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Review of the literature

Panic and pandemic: Narrative review of the literature on the links and risks of panic disorder as a consequence of the SARS-CoV-2 pandemic

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ABSTRACT

Although the "panic" word has been abundantly linked to the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pandemic in the press, in the scientific literature very few studies have considered whether the current epidemic could predispose to the onset or the aggravation of panic attacks or panic disorder. Indeed, most studies thus far have focused on the risk of increase and aggravation of other psychiatric disorders as a consequence of the SARS-CoV-2 epidemic, such as obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and generalized anxiety disorder (GAD). Yet, risk of onset or aggravation of panic disorder, especially the subtype with prominent respiratory symptoms, which is characterized by a fear response conditioning to interoceptive sensations (e.g., respiratory), and hypervigilance to these interoceptive signals, could be expected in the current situation. Indeed, respiratory symptoms, such as coughs and dyspnea, are among the most commonly associated with the SARS-CoV-2 (59–82% and 31–55%, respectively), and respiratory symptoms are associated with a poor illness prognosis. Hence, given that some etiological and maintenance factors associated with panic disorder – i.e., fear conditioning to abnormal breathing patterns attributable or not to the COVID-19 (coronavirus disease 2019), as well as hypervigilance towards breathing abnormalities – are supposedly more prevalent, one could expect an increased risk of panic disorder onset or aggravation following the COVID-19 pandemic in people who were affected by the virus, but also those who were not. In people with the comorbidity (i.e., panic disorder or panic attacks and the COVID-19), it is particularly important to be aware of the risk of hypokalemia in specific at-risk situations or prescriptions. For instance, in the case of salbutamol prescription, which might be overly used in patients with anxiety disorders and COVID-19, or in patients presenting with diarrhea and vomiting. Hypokalemia is associated with an increased risk of *torsade de pointe*; thus, caution is required when prescribing specific psychotropic drugs, such as the antidepressants citalopram and escitalopram, which are first-line treatments for panic disorder, but also hydroxyzine, aiming at anxiety relief. The results reviewed here highlight the importance of considering and further investigating the impact of the current pandemic on the diagnosis and treatment of panic disorder (alone or comorbid with the COVID-19).

1. Introduction

The current SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pandemic is likely to induce, beyond its potentially dramatic impact on health, serious psychological consequences, particularly in terms of the often reported "panic" state it triggered, and the medical disorder potentially linked to this state, i.e., panic disorder [1–5]. Paradoxically, empirical data on the relationship between panic disorder and COVID-19 (coronavirus disease

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2019) are lacking. This may seem all the more counter-intuitive since the respiratory consequences of COVID-19 are well identified and panic attacks occurring in the context of panic disorder may have a marked respiratory component. In this review, we propose to address: (i) the way in which the international literature has used to date the terminology of "panic" in relation to the SARS-CoV-2 pandemic; (ii) the very concept of panic attack, panic disorder and the specificity of the respiratory component frequently associated with it; (iii) and finally, a synthesis of the links and risk factors between COVID-19 and "respiratory" panic disorder.

2. Panic? Did you say panic? How does the medical-scientific literature connect the current pandemic with the terminology of "panic"?

As of 30/04/2020, the literature had abundantly linked the SARS-CoV-2 pandemic with the polysemic term "panic" – we identified 35 references linking COVID-19 (or SARS-CoV-2) and the "panic" word. The latter is used to describe both a global, unspecified state of panic in the population (leading to qualifiers such as "social panic", "societal panic", "panic reactions") (16 references), but also a panic state that can take hold of the healthcare system itself (3 references). This terminology was also used to describe the population's reactions to all the media, whether the information is authentic or erroneous (7 references), or to describe inappropriate behavior (abandoning animals and "panic buying") (5 references). Only one publication to date offered an actual assessment of the "level of panic", and described it as significantly higher in females than males elderly subjects and their caregivers in Arkansas [1].

Surprisingly, this wealth of literature, which does not define "panic" in its strict medical sense as a well-defined entity within the context of anxiety disorders, seems to have neglected the link between panic attacks, panic disorder and COVID-19. Data from psychiatric journals evoking "panic" in the sense of a psychological disorder linked to the current pandemic, mention it only as an example of anxiety disorders, without further developing the relevance of such a link [2–5] and occasionally bringing it closer to a more societal and therefore collective dimension (see for example: "mass hysteria and [the] panic reactions near pandemonium" [4]).

Among other anxiety disorders, the risks of their emergence are well anticipated, such as post-traumatic stress disorder (PTSD) (see e.g. [5,6]) or obsessive-compulsive disorder [7,8]. Assessments of anxiety disorders have also been conducted using the 7-item Generalized Anxiety Disorder Scale (GAD-7; Generalized Anxiety Disorder-7) [9,10].

