AARDS
COVID-19 LONG HAULER CLINIC

Preventing and Treating Long-Haul COVID-19 and Other Types of Inflammation

All active ingredients being included are considered GRAS in the US. **Generally recognized as safe (GRAS)** is a United States Food and Drug Administration (FDA) designation that a chemical or substance added to food is considered safe by experts.

St. John's Wort Extract (Hypericum perforatum)

Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies

We describe a series of individuals with symptoms of 'long COVID', and we posit that this condition may be related to a virus- or immune-mediated disruption of the autonomic nervous system resulting in orthostatic intolerance syndromes. We suggest that all physicians should be equipped to recognise such cases, appreciate the symptom burden and provide supportive management. We present our rationale for an underlying impaired autonomic physiology post-COVID-19 and suggest means of management.

It has been hypothesised that COVID-19 infection affects the autonomic nervous system.[16] The relationship between the two is complex: the well-documented cytokine response storm of COVID 19[17] results from sympathetic activation inducing pro-inflammatory cytokine release.[18,19] Conversely, vagal stimulation results in an anti-inflammatory responses,[17] suggesting possible therapeutic targets in the autonomic nervous system.

Alternatively, COVID-19 related autonomic dysfunction could be mediated by the virus itself. Immune mediated neurological syndromes have been described.[20] It is also well established that autonomic disorders such as OH and POTS are associated with autoantibodies,[21] for example to α-/β-adrenoceptors and muscarinic receptors.[22–25] Cohort studies describe commonly preceding infections in POTS,[26] as well as a link with autoimmune biomarkers and autoimmune disorders.[27] Thus, we speculate that there is an underlying autoimmune component to the post-COVID syndromes that we report.

Any individuals presenting with breathlessness, palpitations, fatigue, chest pain, presyncope or syncope should be evaluated carefully. Cardiovascular, respiratory and neurological examination with vital signs and pulse oximetry are essential. Electrocardiogram, blood tests and imaging should be considered to identify other important diagnoses such as organising pneumonia, pulmonary embolism and myocarditis.

An active stand test should be undertaken, measuring blood pressure and heart rate after 5 minutes lying supine, and then 3 minutes after standing. Orthostatic hypotension is defined as a fall of >20 mmHg systolic and >10 mmHg diastolic after standing for 3 minutes.[28] POTS is characterised by orthostatic symptoms (in the absence of orthostatic hypotension) with an increase in heart rate of 30 beats per minute or more when standing for more than 30 seconds, or 40 beats per minute or more in those aged 12–19 years.[29] A continuous blood pressure and heart rate trace during a tilt table test of an individual with orthostatic intolerance post-COVID is shown in Fig Fig1.1. After adopting the upright position, a marked and continuous rise in heart rate was seen, corresponding with the onset of clinical symptoms and mirrored by blood pressure oscillations in keeping with an adrenergic response. The average heart rate rise was under 30 beats per minute, thus not fulfilling criteria for POTS.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7850225/

Effects of acute administration of selective serotonin reuptake inhibitors on sympathetic nerve activity

The main finding of this research was that the peripheral administration of SSRIs caused acute autonomic cardiovascular and respiratory effects in the anesthetized rat. Because three distinct compounds with similar selectivity regarding the SERT system were used, it can be inferred that these are class effects. The most consistent effect of SSRIs in this study was an early and generally sustained sympathoinhibition, as measured by renal sympathetic nerve activity.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4123834/

Short-term sertraline treatment suppresses sympathetic nervous system activity in healthy human subjects

Increased sympathetic nervous system (SNS) activity has been associated with stress, major depression, aging, and several medical conditions. This study assessed the effect of the selective serotonin reuptake inhibitor (SSRI), sertraline, on sympathetic nervous system (SNS) activity in healthy subjects. Twelve healthy volunteers participated in a double-blind, placebo-controlled, norepinephrine (NE) kinetic study, in which the effects of sertraline on SNS activity were ascertained by determining NE plasma concentrations and NE plasma appearance rates and clearance rates in sertraline or placebo conditions. Subjects received 50 mg of sertraline or placebo for two days and then one week later underwent the same protocol with the other drug. By single compartmental analysis, plasma NE appearance rates were significantly lower in the sertraline compared to the placebo condition (0.26+/-0.10 vs 0.40+/-0.23 microg/m(2)/min; P=0.04). Our study found that the net effect of short-term SSRI treatment is an apparent suppression of SNS activity as indicated by a decreased plasma NE appearance rate in the

sertraline condition.

