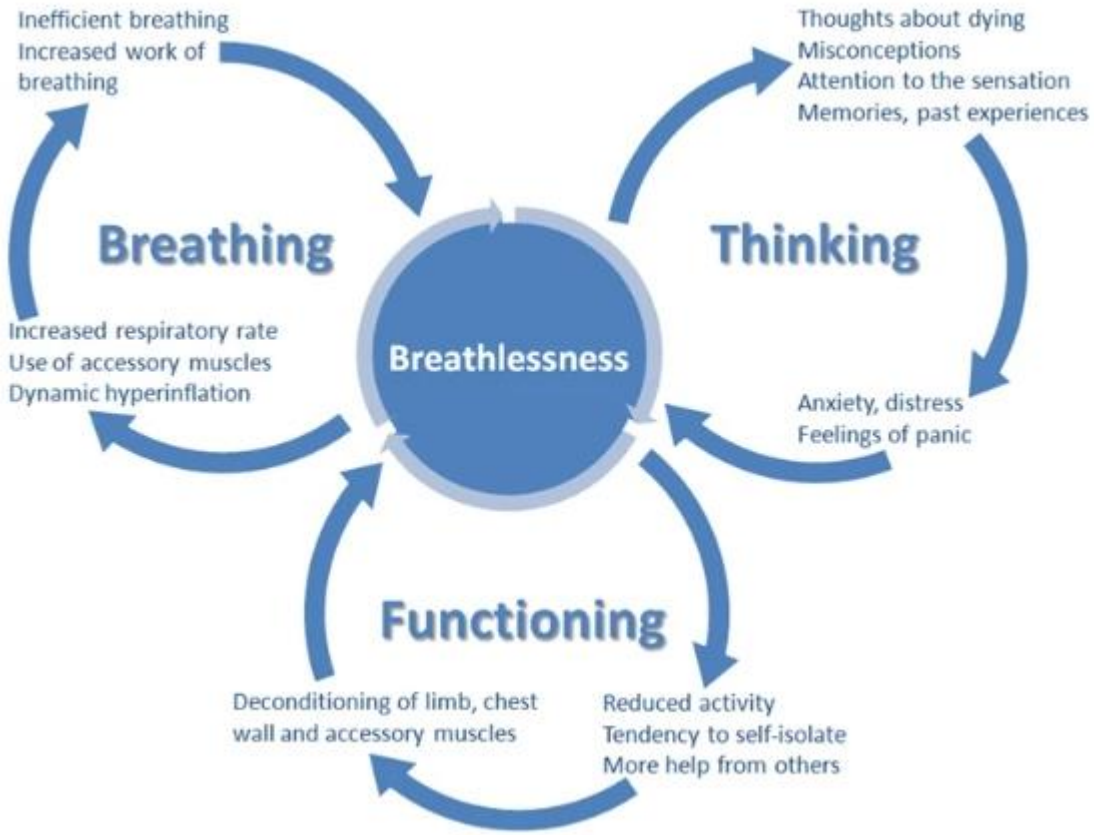
Dyspnea and Anxiety Interplay

Cognitive Response

- **Catastrophic Interpretation:**
  - Pts with COPD and Panic Disorder (PD) have heightened symptom perception & misinterpretations of physical sensations vs COPD w/o PD with similar respiratory condition severity [1]

- **Positive Feedback Loop**
  - Anxiety may lead to hyperventilation [2]



