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POSITION PAPER

Precision management of post-COVID pain: An evidence and clinical-based approach

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Abstract

Background: Pain after a SARS-CoV-2 acute infection (post-COVID pain) is becoming a new healthcare emergency but remains underestimated and most likely undertreated due to a lack of recognition of the phenomenon and knowledge of the underlying pain mechanisms. Evidence supporting any particular treatment approach for the management of post-COVID pain is lacking. Large variability in the patient response to any standard pain treatments is clinically observed, which has led to calls for a personalized, tailored approach to treating patients with chronic post-COVID pain (i.e. 'precision pain medicine'). Applying the global concerted action towards precision medicine to post-COVID pain could help guide clinical decision-making and aid in more effective treatments.

Methods: The current position paper discusses factors to be considered by clinicians for managing post-COVID pain ranging from identification of the pain phenotype to genetic consideration.

Results: The ability of clinicians to phenotype post-COVID pain into nociceptive, neuropathic, nociplastic or mixed type is suggested as the first step to better planification of a treatment programme. Further, the consideration of other factors, such as gender, comorbidities, treatments received at the acute phase of infection for onset-associated COVID-19 symptoms, factors during hospitalization or the presence of emotional disturbances should be implemented into a treatment programme.

Conclusions: Accordingly, considering these factors, management of post-COVID pain should include multimodal pharmacological and non-pharmacological modalities targeting emotional/cognitive aspects (i.e. psychological and/or coping strategies), central sensitization-associated mechanisms (i.e. pain neuroscience education), exercise programmes as well as lifestyle interventions (e.g. nutritional support and sleep management).

Significance: This position paper presents an evidence-based clinical reasoning approach for precision management of post-COVID pain.

1 | INTRODUCTION

The severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), responsible for the worldwide spread of coronavirus disease 2019 (COVID-19), has provoked the biggest health crisis of the current century. After billions of infections, healthcare professionals are now in front of a new health crisis, the development or persistence of symptoms after the acute phase of SARS-CoV-2 infection. In fact, more than 100 post-COVID symptoms affecting multiple systems, e.g. cardiovascular, neurological, respiratory or musculoskeletal, have been described (Hayes et al., 2021). Several meta-analyses have observed that up to 50% of subjects who had survived COVID-19 can exhibit a plethora of symptoms lasting for weeks or months (Chen, Haupert, et al., 2022; Fernández-de-las-Peñas, Palacios-Ceña, et al., 2021; Michelen et al., 2021) and up to 1 year after infection (Alkodaymi et al., 2022; Han et al., 2022).

Different studies identified that individuals with post-COVID pain represent a subgroup of patients (Diem et al., 2022; Global Burden of Disease Long COVID Collaborators et al., 2022; Peter et al., 2022). In fact, the term 'post-COVID pain syndromes' has been proposed due to the heterogeneity of symptoms (Fiala et al., 2022). In fact, the presence of post-COVID pain is associated with reduced health-related quality of life (Moens et al., 2022). However, the prevalence of post-COVID pain is not clearly defined in the current literature as it all depends on when the cross-sectional, prevalence studies are executed after the initial infection. A systematic review including studies investigating multiple long-COVID symptoms identified that 20% of COVID-19 survivors reported post-COVID pain at different follow-up periods during the first 6 months after infection (Fernández-de-las-Peñas, Navarro-Santana, Plaza-Manzano, Palacios-Ceña, & Arendt-Nielsen, 2022). However, the prevalence of post-COVID pain has been estimated at up to 60% of COVID-19 survivors in studies specifically investigating this symptom (Bakılan et al., 2021; Karaarslan et al., 2021; Soares et al., 2021). All these epidemiological studies did not differentiate either musculoskeletal or neuropathic post-COVID pain or post-COVID pain by body area, e.g. neck, headache or lower extremity. The only meta-analysis specifically investigating the prevalence of post-COVID headaches has reported a pooled prevalence ranging between 8.4% and 16.5% in the first 6 months after infection (Fernández-de-las-Peñas, Navarro-Santana, et al., 2021). Accordingly, pain appears to be highly prevalent among COVID-19 survivors and can be an underestimated post-COVID symptom.

For the current position paper, we conducted an electronic search for articles published up to January 1st, 2023, in MEDLINE, CINAHL, PubMed, EMBASE and Web of Science databases. The following search terms were used and combined using Boolean operators: 'long-COVID', 'post-COVID-19 condition', 'post-Acute COVID-19 syndrome' [MeSH], 'pain' [MeSH], 'post-COVID pain', 'phenotype' [MeSH], 'neuropathic pain', 'nociceptive pain' [MeSH], 'nociplastic pain', 'therapy' [MeSH], 'practice guideline' [MeSH], 'meta-analysis' [MeSH], 'systematic review' [MeSH] and 'risk factors' [MeSH].

2 | CURRENT MANAGEMENT OF LONG-COVID

The heterogeneous presentation of long-COVID and the presence of different phenotypes of patients make it highly difficult to find a proper treatment approach for this condition. A multidisciplinary management approach, as recommended in general for chronic pain, has been proposed (Norton et al., 2021), but due to the lack of supporting evidence, there are currently no common guideline treatments for long-COVID. The United Kingdom National Institute for Health and Care Excellence (NICE, 2020) or Scottish Intercollegiate Guidelines Network (SIGN, 2021) guidelines propose the application of self-management/education on long-COVID and rehabilitation for these patients. These recommendations are based on the proposal that patients with long-COVID should be involved in their recovery process from the beginning (Gorna et al., 2021).

Currently, rehabilitation seems to be the safest treatment approach to offer to long-COVID patients, whereas other interventions, e.g. pharmacological intake, are in progress due to a better understanding of the underlying mechanisms of long-COVID (Ora et al., 2023). Different meta-analyses support positive effects of pulmonary rehabilitation (Chen, Shi, et al., 2022) or exercise (Fernández-Lázaro et al., 2022) in health-related quality of life and function in individuals with long-COVID. However, Umesh et al. observed that 50% of clinical trials are focused on pulmonary long-COVID symptoms (Umesh et al., 2022).

The Stanford Hall consensus proposed a multidisciplinary approach for managing long-COVID symptoms including pulmonary/cardiac rehabilitation, exercise therapy, psychological management, musculoskeletal symptoms treatment, neurorehabilitation and medical advice (Barker-Davies et al., 2020). Due to the lack of randomized clinical trials investigating therapeutic interventions for specific treatment of post-COVID pain symptoms, the application of personalized management to post-COVID pain at best can be supported by evidence-based clinical reasoning.