https://pubmed.ncbi.nlm.nih.gov/11259862/

Can Hypericum perforatum (SJW) prevent cytokine storm in COVID-19 patients?

Actually, from our experimental studies on natural compounds able to protect pancreatic β-cells against cytokine-induced damage and death (Menegazzi et al., 2008), we became aware that *Hypericum perforatum* (St. John's Wort, SJW) extract, as well as its main polyphenol component hyperforin (HPF), can potently counteract the pro-inflammatory effects of various cytokines. Indeed, both SJW extract and HPF alone prevented cytokine effects not only in β-cell lines but also in isolated rat and human pancreatic islets (Novelli et al., 2014). The mechanism of action of SJW and HPF is based on the simultaneous blockade of multiple phosphorylation steps, induced by a mixture of IFN-γ/IL-1β/TNF-α (in some way mimicking a cytokine storm), along the JAK/STAT, NF-κB, and MAPK signaling pathways, with the result of avoiding or limiting the transcriptional activation of dysfunctional, apoptotic, and inflammatory target genes, including iNOS, COX-2, CXCL9 and CXCL10 chemokines, ICAM-1 adhesion molecule and others. In particular, SJW and HPF inhibited STAT-1 and NF-κB phosphorylation and DNA binding, as well as the activation of a number of kinases, including IKK, ERK1/2, JNK, and Akt (Menegazzi et al., 2008; Novelli et al., 2016). Furthermore, we got evidence that these natural compounds undergo an efficient intracellular uptake and confer to the cells a long-lasting state of "cytokine resistance" (Novelli et al., 2019). Of note, although SJW extract usually contains other active ingredients at much lower concentrations than HPF (e.g., hypericin, rutin, the flavonoids quercetin and myricetin), no component other than HPF was found to be effective in inhibiting cytokine effects in the 1.0 micromolar range (Menegazzi et al., 2008).

We also showed that SJW extract exerted protective effects in various animal models of acute inflammation. Actually, SJW attenuated carrageenan-induced inflammatory lung injury in mice by inhibiting NF-kB and STAT-3 activation, TNF-α and IL-1β production, ICAM-1 expression, neutrophil lung infiltration, and cellular proteins nitration (Menegazzi et al., 2006). Interestingly, SJW extract was also able to counteract a zymosan-induced multiple organ dysfunction syndrome in mouse (a kind of model of what may occur in shock, sepsis, and presently in severe COVID-19), by reducing peritoneal exudation and migration of neutrophils, as well as pulmonary, intestinal and pancreatic injury, renal dysfunction and myeloperoxidase reaction in lung and intestine (Di Paola et al., 2007). Other authors have likewise documented the anti-inflammatory properties of SJW or HPF, including inhibition of COX and 5-LO activities (Albert et al., 2002), reduction of IL-6 release (Gobbi et al., 2004), decrease of neutrophil activation of matrix metalloproteinase-9, and enhanced resolution of bleomycin-induced pulmonary inflammation model, with consequent reduction of lung fibrosis (Dell'Aica et al., 2007). Thus, there is clear evidence that SJW extract and HPF efficaciously prevent inflammatory damage in various cell types and tissues. In addition, it is worthwhile to consider that SJW extract is largely

employed in Europe and USA as antidepressant and recognized to have a remarkable safety profile, confirmed by extensive clinical trials (Cui & Zheng, 2016).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7300500/

https://www.sciencedirect.com/science/article/abs/pii/S0166354216303692

For further details and the list of all ingredients please click on the link or visit our website www.rheumcare.com/research-ingredient-nutraceutical