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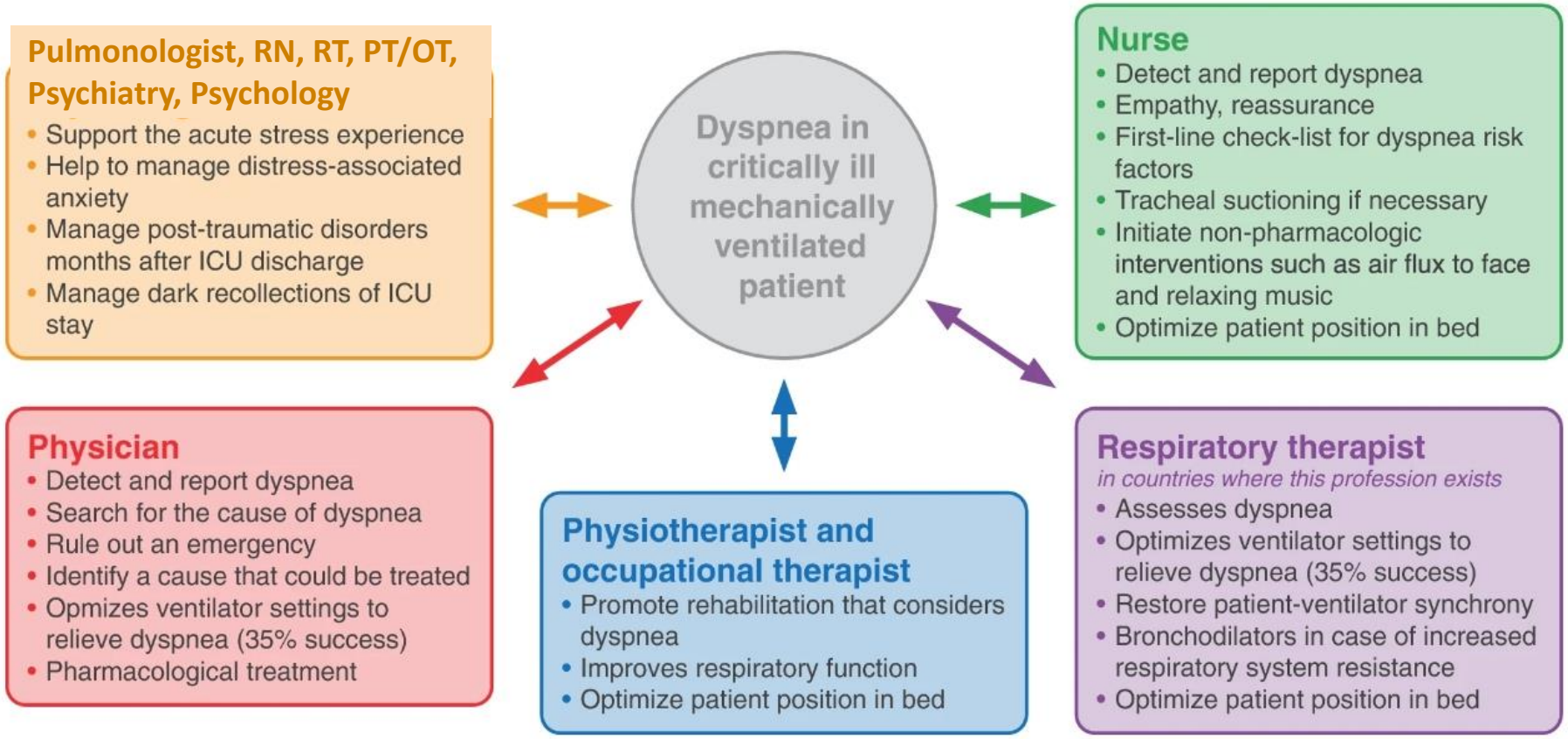
Interventions: Dyspnea-Associated Anxiety



Teamwork management of dyspnea in critically ill mechanically ventilated patients

Figure: Demoule, A., Decavèle, M., Similowski, T. et al. A double plea for dyspnea as the next great cause of all ICU professions and for caution about the dyspnea-breathlessness equivalence. Intensive Care Med 50, 1192–1193 (2024). https://doi-org.ezp-prod1.hul.harvard.edu/10.1007/s00134-024-07482-9

Interventions: Dyspnea

- **Ventilator Settings**
  - Adjusting ventilatory setting improved dyspnea in 35% of patients [1]
- **Oxygen**
  - Decreases hypoxic ventilatory drive
  - ↓peripheral chemoreceptor activity [2]
- **Opioids**
  - Most evidence for morphine [2,3]
  - Decreases respiratory drive via mu opioid receptor: ↓ sensitivity of brainstem respiratory centers to hypoxia, hypercapnia
  - Diminished mismatch between demand and ability to breathe

