Mirtazapine for chronic breathlessness? A review of mechanistic insights and therapeutic potential

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Abstract

Introduction

Chronic breathlessness is a common and distressing symptom of advanced disease with few effective treatments. Central nervous system mechanisms are important in respiratory sensation and control. Consequently, drugs which may modify processing and perception of afferent information in the brain, may have a role. Antidepressants have been proposed, however current evidence is limited. Of potentially suitable antidepressants, mirtazapine is an attractive option given its tolerability profile, low cost and wide availability, along with additional potential benefits.

Areas covered

The paper provides an overview of the physiology of breathlessness, with an emphasis on central mechanisms, particularly the role of fear circuits and the associated neurotransmitters. It provides a potential rationale for how mirtazapine may improve chronic breathlessness and quality of life in patients with advanced disease. The evidence was identified by a literature search performed in PubMed through to October 2018.

Expert commentary

Currently, there is insufficient evidence to support the routine use of antidepressants for chronic breathlessness in advanced disease. Mirtazapine is a promising candidate to pursue, with definitive randomised controlled trials required to determine its efficacy and safety in this setting.

Key words

chronic lung disease, chronic breathlessness, breathlessness perception, mirtazapine, antidepressant

1. Introduction

Breathlessness is a common and distressing symptom of advanced disease, affecting most people living with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) [1, 2, 3]. Breathlessness is 'a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity'[4]. Chronic breathlessness has recently been defined as 'breathlessness that persists despite optimal treatment of the underlying pathophysiology and results in disability for the patient'[5]. Refractory breathlessness is another term used to describe breathlessness that persists despite optimal treatment of the underlying condition[6]. Chronic or refractory breathlessness is often accompanied by episodic breathlessness, defined as 'a severe worsening of breathlessness intensity or unpleasantness beyond usual fluctuations in the patient's perception'[7].

Whilst non-pharmacological interventions take priority initially, the more severe the breathlessness is, the more likely the need for pharmacological treatment[8, 9]. Currently no drugs are licenced for chronic or refractory breathlessness[10]. The benefit of oxygen in the absence of hypoxia remains unclear with evidence from larger trials required[11, 12], and whilst benzodiazepines are sometimes used to treat breathlessness-related anxiety, there is no evidence that they relieve breathlessness itself in people with advanced cancer and COPD[13]. There is evidence to support the use of parental and oral opioids[14]. However, optimal dosing, titration and potential issues arising from long-term use and safety remain to be determined[13, 15, 16, 17, 18]. Further, not all patients are suitable for, want to take, or respond to opioids, and clinicians can be reluctant to prescribe them[17, 19, 20, 21, 22]. Thus, new effective treatments are required.

Breathlessness is multidimensional, comprising distinct sensory (intensity / qualitative) and affective/cognitive components that can be manipulated and measured independently of each other[23, 24, 25, 26]. Consequently, drugs which may modify processing and perception of afferent information in the brain, may have a role. This may be a mechanism of action for opioids. Antidepressants have been proposed, however current evidence is limited[27, 28, 29, 30, 31]. Recently published data found no benefit when sertraline (a selective serotonin reuptake inhibitor antidepressant (SSRI)) was compared to placebo in patients with a Modified Medical Research Council (mMRC) Dyspnea Scale grade of two or above[31]. Mirtazapine is a common antidepressant which is acceptable in the advanced disease population. Its actions on multiple relevant neurotransmitter systems distinguish it from other antidepressants, and this, alongside a favourable side effect profile, make it a promising candidate to explore in the treatment of chronic breathlessness.

The paper reviews the physiology of breathlessness, with an emphasis on central mechanisms, in particular the role of fear circuits, and the associated neurotransmitters. We consider how one particular antidepressant, mirtazapine may improve chronic breathlessness and quality of life in patients with advanced disease. The evidence was identified by searching for key terms in published databases including PubMed through to October 2018. Additional papers were identified through citation searches and expert opinion. Evidence was included based on the consensus of the research team regarding quality and relevance to the review question. Whilst we recognise the relationship between depression, anxiety and breathlessness[32, 33, 34, 35, 36, 37, 38, 39], exploring how treatment of a concurrent mood disorder may affect chronic breathlessness is beyond the scope of this paper. This paper focuses on how mirtazapine may affect the experience of breathlessness in those both with, and without a mood disorder.

2. Mechanisms of breathlessness

2.1 Physiology

The mechanisms of breathlessness are complex and incompletely understood, but are thought to encompass interactions between multiple physiological, psychological, social, and environmental factors[4, 40]. There is evidence that qualitative appraisal of respiratory sensations is mechanistically distinct to breathlessness intensity[23, 41].

