


Long COVID-19 and the Role of the Patient–Clinician Interaction in Symptom Management

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Leonard Calabrese¹  and Luana Colloca²

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There is consensus that a significant proportion of patients recovering from both severe as well as nonsevere coronavirus disease 2019 (COVID-19) have potentially debilitating symptoms beyond 12 weeks, a condition that has been called Long COVID and may affect 10% to 30% of those experiencing infection (1). While still lacking a formal definition, Long COVID is clinically heterogeneous with the most common symptoms including fatigability, somatic pain, “brain fog” and respiratory symptoms (1). Fatigability is among the most severe and disabling symptoms which often displays postexertional features similar to other postviral fatigue states and is only variably relieved by rest. Other prominent symptoms include “brain fog” characterized by poor memory and concentration as well as bodily pain. A recent meta-analysis of Long COVID studies describes over 50 potential long-term effects collectively leading to a high burden of morbidity (2).

The Clinical Challenge of Long COVID

Despite rapid progress and considerable investment in basic research and numerous proposed theories of etiopathogenesis, for now, Long COVID remains largely medically unexplained. This state of uncertainty regarding virtually all aspects of the Long COVID has left clinicians lacking best practices for diagnosis and treatment and patients with the condition seeking reasons for their suffering. Unfortunately, only a small minority of patients with Long COVID have access to the growing number of centers that evaluate such patients offering multispecialty care in the context of a generally integrative approach to therapy focusing on mental health, varying regimens of exercise and symptomatic therapies with only a few specific therapeutics undergoing clinical investigation.

This leaves the vast majority of patients suffering postCOVID sequelae seeking care from their own clinicians who are poorly equipped to meet the challenges of the array of symptoms (i.e. fatigue, brain fog, somatic pain etc.) that traditionally are often considered medically unexplained and lacking

clear guidelines for assessment and treatment. As a result, clinicians tend to minimize these chronic symptoms which often lead to frustration and despair. We believe that clinicians, despite a seeming lack of resources, do indeed have a potent neurobiological therapeutic in hand that can positively or negatively affect daily clinical outcomes. We assert that the very nature of the clinical encounter and the biopsychosocial factors surrounding the patient–clinician interaction can have meaningful effects on clinical outcomes including quality of life and symptom improvements. The scientific bases for this, is derived by the growing literature in placebo science (3).

The Scientific Basis of the Placebo Effect and its Potential in Long COVID

Many common misconceptions surround the field of placebo science such as the need to administer an inert substance or a reliance on trickery. Recent mechanistic research has shed light on specific aspects of the neurobiology of the patient–clinician interaction and its demonstrable effects to serve as a powerful placebo (3). Given the paucity of specific therapeutics for Long COVID, the power of this interaction holds considerable potential for improving patient outcomes. Elements of the patient–clinician interaction such as charismatic aspects of the clinician, patient satisfaction, trust, treatment adherence, and empathy have been relegated to ethical and anthropological aspects of good clinical practice or the art of medicine. While most clinicians readily accept that the patient–clinician

¹Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA

²School of Nursing & School of Medicine, University of Maryland, Baltimore, MD, USA

Corresponding Author:

Leonard Calabrese, Department of Rheumatic and Immunologic Diseases, 9500 Euclid Avenue, Desk A50, Cleveland, OH 44195, USA.
Email: calabrl@ccf.org



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interaction can influence patients (e.g. low satisfaction, distrust, and hopelessness) and clinicians (e.g. lower depersonalization and burnout) negative outcomes, there has been limited consideration of its neurobiological bases.

Very recently, neuroimaging studies have elegantly demonstrated that brain areas related to the theory of the mind and cognitive processing (e.g. expectations of benefits) are involved in the neurobiological bases of the patient–clinician interaction. Observing pain relief in another person activates the temporoparietal junctions producing analgesia in the observer (4). A functional Magnetic Resonance Imaging study conducted in healthy participants, demonstrated that the mere observation of an actor receiving painful stimulations and subsequently a (placebo) cream to reduce pain, lead to an activation of brain areas related to pain aversion (amygdalae), pain modulation (periaqueductal gray), empathy/mentalizing (temporoparietal junctions), and expectations of pain reduction (dorsolateral prefrontal cortex). Functional connectivity between the dorsolateral prefrontal cortex and temporoparietal junctions during the observation was predictive of placebo effects providing a hint into the neural processes underpinning the therapeutic encounter and interaction with another person (4).