Thus, panic disorder is hardly mentioned as an immediate or as a long-term consequence of the current pandemic. This state of affairs seems paradoxical for several reasons. On the one hand, cough-like symptoms and dyspnea appear at high frequencies (59 to 82% and 31 to 55%, respectively) and are potentially identified by patients as elements at risk of unfavorable COVID-19 evolution due to the fear, known or intuitive, of a progression towards an acute respiratory distress syndrome (ARDS) [11]. From a psychopathological standpoint, the etiology and maintenance factors of panic disorder are also linked to conditioned "false alarms", associated with catastrophic interpretations of changes in physiological sensations, such as respiratory rhythm [12].

On the other hand, the link between the recurrence of panic attacks in the context of panic disorder and a potentially respiratory origin has been established, particularly since the 1980s and even more so with Klein's theory in the early 1990s, to which we shall return [13].

3. Panic attacks, panic disorder and the respiratory component

Da Costa's syndrome was associated with one of the pioneering descriptions of panic attacks which were characterized by unpleasant sensations, such as dizziness, dyspnea and palpitations, chest tightness and anxiety [14].

In 1895, Freud described that "the memory of an anxiety attack is often encountered, and in truth what the patient fears is the event of such an attack in the special conditions from which he believes he cannot escape it" [15]. This description partly underpinned the early theories of panic disorder as a condition characterized by a "fear of being afraid" in models derived from "classical conditioning", based on "interactive conditioning", as in Goldstein and Chambless (1978); this model later integrated specific cognitive distortions characterized by hypervigilance towards specific physical manifestations [12]. Cognitive models proposed later (Beck and Emery [1985], Clark [1988] and Barlow [1988]) have integrated behavioral and cognitive aspects of the disorder, especially its hypervigilance of physical sensations component (the basis of integrative conditioning). Hence, the learned alarm reaction is an adaptive physiological response to a "stressor" but might lead to the repetition of panic attacks in panic disorder [12].

In 1993, Donald Klein drew on the observation of CO2 hypersensitivity in patients with panic disorder to propose an etiological hypothesis known as the false suffocation alarm theory [13]. According to this hypothesis, panic attacks occur when some form of central suffocation "monitor" mistakenly signals a lack of air that inappropriately triggers an advanced alarm system. The sensitivity of the brain to CO2 as a panicogenic stimulus could be explained by the fact that an increase in pCO2 (partial pressure of CO2) suggests that suffocation is imminent. Moreover, animal and human models of panic attacks incorporate pharmacological tools that may more or less destabilize respiratory function (doxapram, CO2, sodium lactate, CCK-4, yohimbine, caffeine, corticotropin-releasing hormone [CRH]). [13,16].

The importance of the respiratory component in anxiety in general [17], and in panic disorder in particular, is well known [16,18–22]. The link between the intensity of hyperventilation, dyspnea, and perceived anxiety, and fear of suffocation anticipation, has also been established [23–27]. In 1985, Ronald Ley proposed a hyperventilation theory of panic attacks ("fear of dyspnea theory") and was the first to propose a classification into "subtypes" of these clinical phenomena [28]. Type 1 "classical or respiratory" subtype was characterized by fear, dyspnea and palpitations [28,29]. Subtypes of panic disorder were proposed by Briggs and his colleagues in 1993, making it possible to identify for the first time a "respiratory" subtype of this disorder [30]. The very legitimacy of the individualization of such a disorder is still questioned in the literature [30–33], but certain characteristics can nevertheless lead to a consensus in favor of a "respiratory" panic disorder subtype, such as the increased sensitivity to CO2 and the higher incidence of a family history of panic disorder in these patients, compared to patients with panic disorder described as "non-respiratory" [32,33]. Whether the therapeutic response (to antidepressants, benzodiazepines and cognitive behavioral therapy–CBT) is different in these subtypes remain to be clearly established [33].

Deakin and Graeff (1991) have proposed a neurobiological hypothesis, and several experiments have shown that serotonergic neurons in the nucleus of the dorsal and ventrolateral trophea and the ventrolateral periaqueductal grey matter behave as central chemoreceptors and modulate the behavioural and cardiorespiratory response to panicogenic agents such as sodium lactate and CO_2 [34]. Neuroimaging studies have identified the hippocampus, the medial prefrontal cortex, the amygdala and its projections into the brainstem as an abnormally sensitive in panic disorder [30,31]. In

addition, certain structures of the brain stem, which are minimally or preferentially involved in the respiratory forms of panic disorder, have been identified: (i) the periaqueductal grey matter as a central suffocation alarm system [34]; (ii) the parabrachial nucleus, connected to the "network of fear", in particular through the amygdala, which controls the respiratory rate [31].