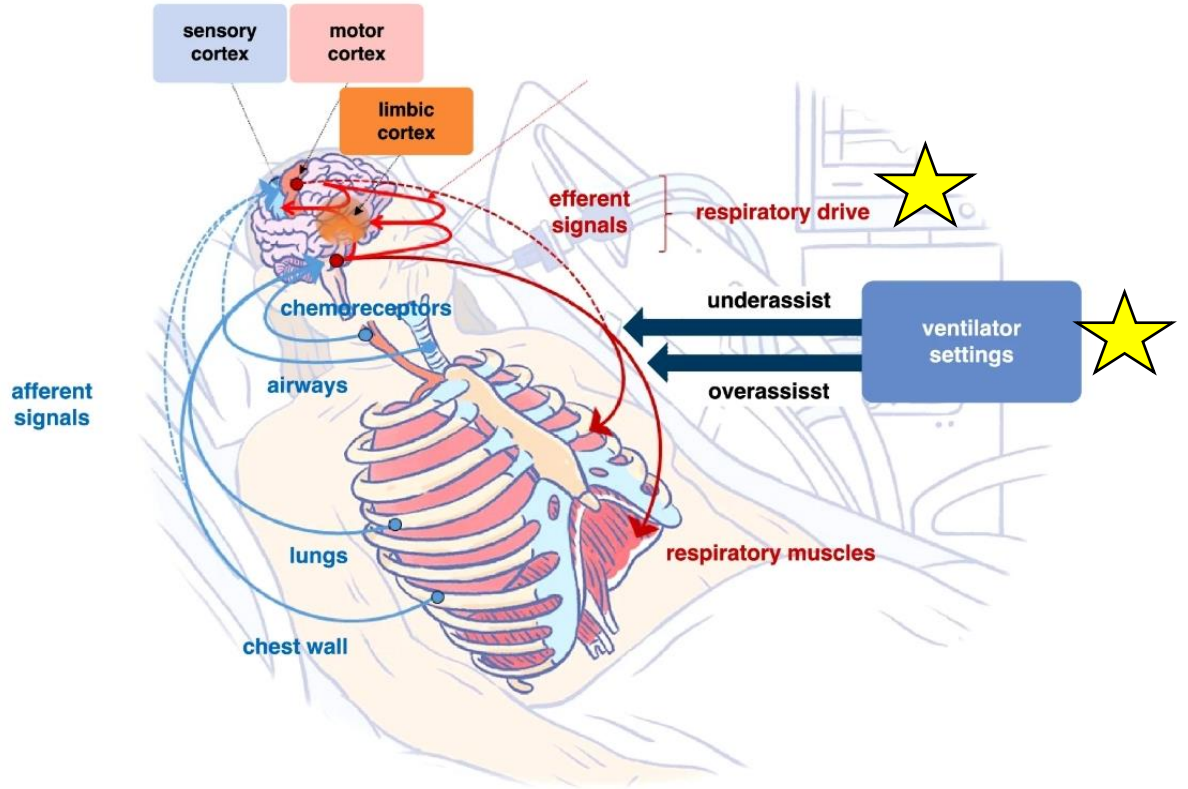


Table 3. Effects of adjusting ventilator settings in the patients reporting dyspnea

Parameter	Mean Variation, cm (95% Confidence Interval)	*p*
Dyspnea VAS	−4.6 (−6.1 to −3.2)	.0005
Anxiety VAS	−1.7 (−3.3 to −0.2)	.041
Pain VAS	+0.3 (−0.7 to +1.2)	.79

VAS, visual analogic scale.

Ventilator settings were considered involved in the pathogenesis of dyspnea if and when the postintervention VAS rating was inferior by at least 1 cm to the preintervention one.