Similarly, there are no controlled clinical trials specifically examining the efficacy of treatments for post-COVID headaches. It is currently recommended to identify the pain pattern of headache presented by the patient (migraine vs. tension-type headache phenotype) and to treat it according to this pattern (Chhabra et al., 2022; Sampaio Rocha-Filho, 2002). Some preventive drugs used for other chronic headaches might be effective, but so far there are few publications on this topic. In a retrospective cohort of 48 patients treated with amitriptyline, the proportion of patients with a >50% reduction in headache days at weeks 8–12 was 43.7% (Gonzalez-Martinez et al., 2022). Therefore, we present an evidence-based clinical reasoning approach for precision management of post-COVID pain.

3 | PRECISION (PERSONALIZED) MEDICINE PRACTICE FOR POST-COVID PAIN

Evidence-based guidelines for management of post-COVID pain will represent a milestone for healthcare clinicians since patients with long-COVID exhibit a plethora of heterogeneous symptoms. Thanks to the introduction of high-throughput innovations into health care (research), such as (genome-wide) DNA-sequencing, imaging, wireless (real-time)-monitoring devices and bid data, it is now widely accepted that the heterogeneity of many disease processes requires treatment strategies must be tailored or 'personalized' to the individual's (epi) genetic, biochemical, physiological and/or behavioural profile (Aletaha, 2020; Goetz & Schork, 2018). Within this view, the terms precision and personalized medicine have often been used (interchangeable). The term personalized medicine can be misinterpreted as if treatments are developed uniquely for each patient. To account for this, here we comply with the global move to precision medicine for post-COVID pain (rather than personalized medicine). Precision medicine refers to the ability to classify patients into subgroups that differ in their susceptibility to, biology or prognosis of a particular disease or in their response to a specific treatment, and thus to tailor treatment to the individual patient characteristics (National Research Council, 2011). Hence, precision medicine refers to an evidence-based method of subgrouping patients based on diagnostic and symptom presentation, and then tailoring specific treatments to individual patient phenotypes based on the prognosis for positive treatment outcomes and susceptibility to negative outcomes (National Research Council, 2011).

Large variability in the individual response to any pain treatment is observed clinically, complying with the global move to precision pain medicine. Precision pain medicine would consist of empirically based clinical decision algorithms that determine optimal interventions or treatment combinations, for specific pain patients (i.e. targeting the right treatment, in the right dose, to the right patient, at the right time). The current consensus paper presents an evidence-based clinical reasoning approach for precision management of post-COVID pain. As there are many layers to precision medicine (Aletaha, 2020), various precision aspects of post-COVID pain will be addressed, including phenotyping post-COVID pain into predominant nociceptive, neuropathic and/or nociplastic pain, sex predisposition, COVID-19 onset symptoms, premorbid pain status, SARS-CoV-2 variants and comorbidities such as anxiety, depression and sleep disorders, as well as genetic polymorphisms.

4 | PHENOTYPING POST-COVID PAIN

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has proposed different phenotypes and potential mechanisms contributing to chronic pain to be considered for identifying which treatments could be more effective for patients with specific characteristics (Edwards et al., 2022). Hence, identification of the dominant pain phenotype in patients with post-COVID pain could help clinicians to adopt therapeutic strategies resulting in more successful outcomes.

First, clinicians should consider the relapsing feature of long-COVID symptoms since the pattern (fluctuating or persisting) and nature (new-onset or exacerbated) of post-COVID pain should be identified. Second, three major pain phenotypes are identified in the literature (nociceptive, neuropathic and nociplastic) as well as a fourth one, e.g. mixed type. Identification of individuals fulfilling a nociplastic pain phenotype has the potential to improve precision pain medicine practice in musculoskeletal pain conditions (Nijs et al., 2021). This could be related to the fact that neuropathic and nociplastic phenotypes are considered more difficult to treat than nociceptive pain phenotypes. Nevertheless, clinicians should consider that a particular patient can fit into more than one phenotype (e.g. mixed type) since identifying one phenotype (i.e. neuropathic) does not exclude another (i.e. nociplastic) (Shraim et al., 2021). A Delphi study reported that, from 196 features, 76 features can be just attributed to nociceptive ($n = 17$), neuropathic ($n = 37$) or nociplastic ($n = 22$) pain phenotype, whereas the remaining 120 features share mechanisms between two phenotypes, i.e. 78 for neuropathic and nociplastic pain (Shraim et al., 2022). Additionally, due to the relapsing feature of post-COVID pain, the same patient may evolve from one to another phenotype, making the identification more challenging, and the possible change in pain phenotype over time may contribute to the complexity. Accordingly, it may be most productive to determine the most predominant pain phenotype instead of just statically classifying a patient into just one phenotype. Fernández-de-las-Peñas et al. have recently proposed the application of the International Association (IASP) clinical criteria/a grading system for clinical identification of nociplastic pain (Kosek et al., 2021) for phenotyping post-COVID pain (Fernández-de-las-Peñas, Nijs, Neblett, Polli, et al., 2022). In this section, the most relevant points of this classification will be briefly discussed.

4.1 | Nociceptive pain

Nociceptive pain is defined as pain attributable to the activation of the peripheral receptive terminals of primary afferent neurons in response to noxious stimuli (Smart et al., 2010). Clinically, nociceptive pain is considered when the pain response is proportional to the nociceptive input (Nijs et al., 2014). Current evidence supports that patients with post-COVID pain symptoms can exhibit nociceptive pain features due to the cytokine and interleukin-associated storms which could lead to sensitization of pain pathways (Coomes & Haghbayan, 2020; Mulchandani et al., 2021). A cohort study including almost 2000 previously hospitalized COVID-19 survivors identified pain of musculoskeletal origin in almost 45% of subjects at 8 (Fernández-de-las-Peñas, de-la-Llave-Rincón, et al., 2022) and 12 (Fernández-de-las-Peñas, Cancela-Cilleruelo, et al., 2023) months after hospital discharge. Almost 80% of the sample reported the presence of musculoskeletal pain in localized body areas (e.g. neck, shoulder, elbow, knee, hip and spine) (Fernández-de-las-Peñas, de-la-Llave-Rincón, et al., 2022; Fernández-de-las-Peñas, Cancela-Cilleruelo, et al., 2023). Similarly, the presence of post-COVID joint pain has been also reported in almost 50% of patients with long-COVID (Nguyen et al., 2022). The knee (38%), hand (25%) and shoulder (19%) are the most frequently involved joints (Cui et al., 2022).