4. COVID-19 and respiratory panic disorder: what are the possible risks and links?

PTSD and panic disorder are usually presented in opposition: PTSD is conditioned by the traumatic event that causes the flashbacks, whereas panic disorder can be thought of as "unconditioned" given that panic attacks seem to occur spontaneously and unexpectedly, with no apparent trigger. Ronald Ley's conceptualization of panic attacks in the 1980s helped to establish the idea of panic – type 1 disorder which is also referred to as "respiratory", "spontaneous" and occurring "unexpectedly" [29]. However, these data are inconsistent with other findings. On the one hand, generally speaking, the very notion of the absence of a conditioned response in panic disorder is widely contested. Indeed, many studies have put forward that fear is conditioned by the presence of specific physiological sensations [12]. On the other hand, suffocation traumas may be the secondary cause of panic disorder with predominantly respiratory symptoms [35,36]. In 1997, Bouwer and Stein demonstrated that among patients with panic disorder, those with a history of traumatic suffocation were significantly more likely to have "respiratory" panic disorder subtype, compared to those who had not experienced this kind of event (they presented with more cardiovascular or occulovestibular symptoms or agoraphobia); these data are hence consistent with the hypothesis of a hypersensitivity to suffocation, which is directly linked to traumatic conditioning [36].

Somatic conditions causing dyspnea, such as asthma, can also shed new light on the link between anxiety and the respiratory difficulties that patients are likely to experience during COVID-19.

Generalized anxiety disorder (GAD) and panic disorder are significantly more frequent in patients with chronic obstructive pulmonary disease (COPD; mainly chronic bronchitis and emphysema) [37]. The link between asthma and panic disorder has been the subject of a large body of literature that addresses in particular: (i) the intuitive link between the fear of suffocation theory in the respiratory forms of panic disorder and the dyspnea observed in asthma [38,39]; (ii) the fact that psychiatric comorbidities, including anxiety disorders such as panic disorder, are common in patients with moderate to severe asthma and (iii) the fact that panic disorder may be associated with poorer asthma management [40,41]. Conflicting data exist, however, which show no link between asthma and mental disorders, but describe instead an association between seasonal allergies and psychiatric disorders, including panic disorder [42]. Moreover, the link between panic disorder and the severity of asthma seems to be based on psychosomatic components only, since studies have shown that patients suffering from panic disorder have asthma with more dyspnea without disturbing the spirometric parameters (forced expiratory volume per second in particular) [43,44]. These data support the hypothesis that panic disorder associated with asthma contributes to a catastrophizing of body symptoms, rather than an aggravation of the pathophysiology of respiratory disease [45]. Finally, it should be noted that elements of asthma complication may aggravate the feeling of respiratory distress. For example, smoking and asthmatic cough can increase the severity of anxiety and panic disorder in particular [46,47].

In the context of the SARS-Cov-2 infection, the respiratory symptoms reported by patients are both frequent and experienced as highly anxiety-provoking (fear of suffocation, anticipation of the highly pejorative consequences of such symptoms and their potential consequences (hospitalization in intensive care, intubation, death).

A recent study on the consequences of the COVID-19 pandemic among 1210 people in China found that sore throat, cough, and breathing difficulties during the past 14 days were significantly associated with higher scores on the DASS-21 anxiety and depression subscales (e.g., 21-item Depression, Anxiety and Stress Rating Scale) [48].

These results suggest two main potential consequences of the pandemic: (i) the accentuation of catastrophic interpretations focusing on disturbed breathing and the aggravation of panic attacks in patients with "respiratory" panic disorder; or greater psychological repercussions in these patients in the event of COVID-19; (ii) possible secondary consequences of the pandemic include an increased proportion of "respiratory" panic disorders due in particular to hypervigilance on breathing symptoms.

Beyond panic disorder, legitimate caution should also be considered in patients already suffering from a chronic anxiety disorder with a respiratory component. This poorly characterized nosography incorporates a number of terms such as: hyperventilation syndrome, psychogenic dyspnea, or central neuronal hyperexcitability syndrome. These patients should be closely monitored, as these anxiety symptoms may transform into panic respiratory disorders.

Finally, respiratory panic disorders, like the psychogenic dyspnoea and related syndromes run the risk of being inadequately treated with psychotropic drugs and anti-asthmatic treatments that may reinforce the patient's erroneous beliefs about the origin and/or severity of his/her respiratory symptoms. In addition, it may be associated with drug overuse [49,50].