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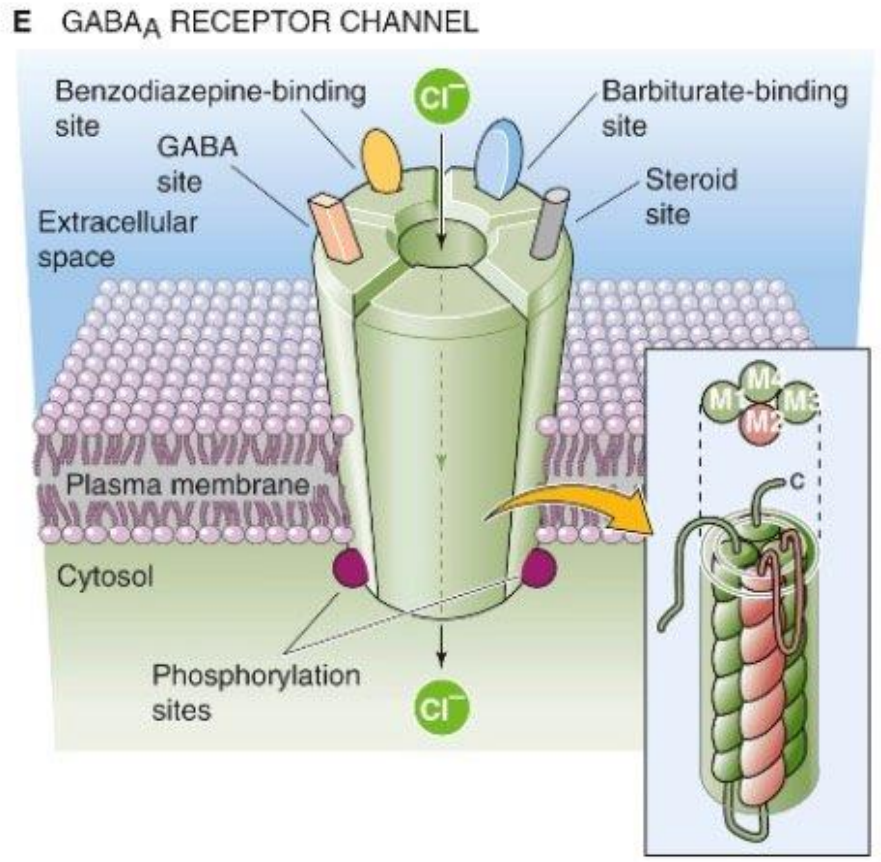
Interventions: Dyspnea-Associated Anxiety (DAA)

Benzodiazepines

- Allosteric modulators of GABA receptors; increase transmission via GABA receptors
- Effective in Anxiety; may be helpful for Dyspnea associated anxiety [1]
- Little evidence for treatment of dyspnea [2]
- Caution in pts with marginal respiratory reserve
- Caution in delirium
    - Independent risk factor in transitioning to delirium [3]