4.2 | Neuropathic pain

Neuropathic pain is defined as pain symptoms limited to a 'neuroanatomically plausible' distribution of the somatosensory nervous system and associated with a lesion and/or disease of the somatosensory nervous system (i.e. central or peripheral nervous system) which is identifiable by imaging and/or laboratory findings (Scholz et al., 2019). A recent meta-analysis estimated a frequency of neuropathic pain in the acute/subacute phase of COVID-19 ranging from 0.4% to 25%; however, this prevalence rate is based on high heterogeneity of studies (Di Stefano et al., 2023). Current evidence also supports that individuals with post-COVID pain symptoms could exhibit neuropathic symptoms due to the neuro-invasive potential associated with SARS-CoV-2, related to the high expression of angiotensin converting enzyme-2 (ACE2) receptors in nervous system cells, including neurons and microglia in the spinal dorsal horn (Torices et al., 2021). The presence of neuropathic pain conditions, e.g. post-herpetic neuralgia, trigeminal neuralgia or brachial plexopathy, is well documented in individuals with long-COVID (Joshi et al., 2022). Two case series found the presence of small-fibre neuropathy in some patients with long-COVID (Abrams et al., 2022; Novak et al., 2022).

Additionally, the presence of self-reported neuropathic pain symptoms has been also identified in almost 25% of patients with post-COVID pain (Herrero-Montes et al., 2022; Oguz-Akarsu et al., 2022). Still, it should be stressed that neuropathic pain cannot be properly diagnosed by using self-reported tools, and no study to date has investigated the real prevalence of post-COVID pain of neuropathic origin including clinical or imaging examination. A recent case series reported that 59% of a sample of 17 patients with long-COVID symptoms were positive on ≥1 test (e.g. skin biopsy—63%; electrodiagnostic findings—17%; or autonomic function test—50%), supporting

the presence of post-COVID pain of neuropathic origin in some patients (Oaklander et al., 2022). Therefore, the prevalence of neuropathic post-COVID pain confirmed with objective measures in individuals with long-COVID is still unknown.

4.3 | Nociplastic pain

Nociplastic pain is defined as 'pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain'. (Kosek et al., 2016). Since no gold standard exists for determining if an individual patient is experiencing a normal or heightened pain response, the definition of nociplastic pain raises several questions (Aydede & Shriver, 2018). Emerging evidence suggests the presence of central sensitization-associated symptoms in a group of COVID-19 survivors with post-COVID pain (Fernández-de-las-Peñas, Parás-Bravo, et al., 2023; Goudman et al., 2021). The presence of widespread symptomatology in several patients with post-COVID pain also supports the presence of altered nociceptive pain processing (Fernández-de-las-Peñas et al., 2022; Fernández-de-las-Peñas, Parás-Bravo, et al., 2023; Goudman et al., 2021; Khoja et al., 2022). This generalized pain pattern may be related to the hypothesis that local connective tissue damage caused by SARS-CoV-2 in patients with joint hypermobility could lead to widespread symptomatology (Gavrilova et al., 2022). Another hypothesis is that long-lasting inflammatory state related to the cytokine storm associated with SARS-CoV-2 infection can sensitize nociceptive neurons, leading to temporal summation or windup and, consequently, altered nociceptive processing (Das & Choy, 2022). In such a scenario, a widespread pain pattern would be indicative of the evolution from nociceptive to nociplastic phenotype which can be present in a subgroup of patients with post-COVID pain. Oronsky et al. (2021) proposed that SARS-CoV-2 provokes PICS (persistent inflammation, immunosuppression and catabolism syndrome). It is possible that this continuum of inflammatory events leads to the progression from nociceptive to nociplastic pain phenotype in individuals with long-lasting post-COVID pain.

Other central nervous system-derived symptoms such as fatigue, sleep disturbances, memory loss, concentration problems or mood disorders, which are typical of nociplastic pain conditions (Fitzcharles et al., 2021), are often present in patients with long-COVID (Alkodaymi et al., 2022; Chen, Haupert, et al., 2022; Fernández-de-las-Peñas, Palacios-Ceña, et al., 2021; Han et al., 2022; Michelen et al., 2021). The same type of symptomatology resembles features of another nociplastic pain condition such as fibromyalgia syndrome. Haider et al. have recently confirmed that patients with long-COVID share a similar phenotype to those with fibromyalgia or chronic fatigue syndrome, but with less severe pain and fatigue overall (Haider et al., 2023).

5 | TREATMENT OF POST-COVID PAIN BASED ON PHENOTYPE

The following section will focus on the three main phenotypes of post-COVID pain: nociceptive, neuropathic and nociplastic pain. The literature search revealed that no controlled clinical trial evaluating the effectiveness of any particular treatment for post-COVID pain has been yet published.

5.1 | Treatment of predominant nociceptive Post-COVID pain

Nociceptive pain phenotype is mainly represented by localized muscular or joint pain syndromes where symptoms are attributable to the activation of peripheral nociceptors. Current treatment approaches include physical therapy and pharmacological treatment.

Evidence supporting any particular treatment for the management of post-COVID pain of nociceptive features is lacking. Post-COVID joint pain has been treated with non-steroidal anti-inflammatory drugs (NSAIDs) and local steroids with potentially good results (Pal et al., 2022). The rationale for applying NSAIDs in this pain phenotype is based on a reduction of the proinflammatory cytokine response (storm) associated with SARS-CoV-2 infection; however, the timing of its application could be relevant, since an early application of NSAIDs, at least at the acute phase of COVID-19 disease, may impact negatively in the initial antiviral immune response (Chen et al., 2021), although this hypothesis needs to be further investigated. The use of corticosteroids for post-COVID pain is located in the same scenario as NSAIDs. Corticoids have been administered at the acute phase of the infection, particularly for decreasing all-cause mortality in severe COVID-19 patients (Zeng et al., 2022); however, their use for managing post-COVID pain has not been properly investigated.

Similarly, since post-COVID joint pain shares similar features that other arthralgic pain conditions, e.g. osteoarthritis or reactive arthritis, interventions including exercise therapy, transcranial magnetic stimulation or electrical stimulation could be also considered (Cordani et al., 2022).

Palmitoylethanolamide, an endocannabinoid-like lipid mediator with documented anti-inflammatory, analgesic, antimicrobial, immunomodulatory and neuroprotective effects, is also proposed for the treatment of nociceptive pain, however, evidence is still unclear (Scuteri et al., 2022). Importantly, it has been recently observed that palmitoylethanolamide is a direct and indirect antiviral agent against SARS-CoV-2 (Fonnesu et al., 2022). Evidence supporting its use in long-COVID is scarce and only based on case series (Raciti et al., 2022), without mention of post-COVID pain.

Management of post-COVID muscle pain, as a new clinical problem, obviously has not so far received intensive attention and controlled studies. Santos and Flores (2022) described a case report of a patient with post-COVID pain where the application of physical therapy was accompanied by improvements in function and quality of life. The application of any physical therapy intervention for managing post-COVID pain of nociceptive origin should be further investigated in future studies.

5.2 | Treatment of predominant neuropathic Post-COVID pain

No controlled clinical trial has specifically evaluated the effectiveness of any particular treatment for post-COVID pain of neuropathic origin.