Directly in the patient and clinician dyad, a more recent study investigated similar brain dynamics using brain functional Magnetic Resonance Imaging hyperscanning that captures simultaneously the neural activity while the patient and clinician brains while they actually interact (5). Using an ecologically controlled clinical encounter, the authors disentangled dynamically the neurobiological mechanisms beyond mirroring face expressions and patient–clinician brain concordance. When a pain patient interacts with her/his acupuncturist, the temporoparietal junctions, ventrolateral prefrontal cortex, and anterior insula are activated in both the patient and clinician in the anticipation of pain and subsequent, treatment-induced pain relief. The temporoparietal junctions are relevant in creating such an empathic synchrony between a chronic pain patient and the acupuncturist brain resulting in symptoms reduction. However, that brain activity concordance occurs only if the dyad had established a clinical relationship prior to being scanned (5). From a scientific perspective, there is a need to both further investigate the brain-by-brain mechanisms that characterize the patient–clinician interaction,

reciprocity and alliance as well as intentionally apply some practical lessons from this area of research, to current management of patients with Long COVID symptoms.

The Role of Patient–Clinician Communication and the Placebo Effect in Long COVID

In closing and as noted above, it is vitally important to emphasize that our advocacy for applying the principles of placebo science mediated by the patient–clinician relationship does not in any way diminish or invalidate the suffering of patients so afflicted by Long COVID but rather opens up new areas to explore neurobiologically based emerging science. Following from this position, we should logically then ask how can we begin to apply these findings in the daily care and caring of Long COVID patients? The cornerstone of exploiting these mechanisms can be, one the one hand, merely transactional, a process that includes accurate diagnosis and pharmacotherapy accompanied by what some would refer to as good bedside manner including good listening skills, positive framing and warm competence. We would argue however, that a mutually more beneficial approach to Long COVID should stem from establishing a relationship in which both the patient and clinician are jointly better served when the clinician seeks empathetically a brain-by-brain concordance in understanding the patient’s experience of sickness. This begins with an educated patient, optimally prepared to bridge the gap between what they are seeking in terms of diagnosis and relief and the clinician’s uncertainties surrounding the condition while still desiring to help and address their concerns (6) This is particularly important as the diagnosis itself of Long COVID carries with it a strong personal dimension, as it is intricately bound up in the phenomenon of meaning, for the diagnosis itself is attended by considerable uncertainty and mystery and fear. It is in this individual domain that the role of the patient–clinician relationship can serve as a therapeutic force both for the patient as well as the clinician (see Table 1). Patient–clinician communication which not only validates the patient’s symptoms but also expunges them of guilt by dispelling their concerns that their complaints may be viewed as merely “in their head” or in some way their fault can be a therapeutic message (7). Such an approach may also benefit the clinician, who by virtue of establishing a genuine working relationship with the patient can also find meaning and compassion and perhaps, less burnout when faced with such a complex problem as Long COVID which for now has no easy answers.

Table 1. Six Recommendations for Leveraging the Patient–Clinician Interaction to Optimize Symptom Management

Treat the symptoms and causes while empathically understanding the patient’s experience of sickness
Recognize that the diagnosis itself of Long coronavirus disease (COVID) carries with it a strong personal dimension
Validate the patients’ symptoms and expunge them of guilt
Dispel patients’ fears surrounding the diagnosis of Long COVID
Establish a genuine working relationship with the patient
Find meaning and compassion to minimize burnout when facing such a complex problem as Long COVID.

Call to Action

We described the physical and psychological impact of Long COVID as well as detailed the neurobiology of the patient–clinician interaction and placebo science. While there are many unknowns we struggle with, placebo effects (and not mere placebo pills) can be potentially exploited as adjuvants for

symptom managements. Namely, we recommend: (1) Educating the patient about her experience of sickness to align it with the clinician perspective of treating the symptoms and causes of the disease; (2) conveying awareness about the diagnosis itself of Long COVID and its strong personal dimension; (3) engaging with patients' perspectives to expunge them of guilt; (4) dispelling fears surrounding the diagnosis of Long COVID; (5) establishing a genuine patient–clinician concordance and alliance to manage Long COVID; and (6) engaging with patients to identify their needs in order to minimize burn out deriving from Long COVID (Table 1).

Overall, the reflections presented here are based on current knowledge of Long COVID, the science of placebo effects with a focus on the neurobiology of the patient–clinician relationship with the scope to bridge these two research fields to translate the take-home messages helping patients cope and manage their Long COVID symptoms.


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ORCID iD

Leonard Calabrese  <https://orcid.org/0000-0002-1789-4923>

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