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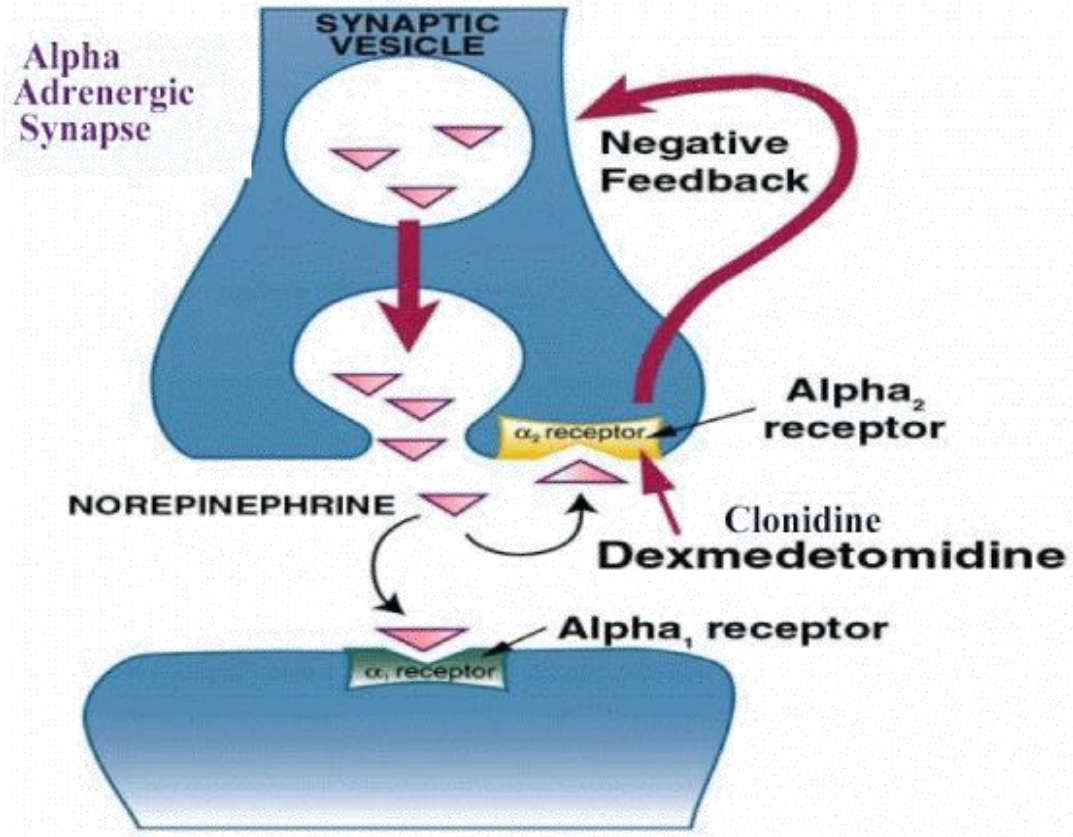
Interventions: Dyspnea-Associated Anxiety (DAA)

Alpha 2 receptor Agonist: Dexmedetomidine, Clonidine, Guanfacine

- Decrease pre-synaptic release of norepinephrine; decrease activation of sympathetic CNS activity
- Helpful for anxiety



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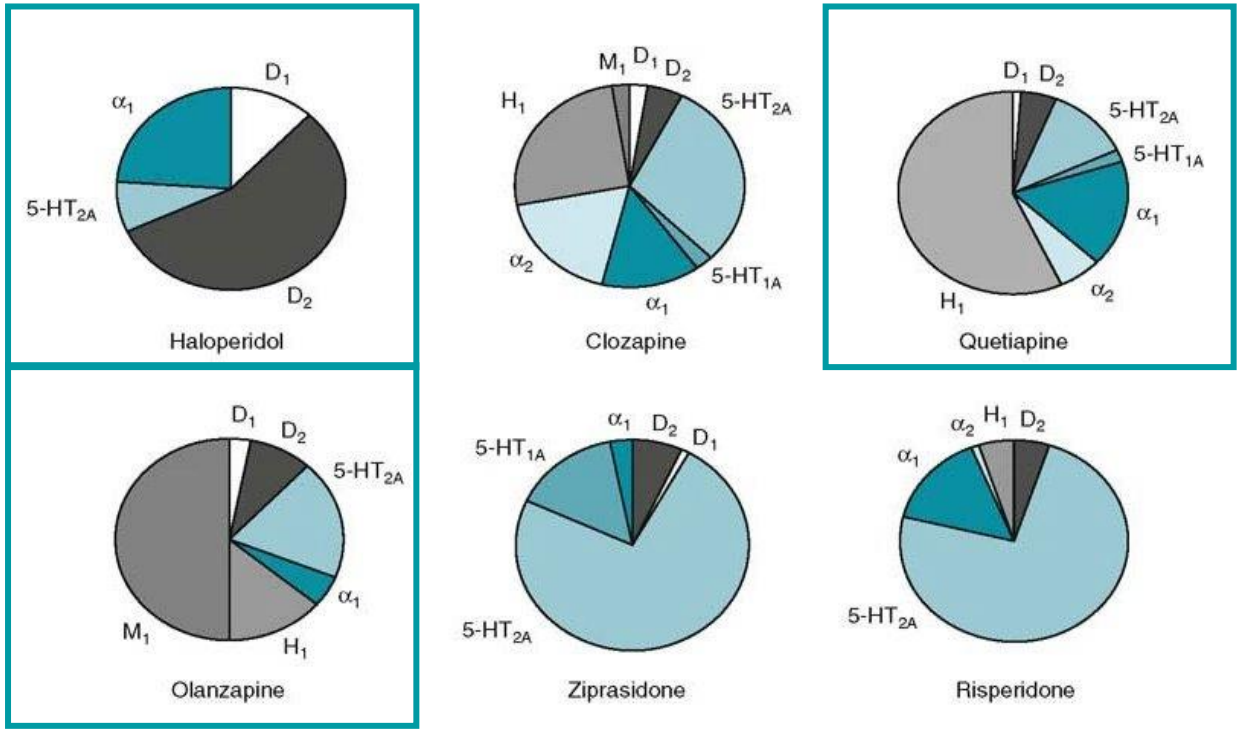
Interventions: Dyspnea-Associated Anxiety (DAA)