Finnerup et al. provided the following recommendations for pharmacological treatment of neuropathic pain: strong evidence for the use of tricyclic antidepressants (e.g. amitriptyline and desipramine), serotonin–noradrenaline reuptake inhibitors (e.g. duloxetine, venlafaxine) or GABA analogues (e.g. pregabalin and gabapentin) as first-line treatment; weak recommendation for local anaesthetics/lidocaine patches, capsaicin high-concentration patches and opioids such as tramadol as second-line treatment; and weak recommendation for strong opioid (e.g. morphine and tapentadol) and botulinum toxin A as third-line treatment (Finnerup et al., 2015). No studies have yet investigated the application of these interventions for the management of post-COVID pain of neuropathic origin. A recent study found that 45% of patients with long-COVID intake benzodiazepines (e.g. lorazepam) and Z-hypnotics (e.g. Zolpidem) for managing anxiety or depression associated with their pain (Carrasco-Garrido et al., 2022). Similarly, the prevalence of opioids and non-opioid analgesic consumption in people with long-COVID can reach 24.1% and 82.3%, respectively (data not published), although long-time use of opioids in neuropathic pain is a problematic treatment path.

Some physical therapy interventions, e.g. laser and electromagnetic stimulation, could be also applied for managing peripheral neuropathic pain, although evidence is conflicting (Kannan et al., 2022). No study has investigated any of these interventions in neuropathic post- COVID pain. Similarly, current evidence also supports that exercise therapy programmes could be helpful to alleviate neuropathic pain (Zhang et al., 2021), however, no consensus exists on which type of exercise (e.g. stretching, aerobic, motor control, strengthening and exercise therapy according to cognitive-behavioural principles) should be applied.

Finally, Córdova-Martínez et al. (2022) have recently proposed nutraceutical strategies, i.e. α-lipoic acid, acetyl-L-carnitine and vitamins D, B_1, B_6 or B_{12}, which have been used in diabetic neuropathies in order to improve the symptomatology of neuropathic pain in patients who had survived COVID-19. The rationale for applying, for instance, B_{12} vitamin is based on the fact that several long-COVID symptoms are similar to those experienced by people with various vitamin B_{12} deficiencies. In fact, B_{12} vitamin is involved in the regulation of the immune system and has antiviral activity, therefore, its potential application in post-COVID neuropathic pain would be feasible (Batista et al., 2022). However, the appropriate choice of the chemical form of these nutrients, the dose and treatment time will depend on individual factors such as age, pre-existing diseases, type of methylation gene and medication used (Córdova-Martínez et al., 2022). Overall, no clinical trials have investigated the management of treatment strategies in neuropathic post-COVID pain.

5.3 | Treatment of predominant Nociplastic Post-COVID pain

Since nociplastic pain is usually associated with central nervous system symptoms (e.g. poor sleep quality, fatigue or mood disorders), multimodal/multifactorial treatment approaches integrated into a biopsychosocial model, addressing relevant comorbidities and lifestyle factors, will be required to achieve potential successful treatment outcomes.

There are no clinical trials applying multimodal programmes for the management of post-COVID pain symptoms of nociplastic features. Exercise therapy will be used as an example of intervention that must be adapted in individuals if a nociplastic pain phenotype is identified. Exercise therapy is a therapeutic approach recommended for patients with chronic pain and has been proposed for individuals with long-COVID (Jimeno-Almazán et al., 2021). Current evidence supports the use of resistance and aerobic exercises for improving functional capacity and quality of life in individuals with long-COVID (Ahmadi Hekmatikar et al., 2022). In fact,

it should be noted that rehabilitation programmes applied in people with long-COVID focus on aerobic and endurance exercises (Bailly et al., 2022). However, the presence of nociplastic pain will provoke adaptations in treatment to optimize the exercise prescription (Ferrero Moura Franco et al., 2021). This topic is of importance in individuals with long-COVID since almost 60% of patients also exhibit post-exertional malaise (PEM) in a similar proportion to patients with myalgic encephalomyelitis or chronic fatigue syndrome (Twomey et al., 2022). In such cases, exercise programmes must be provided with caution, and pacing and other cognitive approaches should be also incorporated (either in isolation or combined with exercise). More precisely, PEM represents a pitfall for clinicians applying exercise therapy to patients with predominant nociplastic post-COVID pain, as symptoms of PEM can be incorrectly interpreted as signs of tissue damage or overtraining. Peripheral and particularly central nervous system sensitization is considered the major underlying mechanism of nociplastic pain (Kosek et al., 2016; Kosek et al., 2021). Central nervous system sensitization is defined as an amplification of neural signalling that elicits pain hypersensitivity (Woolf, 2011), and implies that pain is no longer a reliable messenger. Hence, exercise therapy for patients with predominant nociplastic post-COVID pain should not be applied/graded in a pain- (or fatigue) contingent way, but in a time-contingent way (Nijs et al., 2019) and randomized controlled trials are needed. This is in line with evidence-based exercise therapy approaches for chronic pain such as graded exercise therapy, behavioural graded activity and exposure in vivo, which apply cognitive behavioural principles.

Further, management of comorbid symptomatology which can perpetuate and interact with pain (e.g. sleep disturbances, fatigue, dyspnoea or autonomic disturbances) is essential for optimizing treatment outcomes in patients with nociplastic pain phenotype (Cattadori et al., 2022). In fact, successful outcomes are less likely if treatment is just focussed on improving underlying pain mechanisms (i.e. decreasing sensitization in nociplastic pain phenotype) without proper management of its associated factors. Accordingly, patients with a nociplastic pain phenotype will need additional treatment approaches, such as pain neuroscience education, cognitive behavioural techniques or self-regulation/mindfulness strategies, in synergy with exercise and physical therapy modalities aiming to improve central sensitization-related mechanisms (Arribas-Romano et al., 2020). This reasoning is supported by a recent study where authors applied identified three clusters and where one cluster resembling those features of nociplastic pain phenotype (pain, fatigue and many other symptoms as well as anxiety/depression and sleep disorders) received a multimodal approach including medication, rehabilitation and psychological therapy (Frontera et al., 2022).

6 | TREATMENT OF FACTORS ASSOCIATED WITH POST-COVID PAIN

6.1 | Sex predisposition and Post-COVID pain

In this first step, two biological non-modifiable factors such as age and sex should be considered. Similarly, female sex has been clearly identified as a risk factor for the development of long-COVID symptomatology (Maglietta et al., 2022). The role of age as a risk factor for long-COVID symptoms is still controversial since Thompson et al. found that older age was associated with more long-COVID symptoms (Thompson et al., 2022), whereas Notarte et al. (2022) reported that although single studies showed that age can be associated with long-COVID, pooled meta-analysis did not reveal any significant association.