Theories about breathlessness perception can generally be divided into two categories. In the first, breathlessness is explained as being driven by cortical integration of an ascending copy of the descending motor activity to respiratory muscles (the 'neural respiratory drive' (NRD)) together with feedback from respiratory sensory afferents[4]. The second category presents the theory of interoception, where the brain generates sensations (priors) based on expectations learnt from past experience. These priors are then compared against incoming afferent signals to generate a symptom experience[48].

Patient-reported breathlessness intensity in chronic respiratory disease has been shown to be closely related to increased levels of NRD, reflecting the increased load on, and/or reduced capacity of, the respiratory muscles as a consequence of impaired respiratory mechanics[42, 43, 44, 45]. These observations support the hypothesis that the perception of breathlessness intensity in humans is mechanistically linked to the awareness of increased NRD as sensed by increased 'central

corollary discharge', which refers to the simultaneous projection of resultant neural signals from the motor cortex and/or respiratory centres of the brainstem to the respiratory muscles and sensory areas of the brain[46, 47]. Distinct sensations of breathlessness, most importantly "work/effort", "air hunger" ("unsatisfied inspiration"/"urge to breathe") and "chest tightness", are however likely to originate from central integration of differing sources of afferent information[4, 40, 45].

Neuroimaging studies are beginning to elucidate complex interactions between neural networks underpinning emotional and sensory perception of breathlessness, offering important insights into the role of higher cortical processing in respiratory sensation[48, 49, 50, 51, 52, 53]. Initial studies of induced breathlessness in healthy volunteers have confirmed activation of the insula, amygdala and anterior cingulate cortex, areas of the brain known to be active during perceived threat, with processing of the affective unpleasantness of perceived dyspnea in the right anterior insula and amygdala[48, 49, 50, 53]. In addition it has recently been shown that simply observing dyspnoea in others can elicit dyspnoea, negative affect and increased brain responses in the absence of physiological changes[54]. This supports the idea that central brain processes can elicit or intensify the experience breathlessness. More recently, studies have included people with chronic lung disease. A feasibility study of magnetoencephalography scanning found increased β band activity indicating constant 'vigilance', or an anticipatory state with regard to peripheral respiratory stimuli[55], and preliminary findings from a fMRI feasibility study suggest that the degree of disconnection between the left anterior insula and dorsal anterior cingulate cortex correlates with unpleasantness/discomfort of breathlessness (Meng D, Cottam W, Weller J, et al. European Society of Radiology Congress; 2018; Vienna, Austria).

2.2 Fear circuits and the perception of threat

The regions identified in the above studies closely relate to neurological circuits involved in threat perception and the experience of fear[48, 50, 53]. The ability to perceive threat is vital for survival. The response to threat is multi-faceted and regulated by numerous neuronal connections entering and leaving the amygdala (Figure 1). These pathways are responsible for the motor and endocrine features of the 'fight or flight response', combined with the conscious perception of fear[56, 57]. The fight or flight response is mediated by neuronal transmission from the amygdala to the periaqueductal grey area. Ongoing transmission to the hypothalamus and areas of the brainstem results in a rapid release of cortisol, and an autonomic response is triggered by the locus coerulus which can include an increase in heart rate and blood pressure[57]. The emotional response to a

threat involves neural transmission between the amygdala, the orbitofrontal cortex and the anterior cingulate cortex [58]. Given the potential role of fear circuits in the perception of breathlessness, drugs acting within these regions such as mirtazapine may be beneficial. This is further discussed in section 3.2.