Antipsychotics[1]

- Block dopamine receptor; additional antihistaminergic, serotonin modulating effects
- Caution with Alpha-1 antagonism; anti-cholinergic activity, Qtc prolongation
- Case report for dyspnea: Chlorpromazine [2]
- ***Quetiapine:** sedating: **H1,** Alpha-1, mild Alpha-2
- **Olanzapine:** sedating: Anticholinergic, H1, Alpha-1
- **Haloperidol:** D2 blockade; little adrenergic



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Interventions: Dyspnea-Associated Anxiety (DAA)

Antihistaminergic medications

- Hydroxyzine: helpful for anxiety, though no evidence in dyspnea in the ICU or dyspnea associated anxiety [1]
- Quetiapine (at low doses <300 mg)
- Trazodone (mild H1 activity)

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Interventions: Dyspnea-Associated Anxiety (DAA)

Serotonin modulators

- Increase availability of serotonin
- Helpful for anxiety, little evidence for dyspnea associated anxiety
- *Use when known pre-morbid anxiety disorder
- **SSRI:**
  - 2011 Cochrane review: no conclusive evidence for managing breathlessness or anxiety (Paroxetine associated with decreased anxiety and increased exercise tolerance) [1]
  - RCT comparing sertraline vs placebo found no difference in breathlessness between sertraline and placebo [2]
- **Buspirone (5HT1 agonist)**
  - RCT of 432 cancer patients found addition of buspirone did not result in significant improvement in dyspnea or anxiety [3]

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Interventions: Dyspnea-Associated Anxiety (DAA)

- Antipsychotics (Quetiapine, Haloperidol, Olanzapine)
- Antihistaminergic Agents (Hydroxyzine, low dose Quetiapine)
- Benzodiazepines (Lorazepam, Alprazolam)*
- Alpha-2 Agonists (Dexmedetomidine, Clonidine, Guanfacine)
- Gabapentinoids (Pregabalin, Gabapentin)
- Serotonergic: SSRI, Buspirone

- <u>Pre-morbid Anxiety Disorder</u>:
  - Consider SSRI augmentation or increase
- <u>*Co-morbid Delirium</u>:
  - Avoid Benzodiazepines

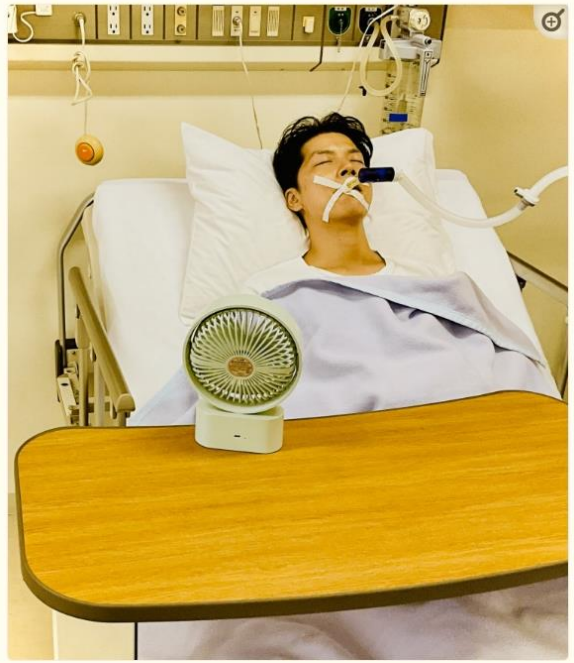
- *Assess efficacy at expected peak level depending on route (IV/IM/PO)*
- *Optimize dose before switching agents*
- *Consider dosing prior to tasks (e.g. physical therapy)*