Similar data were reported specifically for post-COVID pain. Female sex was found to be associated with musculoskeletal post-COVID pain in a previous cohort study (Fernández-de-las-Peñas, Cancela-Cilleruelo, et al., 2023; Fernández-de-las-Peñas, de-la-Llave-Rincón, et al., 2022). Zis et al. (2022) have recently observed that female sex and also older age were factors associated with overall post-COVID pain. An association between female sex and post-COVID pain is expected since pain is overall more prevalent in females than in males (Mills et al., 2019). In fact, it has been reported that those biological gender differences in the expression of ACE2 and transmembrane protease serine 2 (TMPRSS2) receptors between females and males can be related to a higher survivor rate but a higher prevalence of long-COVID symptoms in females (Bwire, 2020).

For instance, it has been recently observed that women exhibit a more reduced alveolar diffusion capacity and exercise tolerance than men after surpassing SARs-COV-2 infection (Spicuzza et al., 2023). This sex difference should be considered by clinicians when designing exercise programmes for managing post-COVID pain in females. Accordingly, biological (i.e. hormones and immune responses) (Melchior et al., 2016) and sociocultural (i.e. sanitary-related behaviour, psychological stress and inactivity) aspects should be considered when managing female patients with post-COVID pain (Gebhard et al., 2021).

6.1.1 | Myalgia and/or headache as COVID-19-onset symptom and post-COVID pain

Some studies have suggested that a higher number of onset symptoms at the acute phase of the infection could be a risk factor for the overall developing of long-COVID symptoms (Maglietta et al., 2022; Thompson et al., 2022). Particularly, the presence of myalgia and headache as onset-associated COVID-19 symptoms has been associated with development of long-term musculoskeletal post-COVID pain (adj OR 1.41, 95% 1.04–1.90) (Fernández-de-las-Peñas, Rodríguez-Jiménez, et al., 2021), whereas the presence of headache as an onset COVID-19 symptom has been also associated with the presence of neuropathic post-COVID pain (Zis et al., 2022). Interestingly, the presence of headache as an onset-associated COVID-19 symptom has been also associated with the development of persistent tension-type like headache as a new post-COVID symptom (adj OR 2.65, 95% CI1.66–4.24) and post-COVID fatigue (adj OR 1.55, 95% CI 1.07–2.24) (Fernández-de-las-Peñas, Gómez-Mayordomo, et al., 2021). Since the overall prevalence of headache as onset COVID-19 symptom can reach up to 47.1% (95% CI 35.8–58.6) (Fernández-de-las-Peñas, Navarro-Santana, et al., 2021), early monitoring of this symptom at the acute phase of the SARS-CoV-2 infection could be essential for developing preventive strategies against the development of post-COVID pain symptoms, including headache. In fact, despite the lack of randomized controlled trials on this topic, evidence suggests that when individuals with COVID-19-related headaches did not improve in the first 2 months after the acute phase, this symptom becomes persistent and adopts a chronic post-COVID pattern (Garcia-Azorin et al., 2022). Unfortunately, to date, there are no headache-specific guidelines to guide the treatment of this symptom at the acute phase of COVID-19, however, most experts recommend the treatment of COVID-19-related headache according to the clinical phenotype (tension-type-like or migraine-like headache) (Costa et al., 2021).

6.1.2 | Previous history of musculoskeletal pain and the influence on Post-COVID pain

It should be noted that several individuals who have been infected by SARS-CoV-2 had a previous history of chronic pain. It would be reasonable to consider that these individuals might respond differently and may be more susceptible to long-COVID pain than individuals without previous chronic pain symptoms. Hence, clinicians should differentiate between the appearance of 'new onset' post-COVID pain (i.e. development of pain symptoms not related to previous pain symptomatology) from 'exacerbated' post-COVID pain (i.e. a worsening of previous pain symptoms experienced after the infection). In such a scenario, premorbid pain could lead to a worse prognosis of post-COVID pain and can represent a risk factor for future development of nociplastic pain phenotype. Fernández-de-las-Peñas et al. found that patients who are infected by SARS-CoV-2 and suffered from a previous history of musculoskeletal pain exhibit a higher risk of developing post-COVID pain symptoms at long-term (adj OR 1.55, 95% CI 1.27–1.89) (Fernández-de-las-Peñas, Cancela-Cilleruelo, et al., 2023; Fernández-de-las-Peñas, de-la-Llave-Rincón, et al., 2022). In addition, a previous history of musculoskeletal pain was also associated with the presence of myalgia as onset-associated COVID-19 symptom (adj OR1.62, 95% CI 1.10–2.40) (Fernández-de-las-Peñas, de-la-Llave-Rincón, et al., 2022; Fernández-de-las-Peñas, Rodríguez-Jiménez, et al., 2021). Accordingly, a proper clinical history identifying these risk factors could be essential for more appropriate therapeutic strategies. In fact, we do not currently know if management of new post-COVID pain would be different from treatment of previous pain symptoms or albeit the worsening of previous pain symptoms would lead to changes in their management. Today, no study has investigated these hypotheses yet.

Figure 1 graphs a potential classification of post-COVID pain according to a previous history of pain symptoms and the presence or absence of myalgia/headache as onset-associated COVID-19 symptoms. Two classifications are interconnected. First, if the patient reports the presence of previous symptoms, clinicians should differentiate if post-COVID pain is a 'new' symptom or an 'exacerbated' symptom. Second, the presence of myalgia at the acute phase of the infection could lead to persistent post-COVID pain, since a patient who suffered from myalgia (pain) at the acute phase of infection will continue with post-COVID pain without interruption. In those patients not presenting myalgia as an onset symptom, the development of post-COVID pain will start after the acute phase, accordingly, it should be considered 'delayed-onset', since the patient did not experience pain at the acute phase of the infection but develops pain symptoms after the infection (usually considered in the first 2 months after).