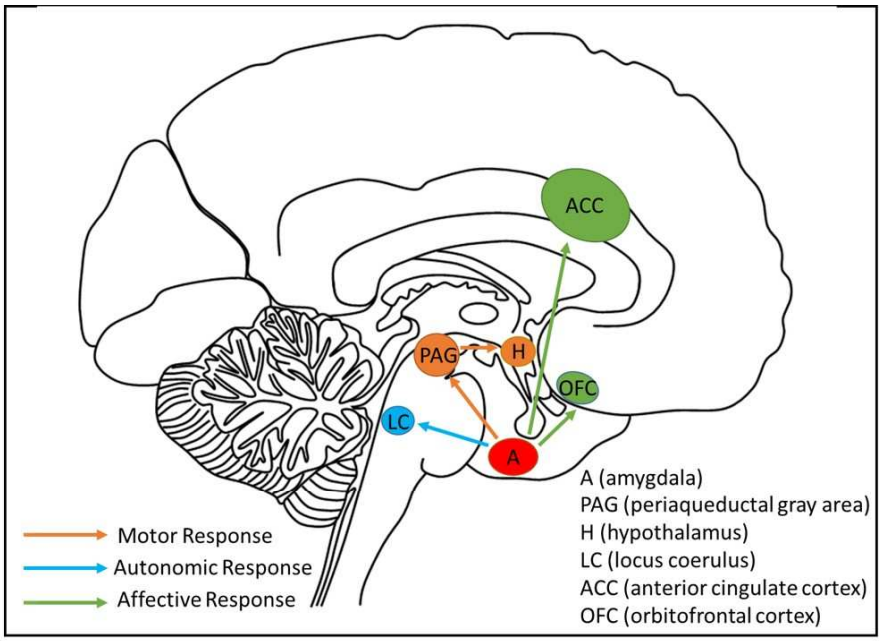

Figure 1: Fear circuits and the amygdala

Motor response as neuronal transmission from the amygdala to the periaqueductal grey area, hypothalamus and areas of the brainstem.

Autonomic response triggered by the locus coerulus.

Affective response involves neural transmission between the amygdala, the orbitofrontal cortex and the anterior cingulate cortex.

Whilst fear is often experienced and forgotten, the amygdala assimilates stimuli associated with previous fearful situations, and when exposed to this stimuli again, triggers a response (fear conditioning)[57]. This could explain how an episode of breathlessness and severe panic may lead to recurrent panic when the patient is exposed to a similar trigger. During interoception the brain generates sensations referred to as priors based on expectations learnt from a past experience. These priors are then compared against incoming afferent signals to generate a symptom experience[59]. These interactions can be influenced by many factors including fatigue and depression[60], and recent work has demonstrated how a rehabilitation programme for breathlessness can lead to changes in associative learning and the resetting of breathlessness related priors[61]. A number of other factors have been associated with an increased perception of threat including the environment, psychiatric illness, and personality traits[62, 63, 64, 65].

2.3 The function of neurotransmitters in breathlessness

A number of neurotransmitters have been identified as important in breathlessness, in particular, serotonin (5-HT) and norepinephrine (NE). Other neurotransmitters (GABA, dopamine, acetylcholine and NMDA) may also play roles in symptom perception through their contribution to interoceptive processes.

5-HTplays a role in the central control of respiration via multiple receptor subtypes, contributing to chemosensitivity and mediating ventilatory response to changes in CO_2/pH, and by maintaining regulatory function as part of respiratory neuroplasticity[66, 67, 68, 69, 70, 71, 72]. 5-HT also regulates anxiety and panic through connections between the amygdala, and the prefrontal cortex, striatum and thalamus, and may therefore be important in the conscious perception of breathlessness[73]. An inhibitory effect on the amygdala results in suppression of fear circuits and thus drugs which increase 5-HT can reduce levels of anxiety and panic [57, 74]. Further, the importance of serotonergic modulation is suggested by a reduction in panic following administration of L-5-hydroxytryptophan (the immediate precursor of 5-HT), sertraline or citalopram to patients with panic disorder breathing a mixture containing 35% CO_2 [75, 76]. However, despite strong evidence of the role of serotonin in respiration, clinical benefit has not yet been demonstrated[31].

NE is important in neuronal connections between the amygdala and the locus coeruleus, the centre involved in generating the physiological response to stress and panic, e.g. increased heart rate, blood pressure and respiratory rate[57]. Whilst the role of NE during an acute stress is hyperactivity, chronic stress (for example in mood disorders) causes hypo-reactivity of the NE system[77], and in animal studies exposure to chronic stress has been correlated with a decrease in the release of NE in the brain, as well as atrophy of NE axonal projections[78, 79]. Further, venoarterial levels of NE and 3-methoxy-4-hydroxyphenylglycol (the metabolite of NE) are significantly lower in people diagnosed with depression compared to controls[80]. In addition a rise in circulating norepinephrine causes relaxation of bronchial muscles and a decrease in fluid secretion from bronchial glands therefore improving respiration[81, 82]. Other neurotransmitters of interest include endorphins[83], cannabinoids and neurokinin[84].

3. Mirtazapine for chronic breathlessness

3.1 Mechanism of action

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) which is well tolerated, relatively cheap and available in generic form worldwide[85, 86, 87]. Mirtazapine antagonizes α_2 auto- and hetero-receptors resulting in enhanced noradrenergic transmission and reduced inhibition of 5-HT release (Figure 2)[88, 89]. NE release in the raphe nuclei also stimulates postsynaptic α_1 receptors of neuronal cell bodies, causing 5-HT release from downstream axon terminals such as those in the cortex (Figure 2)[57]. This enhanced noradrenergic and serotonergic transmission is mostly responsible for the antidepressant and anxiolytic effects of mirtazapine.