Benzodiazepine overuse, beyond the problem of addiction, can be dangerous in at least two ways. First, it may be involved in the long-term maintenance of panic disorder [51]. Several studies have demonstrated the adverse effects of chronic use of high potency benzodiazepines (such as alprazolam) on the short and long-term outcomes of cognitive behavioral treatments (CBT) for panic disorder [51]. Specifically, benzodiazepines, because of their rapid onset of action may contribute to long-term relapse, either by decreasing motivation to engage in CBT or because therapeutic success will be likely attributed to medication and not to the patient himself [51]. In other words, they can lead to immediate symptom relief but are not curative (i.e., body symptoms continue to be misinterpreted), contributing to the maintenance of fear and avoidance in the long term [51]. Second, benzodiazepines have a known risk of inducing respiratory depression, which is particularly relevant in the context of the SARS-CoV-2 pandemic [11]. The use of benzodiazepines can cause respiratory distress (severe respiratory insufficiency, sleep apnea syndrome, overdose), and the prevalence of dyspnea during COVID should also encourage the anticipation of other risk situations, including high doses of high-potential benzodiazepines, as well as situations of risk associations of several central nervous system depressants [11]. Hence, patients presenting with both respiratory panic disorder and substance abuse (e.g., high dose benzodiazepines and morphine) are likely to be particularly at risk. Overall, the risk of benzodiazepine-induced respiratory depression during COVID should not be overlooked (for patients with a combination of risk factors) or misinterpreted (with regard to the benefit of these treatments for anxiety, including in situations of dyspnea) [11,52].

Asthma treatments are mainly based on the use of short-acting inhaled beta-2 mimetics – treatment of the attack – and on a potential background treatment that may combine inhaled corticosteroids and long-acting β-stimulants. Short-acting β-stimulants, such as salbutamol (or albuterol), are quickly identified

by patients as a treatment for their symptoms and may induce drug overuse [53,54]. In addition, depression, like anxiety, may be associated with overuse [49,50].

These elements are thus risk factors in subjects with co-morbid asthma and panic disorder (or the latter disorder alone misdiagnosed as asthma) specifically in the case of COVID-19. Indeed, among the symptoms of viral infection, diarrhea and vomiting may occur and represent a potassium leakage, leading to potential hypokalemia [11]. The interaction of SARS-CoV-2 with the renin-angiotensin-aldosterone system can also lead to significant hypokalemia [11]. Furthermore, hypokalemia is also a well-identified risk with β2-agonist treatments, particularly at high doses and/or when other therapies are administered simultaneously, or in pathophysiological, hypokalemia-causing situations. One should be particularly aware of the combination of risk factors for hypokalemia and the risk of excessive prolongation of QTc and, ultimately, of torsades de pointes [11]. This is all the more the case in mental health settings because of the frequent prescription of treatments such as citalopram and escitalopram – both are first-line treatments for panic disorder – and treatments such as cyamemazine or hydroxyzine – regularly used for anxiolytic purposes. It should be noted that some treatments potentially prescribed for COVID-19 might also contribute to QT prolongation: (hydroxy)chloroquine ± azithromycin combinations, mainly, but also the lopinavir/ritonavir combination [11,55].

5. Discussion/conclusion

Overall, our review considers the evolution of patients suffering from anxiety disorders with a pre-existing respiratory focus. Patients suffering from panic disorder that can be described as "respiratory" should be given appropriate therapeutic follow-up. The use of psychotropic drugs with anxiolytic aims, mainly benzodiazepines, but also antiasthmatics of the salbutamol type may prove counterproductive or even dangerous for the development of anxiety disorders, but also with regard to the SARS-CoV-2 pandemic. Specifically related to the latter aspect, the risk of hypokalemia must be anticipated given the multiple risk factors in patients with panic disorder and potential asthma: (i) the use of high-dose salbutamol; (ii) SARS-CoV-2 infection and even more so in the event of digestive symptoms (diarrhea and vomiting). This is related to the fact that hypokalemia increases the risk of QTc prolongation and that patients with mental disorders, particularly panic disorder, can receive treatments that increase the QT interval, i.e., (i) psychotropic drugs, such as citalopram and escitalopram, as well as hydroxyzine, or phenothiazines (chlorpromazine, cyamemazine, levomepromazine, propericiazine); (ii) but also with potential treatments of COVID-19, such as (hydroxy)chloroquine ± azithromycin combinations or the lopinavir/ritonavir combination [11].

Dyspnea, which is anxiety-provoking and probably even more so in a pandemic context, could lead to an increase in the prevalence of panic disorder, particularly the respiratory type. It is also likely that panic disorder with co-morbid agoraphobia cases might also increase, as a consequence of long-term lockdown that could reinforce dysfunctional avoidance behaviors.

The mechanisms involved in the physiological sensations associated with the feeling of an interoceptive threat, which might lead anxiety to become a panic attack, seems key to prevent the consequences of traumatic dyspneic experiences [25]. This is all the more important since, in the case of asthma, especially in its severe forms, traumatic experiences associated with a feeling of imminent death can develop into catastrophic cognitions and participate in the onset of panic disorder, and possibly even increase the risk of suicide [56].

Disclosure of interest

The authors declare that they have no competing interest.

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