6.2 | SARS-CoV-2 variants and Post-COVID pain

The natural evolution of SARs-COV-2 has led to the appearance of several variants. Alpha (B.1.1.7), Delta

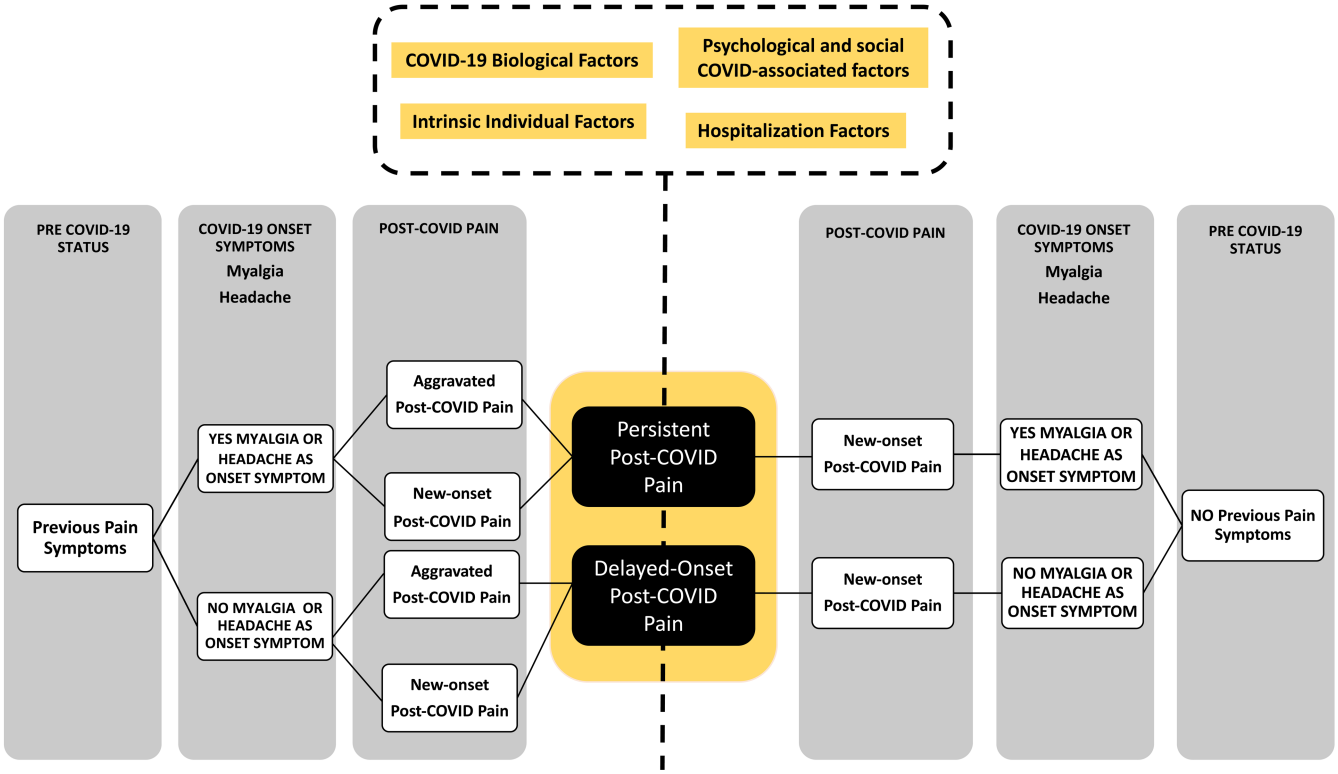

FIGURE 1 Proposal model for post-COVID pain.

(B.1.617.2) and Omicron (B.1.1.529/BA.1) variants are considered the relevant variants of concern due to their worldwide spread, in addition to the historical/wild-type (20A.EU2) strain (Thye et al., 2021).

Due to the quick evolution of SAR-CoV-2 into these variants, researchers and clinicians have questioned if the development of long-COVID would be different. A systematic review found that the prevalence of overall long-COVID symptoms seems to be higher in individuals infected with the historical/wild-type strain compared to those infected with the Alpha, Delta or Omicron variants. Additionally, the prevalence of long-COVID tends to decrease since people infected with the Omicron variant exhibit fewer long-COVID symptoms (Fernández-de-las-Peñas, Notarte et al., 2022). The review found that fatigue is the most prevalent long-COVID symptom in all SARS-CoV-2 variants (Fernández-de-las-Peñas, Notarte et al., 2022). Similar results have been found in the meta-analysis by Du et al (Du et al., 2022). These authors pooled data for post-COVID pain and, surprisingly, observed that the prevalence of this symptom was higher in patients infected with the Omicron variant (11.7%) as compared with those infected with the historical strain (9.4%) (Du et al., 2022). The only study specifically comparing the prevalence of musculoskeletal post-COVID pain between different SARS-COV-2 variants found that post-COVID pain was more prevalent in individuals infected with the historical/wild-type strain (47.7%) than in those infected with the Alpha (38.3%) or Delta (41%) variants (Fernández-de-las-Peñas, Cancella-Cilleruelo, et al., 2022). Additionally, this study observed that a higher proportion of individuals infected with the historical/wild-type strain reported widespread pain symptomatology (20.5%) when compared with those infected with the other variants (Fernández-de-las-Peñas, Cancella-Cilleruelo, et al., 2022).

Although SARS-CoV-2 variants exhibit several differences such as viral load, potential transmissibility, potential escape to vaccines or ability to reinfection (Tani-Sassa et al., 2022), no clear differences in molecular and host-immune responses among the variants have been identified; which would explain why no differences in potential treatments of long-COVID symptoms should be needed. In fact, Fernández-de-las-Peñas et al. were unable to identify risk factors for developing post-COVID pain depending on the SARS-CoV-2 variant (Fernández-de-las-Peñas, Cancella-Cilleruelo, et al., 2022), supporting that those differences in prevalence rates should be attributed to COVID-19 surrounding factors. This hypothesis would be supported by the fact that Due et al. identified that the presence of associated symptoms such as sleep disorders was higher in individuals infected with the historical/wild-type strain (24.5%) (Du et al., 2022).

6.3 | Anxiety, depression and sleep disorders and Post-COVID pain

The relevance of emotional disorders (George et al., 2011) and sleep disturbances (Finan et al., 2013) as factors associated with chronic pain is supported in the former literature. In fact, a bidirectional effect is suggested, in which pain can lead to emotional disorders and poor sleep quality, and the presence of poor sleep quality and emotional problems can promote and precipitate pain. This bidirectional effect is based on the fact that emotional problems can negatively impact the central nervous system by reducing descending pain inhibition and amplifying pain-related signals (Terry et al., 2013). Similarly, sleep deprivation (poor sleep) is able to induce peripheral and central sensitization in healthy people (limited to moderate evidence), although its effect on people with chronic pain is not conclusive (very limited evidence) (Chang et al., 2022). Interestingly, sleep disturbances and depression are independently associated with pain sensitivity, supporting an independent role of each factor (Chiu et al., 2005).