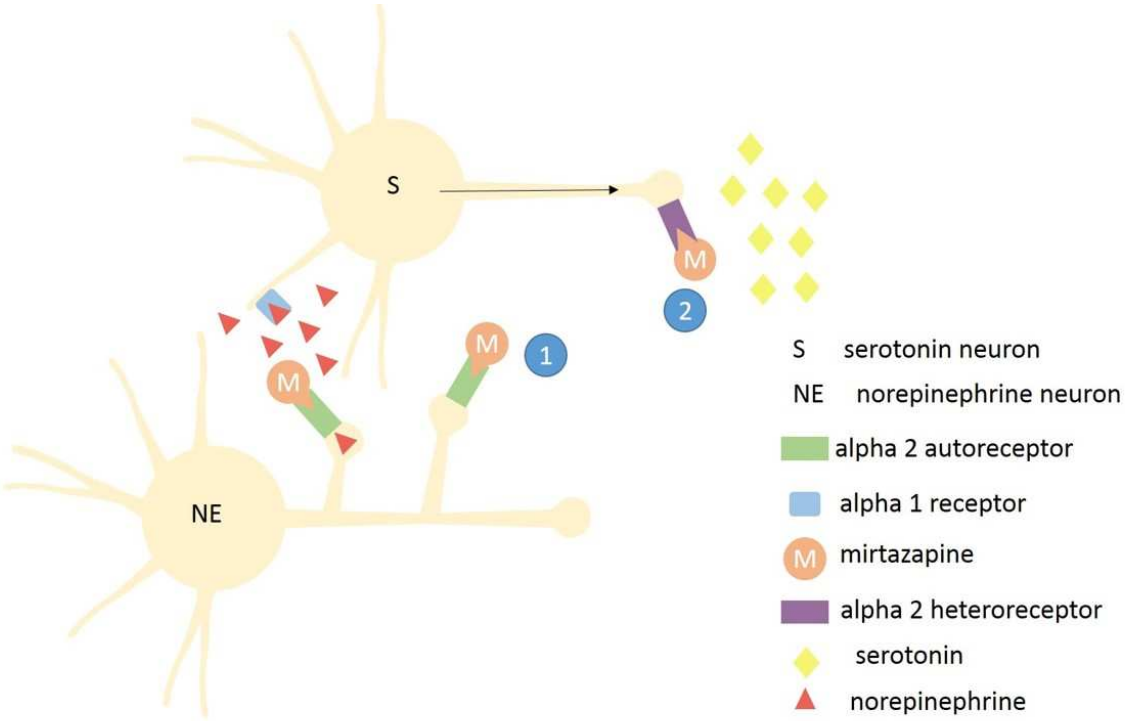

Figure 2: Mechanism of action of mirtazapine: (1) Blockade of α-2 autoreceptors increases synaptic norepinephrine, stimulating α1 receptors and resulting in serotonin release. (2) Blockade of α2 heteroreceptors reduces inhibition of serotonin release (adapted from Stahl's essential psychopharmacology 2013.)

Mirtazapine also antagonizes 5-HT_2 and 5-HT_3 receptors and as a consequence, unlike with SSRIs, gastro-intestinal effects (e.g. nausea, diarrhoea) and sexual dysfunction are uncommon[89]. It is a potent antagonist of histamine H_1 receptors[88] explaining the most common side effects of somnolence, increased appetite and weight gain[86]. At higher doses, sedation is less commonly reported, possibly due to increased noradrenergic transmission counteracting the antihistamine effect. It is not known to be associated with a reduced respiratory drive which is an advantage in chronic lung disease management[90]. It is worth noting that mirtazapine is metabolized by CYP1A2, CYP2D6, and CYP3A4 and caution should be taken with concurrent use of drugs which inhibit or induce these enzymes. This should be considered in a population likely to have high levels of comorbidity and polypharmacy[91].

Mirtazapine is authorised for the treatment of depression; additional beneficial effects on anxiety, psychological distress and sleep disturbance are seen compared with placebo[92]. Mirtazapine is significantly more effective at treating depression at two weeks compared to selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) [93]. A systematic review and meta-analysis of the efficacy and acceptability of 21 antidepressant drugs in adults with depression found that mirtazapine had a higher response rate and lower dropout rate than the other antidepressants when compared with placebo[85]. Although an anxiolytic effect has been demonstrated for mirtazapine[94], it is not currently authorised for the treatment of anxiety disorders. It is however, free from the initial worsening of anxiety or agitation that can occur with SSRIs.