Non-Pharmacological Interventions

Acute Interventions

- Pursed lip breathing [1,2]
- Positional Changes [3]
- Air flow/Fan [4, 5]
- Music therapy [6]
- Education, reassurance, validation

Figure 1



Fan therapy

Fan therapy consists of holding the fan at a convenient distance from the face and directing the wind to the areas innervated by the second and third branches of the trigeminal nerve.

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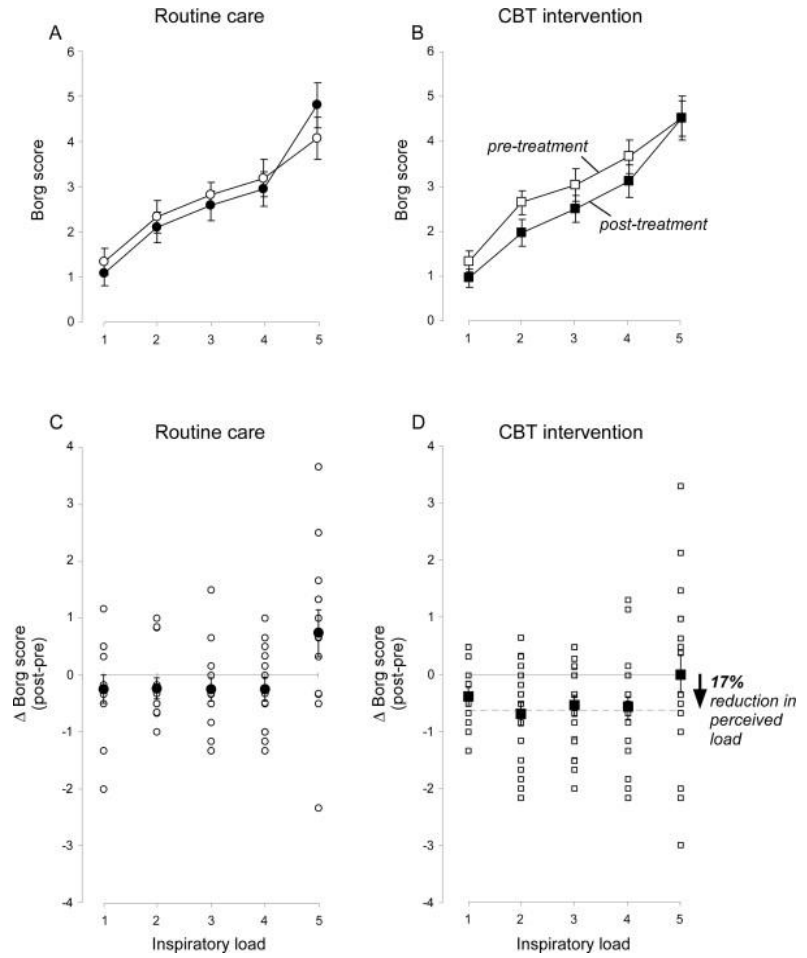
Non-Pharmacological Interventions

Outpatient Interventions

- **Pulmonary Rehabilitation**
  - Improves dyspnea and anxiety [1,2]
  - Superior improvement in dyspnea in patients with co-morbid anxiety and depression [1]

- **Cognitive Behavioral Therapy (CBT)**
  - Meta-analysis of 16 RCTs found significant improvement in anxiety, QOL, ED visits after CBT [3]