The presence of physical repercussions and emotional symptomatology in people with long-COVID supports the observation that biological and behavioural factors interact in these patients (Hall et al., 2021). The presence of anxiety and depressive symptoms as well as sleep disturbances in individuals with long-COVID is clear in the literature (Iqbal et al., 2021; Mazza et al., 2022). It has been found that depressive symptoms are associated with a higher risk of physical post-COVID symptoms, e.g. fatigue (Al-Jassas et al., 2022) or dyspnoea (Bottemanne et al., 2021). Similarly, sleep disturbances have also been associated with physical aspects in long-COVID patients (El Sayed et al., 2021). Merikanto et al. proposed that long-lasting sleep problems were at the core of long-COVID symptoms and were associated with COVID-19 severity (Merikanto et al., 2022). It has been found that poor sleep quality is associated with increased depressive and anxiety levels (Nowakowski et al., 2022), however, clinical experience suggests that these disorders are complexly associated, for example, sleep quality mediates the association between sensitization-associated symptoms and depressive/anxiety levels with the quality of life in people with post-COVID pain (Pacho-Hernández et al., 2022). In fact, a Bayesian data-driven model has recently proposed that psychological factors play a relevant mediating role among central sensitization symptoms, post-COVID pain and sleep quality (Fernández-de-las-Peñas, Liew, et al., 2022).

Current data suggest that management of psychological disturbances, including sleep problems, could be essential for treating post-COVID pain. Cognitive behavioural therapy has been found to be an effective strategy for improving sleep in people with chronic pain, but its effect on physical function is not clear (Whale et al., 2022). In fact, cognitive behavioural therapy can be effective in improving different aspects of sleep: sleep initiation, sleep maintenance, sleep quality and pain interference with daily functioning. It is commonly observed in the literature that including cognitive behavioural strategies in physical therapy interventions can be highly efficacious for chronic pain conditions (Nijs et al., 2018). Since cognitive behavioural therapy is able to directly affect sleep, its combination with exercise programmes or other interventions discussed in the current study for individuals with post-COVID pain could lead to better clinical outcomes in these patients.

6.4 | Genetic polymorphisms and Post-COVID pain

It has been observed that COVID-19 spread has shown a marked geographical variation. This evidence can be explained by a potential genetic variation not only of the SARS-CoV-2 virus itself mutating but also by a genetic predisposition of the host towards the infection. Within these DNA alterations, single nucleotide polymorphisms (SNPs), induced by human evolution, allow the population to live in different environments and cause changes in many proteins' products (Delanghe et al., 2021). An estimation calculated that there are more than 10 million SNPs, and generally, these variants can be silent (synonymous) causing no change in protein product sequence or changing the sequence with no phenotypical effects (Ng & Henikoff, 2006). Other variants are missense or nonsense resulting in a different or potential truncated protein product (non-synonymous and premature stop codon), and being the main reason for interpersonal genetic variability (Ng & Henikoff, 2006).

Polymorphic alterations of candidate genes have been investigated for the role they may play in post-COVID pain and viral aggressiveness. Among the different genes, the ACE2 and the TMPRSS2 polymorphisms are candidates for what concerns the effect of viral infection (Adli et al., 2022), whereas the more canonical genes previously associated with pain perception and some chronic pain conditions are the SNP of the μ-opioid receptor gene (OPRM1), the Val158Met catechol-O-methyltransferase gene (COMT), the brain-derived neurotrophic factor (BDNF) and the 5-hydroxytryptamine receptor 1B gene (HTR1B) (Kouraki et al., 2022). Polymorphisms of pain

process genes have been mostly associated with altered activity of protein products leading to pain features and alteration in pain signalling (Zorina-Lichtenwalter et al., 2016).

Importantly, among candidate genes, specific SNPs of COMT and OPRM1 have been largely associated with pain transmission and their involvement in analgesic approaches (Peiró, 2018). The COMT plays a role in the modulation of neurotransmission both dopaminergic and adrenergic, resulting in the regulation of response to opioids; in the same direction is the function of the OPRM1 gene which codifies for an isoform of the opioid receptors (Ruano & Kost, 2018). SNP variants of these genes, such as A118G *rs179997* and Val158Met *rs4680*, can induce the altered activity of the receptor and decrease enzymatic activity, leading to a loss of metabolic function and toxicity, associated with chronic pain conditions (Tammimäki & Männistö, 2012).

A better understanding of genetic influence can be applied to treatment strategies. For instance, since SARS-CoV-2 binds to human cells via ACE2 receptors, ACE2 is suggested as a vital medication target of COVID-19 therapy (Hetta et al., 2021). This reasoning applies to several drugs, e.g. NSAIDs. At the beginning of the pandemic, NSAIDs were contraindicated for the acute phase of COVID-19 since it was hypothesized that NSAIDs could interact with ACE2 receptors. However, later research reveals that several NSAIDs, e.g. ibuprofen, flurbiprofen, etoricoxib or paracetamol, had no effects on ACE2 expression or activity in vitro or in vivo (de Bruin et al., 2022). A human study also observed that NSAID use was not associated with increased COVID-19 severity (Reese et al., 2022). However, the effects of NSAIDs for managing post-COVID pain have not been investigated yet.

There are several gene therapies being developed to treat pain, although most are still in their early stages of development. A possible approach to gene therapy for pain involves the regulations of candidate genes that produce and regulate the action of pain-related molecules, such as the use of opioid growth factor (OGF) or OGF–opioid receptor (OGFr), which bind to opioid receptors and inhibit the action of the enzymes involved in the nociceptive process (Zagon et al., 2002). Therapies that include the usage of these molecules are now in their experimental phase for treating post-cancer pain in different specific types of cancer, pointing towards a promising future use (Smith et al., 2010; Wang et al., 2019). Another approach that could be used as gene therapy for pain has been recently investigated at the preclinical level (Moreno et al., 2021). Researchers have shown that the genetic repression of $Na_V1.7$ in the dorsal root ganglion of a mice model reduces thermal hyperalgesia and decreases tactile allodynia, causing no alteration in normal motor function (Moreno et al., 2021). All these therapeutic strategies could be applied for managing post-COVID pain if an association with these polymorphisms is identified.

Concerning COVID-19, only a few candidate genes have been previously investigated, showing BDNF as a potential tool for the prediction of worsened prognosis in infected patients (Minuzzi et al., 2021) and COMT, suggesting that Val158Met polymorphism of this gene may be associated with a higher impact of COVID-19 (Rajkumar, 2020). Nonetheless, more and more studies are coming up focusing on genetic variations for the identification of potential demographic or gender predisposition towards the possibility to develop post-COVID symptoms, such as pain, but a possible target for genetic personalized therapy remains elusive.