3.2 Mirtazapine as a treatment for breathlessness and other symptoms in chronic lung disease

Mirtazapine may benefit chronic breathlessness indirectly through known effects on mood. However, mirtazapine may also have direct beneficial effects, through inhibition of fear circuits and fear conditioning, and by causing bronchodilation. Even in healthy volunteers, mirtazapine has rapid effects. Two hours after a single dose of mirtazapine, there are changes in keeping with a decreased processing of threatening stimuli, an increased processing of positive or rewarding stimuli and reduced self-referential processing[95, 96, 97, 98]. At the neural level, there are decreased right amygdala-hippocampal and fronto-striatal responses to fearful vs. happy facial expressions, increased responses of the parietal cortex to a reward task, and reduced responses in the dorsomedial prefrontal cortex, ventromedial prefrontal cortex and ventral anterior cingulate cortex, considered the self-referential network[95, 97, 98]. In response to more natural and complex

emotional stimuli, mirtazapine leads to large-scale changes spanning limbic, sensorimotor and cortical midline structures[99]. Taken together, these changes suggest that mirtazapine impacts rapidly on neural circuits involved in vigilance and the perception of, and the emotional response to, unpleasant stimuli (of which breathlessness is one) through the process of interoception.

In addition mirtazapine may benefit additional symptoms common in this population. Mirtazapine is a potent antagonist of histamine and therefore common side effects including somnolence, increased appetite and weight gain may be of benefit to patients with chronic lung disease who frequently report sleep disturbance, poor appetite and weight loss[86, 88, 100, 101]. Further, depression, anxiety and panic are common in this group, and associated with increased healthcare utilisation[32, 33, 34, 35, 36, 37, 38]. Generally, mood disorders are underdiagnosed and thereby undertreated in the medically ill. In a large study of 1334 people with chronic lung disease, 80% screened positive for depression, anxiety or both, yet only 31% were receiving treatment for anxiety or depression[39]. Thus, by treating an underlying anxiety or depressive mood disorder, mirtazapine may have beneficial effects on the emotional and behavioural response to chronic breathlessness[57].

Conclusions

In addition to its known effects on mood, Mirtazapine has effects that are potentially beneficial for the management of chronic breathlessness, predominantly by modifying the processing and perception of afferent information in the brain. Mirtazapine is an attractive candidate to explore as is well-tolerated, affordable and available, with a quick onset of action. Antagonism of 5-HT_2 and 5-HT_3 receptors means mirtazapine does not share some of the common side effects of other commonly used antidepressants, and antagonism of H1 receptors can result in improved appetite and sleep which may be beneficial in patients with advanced disease. High quality evidence from definitive randomised controlled trials is needed to determine the effectiveness of mirtazapine, on the distressing and common symptom of chronic or refractory breathlessness.

Expert Commentary

Chronic breathlessness remains a common and distressing symptom of advanced disease with few effective treatment options. Whilst there is evidence to support the use of parental and oral opioids, not all patients report benefit, and long term safety data is currently lacking. The goal should be to

identify new effective treatments so that clinicians and patients have more options. In recent years thinking has moved towards drugs which may modify the processing and perception of afferent information in the brain, such as antidepressants. The repurposing of existing inexpensive medications that are off patent and widely available is an attractive option, however, data remains limited. Mirtazapine is a promising candidate, but there is currently insufficient evidence to support use to treat breathlessness in clinical practice. The concern is that clinicians may nevertheless opt to give antidepressants including mirtazapine for chronic breathlessness, particularly as they are inexpensive and off patent. It is important to ensure that patients are not being given medicines that are ineffective in treating breathlessness. Blinded randomised controlled trials are therefore urgently needed to provide appropriate evidence on the effectiveness of mirtazapine in reducing breathlessness in patients with and without depression and anxiety.

Five-year view

In the next 5 years we anticipate that blinded randomised trials will be conducted to determine the effectiveness of antidepressants including mirtazapine to treat chronic breathlessness. Results of these trials will aid national and international clinical guidelines and policy recommendations by providing a much needed evidence base.

Key issues

- Chronic breathlessness remains a common and distressing symptom of advanced disease with few effective treatment options
- Whilst there is evidence to support the use of parental and oral opioids, not all patients report benefit, and long term safety data is currently lacking
- Therefore new effective treatments are urgently needed
- In recent years thinking has moved towards drugs which may modify the processing and perception of afferent information in the brain, such as antidepressants
- Mirtazapine is a promising candidate, but there is currently insufficient evidence to support routine use to treat breathlessness in clinical practice
- Definitive randomised controlled trials are needed to provide evidence to guide clinical practice

Conflict of Interest statement:

The authors declare that they have no conflict of interest.

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