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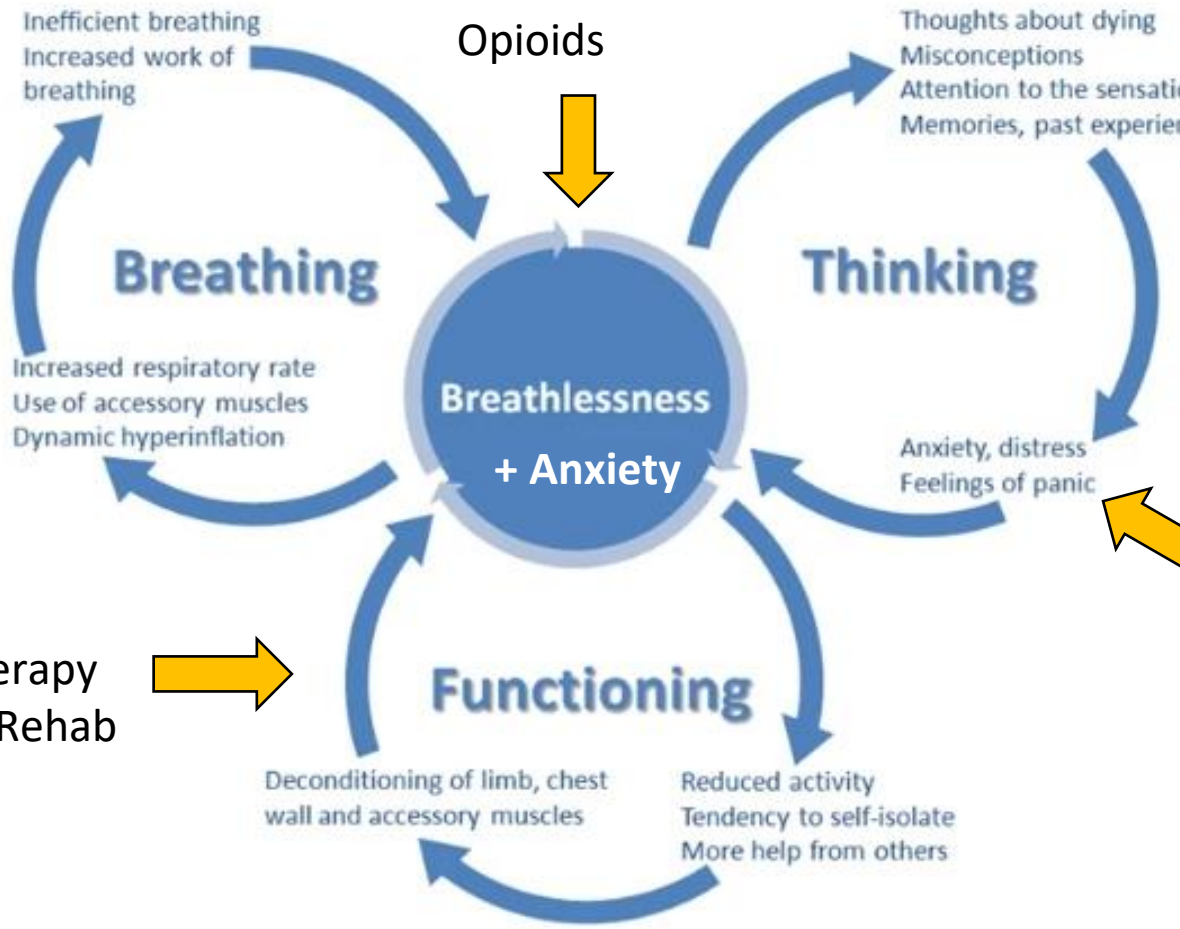
Dyspnea Associated Anxiety

Ventilator Setting Adjustment
O2
Opioids

Reassurance, Validation,
Education
CBT

Pursed lip breathing
Positional Changes
Cool Air



Physical Therapy
Pulmonary Rehab

Pharmacologic Strategies
- Antipsychotics
- Alpha 2 Agonists
- Antihistaminergic
- Gabapentinoids
- SSRI
- Benzodiazepines

Music Therapy
CBT

Pain, Delirium, Sleep, ABCDEF Bundle
Reduce Communication Barriers, Isolation

Thank you!

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