Recently, our research group has aimed at the identification of genetic variances of candidate genes and their potential association with post-COVID pain symptoms, including not only genes involved in the SARS-CoV-2 pathogenesis (Fernández-de-las-Peñas, Arendt-Nielsen, et al., 2022) but also ones regulating inflammation response (Fernández-de-las-Peñas, Giordano, Díaz-Gil, Gómez-Esquer, et al., 2022) and pain perception (Fernández-de-las-Peñas, Giordano, Díaz-Gil, Gil-Crujera, et al., 2022). These studies showed an evaluation of a specific cohort recruited in the Spanish population after infection with SARS-CoV-2, reporting an absence of associations between specific allelic alteration and pain or other symptoms in patients with long COVID (Fernández-de-las-Peñas, Arendt-Nielsen, et al., 2022; Fernández-de-las-Peñas, Giordano, Díaz-Gil, Gil-Crujera, et al., 2022; Fernández-de-las-Peñas, Giordano, Díaz-Gil, Gómez-Esquer, et al., 2022). To date, genetic variability has not been identified to be related yet to post-COVID pain and potential treatments for pain based on potential genetic targets are not clear, this open problem makes mandatory more studies in this direction. Within this view, it seems also relevant to examine possible epigenetic change associated with post-COVID pain. Indeed, both the viral infection itself and associated comorbidities (sleep disorders, anxiety and depression) can trigger epigenetic changes (e.g. DNA methylations and chromatin remodelling) that switch on inflammatory genes (or silence anti-inflammatory genes) to create a low-grade inflammatory status (Ramos-Lopez et al., 2021). Obviously, identification of epigenetic signatures of post-COVID pain would create new avenues for precision pain medicine in this population.

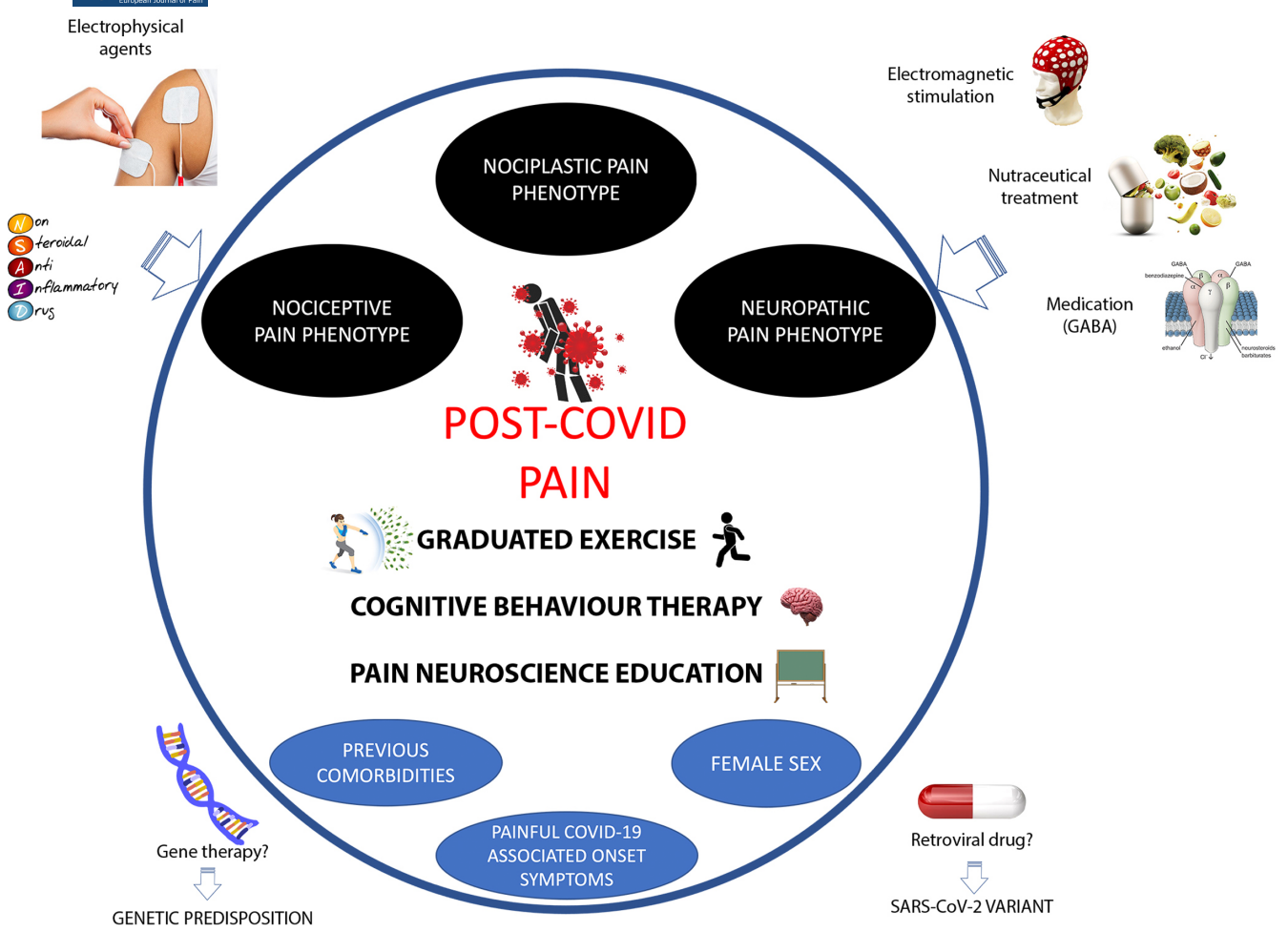

FIGURE 2 Clinical decision-making for personalized, tailored management of post-COVID pain.

7 | CONCLUSION

Post-COVID pain remains an underestimated and undertreated condition to a lack of recognition of the phenomenon and knowledge of the underlying mechanisms. Evidence from randomized controlled trials is lacking to support any particular interdisciplinary, treatment approaches for the management of post-COVID pain. A better understanding of the underlying causes and symptoms may pave the way for developing precision medicine to manage post-COVID, and hence guide clinical decision-making. The current study discusses several potential factors to be considered by clinicians for managing post-COVID pain. The ability of clinicians to phenotype patients with post-COVID pain into nociceptive, neuropathic, nociplastic or mixed type could be a first step to better planification of multimodal treatment strategies. Second, consideration of surrounding factors, such as female sex, previous comorbidities, treatments received at the acute phase of the infection for specific onset-associated COVID-19 symptoms or the presence of emotional disturbances should be also implemented. Accordingly, with consideration of these factors, management of post-COVID pain should include a multimodal treatment, targeting emotional/cognitive aspects (i.e. psychological and/or coping strategies), central sensitization-associated mechanisms (i.e. pain neuroscience education), exercise therapy programmes as well as lifestyles interventions (e.g. nutritional support and sleep management). Figure 2 graphs different aspects of the proposed clinical reasoning for a precision management approach to post-COVID pain.

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CONFLICT OF INTEREST STATEMENT

Jo Nijs and the Vrije Universiteit Brussel received lecturing/teaching fees from various professional associations and educational organizations. JN authored a book on pain neuroscience education, but the royalties are collected by the Vrije Universiteit Brussel, Brussels,

Belgium. The remaining authors have nothing to disclose.

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