Protracted Antidepressant Withdrawal Is (Usually) Central Sensitization

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When I forgot to take my morning dose of Lexapro, I would realize it by 2 or 3pm ir the afternoon—an insidious sense of malaise and discomfort difficult to put into words. By 5pm, debilitating dizziness, nausea and irritability would set in. Rushing home from work, I would chew a 10mg tablet of lexapro (which incidentally makes your tongue numb: a coincidence or another manifestation of SRI-induced numbing wash it down with water, and within 30 minutes, symptoms would abate completely

This is a typical timeline for *acute* antidepressant withdrawal, but having treated, supervised, and discussed thousands of antidepressant withdrawal cases over the la five to six years, a significant subset of patients develops persistent withdrawal symptoms that do not reliably improve with reinstatement of the drug, a phenomen termed "protracted withdrawal."

In my experience, protracted withdrawal is most likely to occur in patients who: (1) stop their medication cold turkey or taper too quickly; (2) do not reinstate treatmen when they experience withdrawal symptoms ("white-knuckling"), or reinstate only weeks later after prolonged suffering; (3) have a biological or environmental predisposition to nervous system sensitization, reflected by personality traits (high neuroticism, conscientiousness, and/or obsessive-compulsivity) and significant adv childhood experiences, complex trauma, or PTSD.

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The most concerning aspect of protracted withdrawal is that symptoms do not relia improve when reinstating treatment, whether this occurs month or a year after stopping. Note: A proportion of these patients *do* improve with reinstatement, but a comparable proportion get a lot worse when restarting, termed a "paradoxical reaction." This makes the risk-benefit calculus of reinstatement very unclear, and w have not yet identified predictors of successful outcomes in PW reinstatement. We generally recommend starting very slowly and make cautious adjustments at closely monitored weekly intervals, if reinstatement is attempted.

Question #1: If protracted withdrawal symptoms do not reliably improve with reinstatement, is it truly *withdrawal?* Withdrawal suggests a deficit that can be fille or replaced with what was lost. But because it frequently can't, turned to the phrase "drug injury" or nervous system injury" to phenomenon of postacute withdrawal.

Question #2: Is there truly any evidence of injury? And does i of receptors and synapses? To date, there is limited neurobiol suggesting that the serotonergic system (SERT, the 5-HT trans postsynaptic 5-HT receptors, and metabolism and release of in unable to recalibrate long-term after prolonged SRI exposure, and there is no evidence correlating any persistent change with functional outcomes. A small PET imaging study (n=8) in monl SERT upregulation 1.5 years after discontinuation, though was exposure (the monkeys were exposed to the antidepressants at social behaviors assessed in the setting of upregulated SERT, no deficits were observed, suggesting that the serotonergic system can *change* (e.g adapting to

persistently upregulated SERT with compensatory shifts in serotonin synthesis, metabolism, receptor density) without a net difference in serotonergic transmissior overall functional status. There are data indicating short-term (weeks-long) changes transporter and receptor expression changes after SRI treatment is withdrawn in animals (reviewed by Horowitz et al. in 2023), but these appear to reflect the standa time course of homeostatic recalibration.

Nonetheless, it is well-established that psychiatric drugs can cause neurobiological "injury", the best example being antipsychotic-induced tardive dyskinesia (TD). Evidence of the D_2 hypersensitivity hypothesis has been observed in humans, and tl theory is supported by clear efficacy of VMAT2 inhibitors which reduce the synapt release of dopamine to limit stimulation of upregulated D_2 receptors. Although TD can present with symptoms other than involuntary orofacial movements, it is much more differentiated and well-defined than protracted SRI withdrawal. To date, no pharmacologic intervention (serotonergic or other) has demonstrated efficacy, even anecdotally, in meaningfully relieving protracted withdrawal symptoms. Protracted withdrawal's resistance to serotonergic and non-serotonergic treatment suggest tha we may be looking for solutions in the wrong place, when the more apt comparison may be to an increasingly recognized category of medical conditions.

The Rise of Medically Unexplained Disorders

In the Western world, there has been a massive rise in diagnoses of various syndron (symptom clusters) with unclear pathophysiology. It doesn't take much time on redc to discover highly-populated and active subreddits for various medically unexplaine conditions:

For starters:

- Adrenal fatigue
- Atypical facial pain

- Benign fasciculation syndrome
- Burning mouth syndrome
- Central sensitization syndrome
- Cervicogenic dizziness
- Chronic abdominal pain
- Chronic dizziness
- Chronic fatigue syndrome / myalgic encephalomyelitis (ME/CFS)
- Chronic Lyme disease or persistent symptoms attributed to Lyme disease
- Chronic low back pain, nonspecific
- Chronic migraines
- Complex regional pain syndrome
- Costochondritis or persistent noncardiac chest-wall pain
- Cyclic vomiting syndrome
- Dysautonomia, unspecified
- Electromagnetic hypersensitivity
- Fibromyalgia
- Functional dyspepsia
- Functional neurological disorder
- Functional seizures / psychogenic nonepileptic seizures
- Functional urinary symptoms
- Heavy-metal toxicity, suspected or unconfirmed
- Histamine intolerance
- Hypermobile Ehlers–Danlos syndrome
- Hypermobility spectrum disorder

- Idiopathic intracranial hypertension without clearly documented objective findings
- Idiopathic neuropathic pain
- Idiopathic pruritus
- Interstitial cystitis / bladder pain syndrome
- Irritable bowel syndrome
- Long COVID / post–COVID-19 condition
- Mast cell activation syndrome (MCAS)
- Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
- Myofascial pain syndrome
- Noncardiac chest pain
- Non-celiac gluten sensitivity
- Post-infectious fatigue syndrome
- Postural orthostatic tachycardia syndrome (POTS)
- Pudendal neuralgia
- Somatic symptom disorder
- Temporomandibular disorder (TMJ)
- Tension-type headache, chronic
- Tinnitus without an identified structural cause
- Vulvodynia
- Whiplash-associated disorder, chronic

It has saddened me as a clinician to witness the scale of suffering of people diagnos with these conditions. It is also interesting how profound the overlap between thes conditions, to the point that an assigned diagnosis for any individual patient with a cluster of symptoms may be most influenced by context: If the cluster of symptoms

slightly pain-predominant and you're in a rheumatologist's office, it's fibromyalgia. it involves GI distress and you're seeing a gastroenterologist, it's IBS. A psychiatrist functional neurologic disorder or somatic symptom disorder.

Did these syndromes commonly occur in humans 10,000 years ago? Or is it that we chronically stressed, sit longer, exercise less, work harder, less social and connected and overstimulated (including by highly emotionally-charged news networks, TikTo and instagram)? Are they truly attributable to stress and trauma, or will some of the conditions soon have a well-defined, non-CNS-based pathophysiology?

Central Sensitization: A Unifying Theory

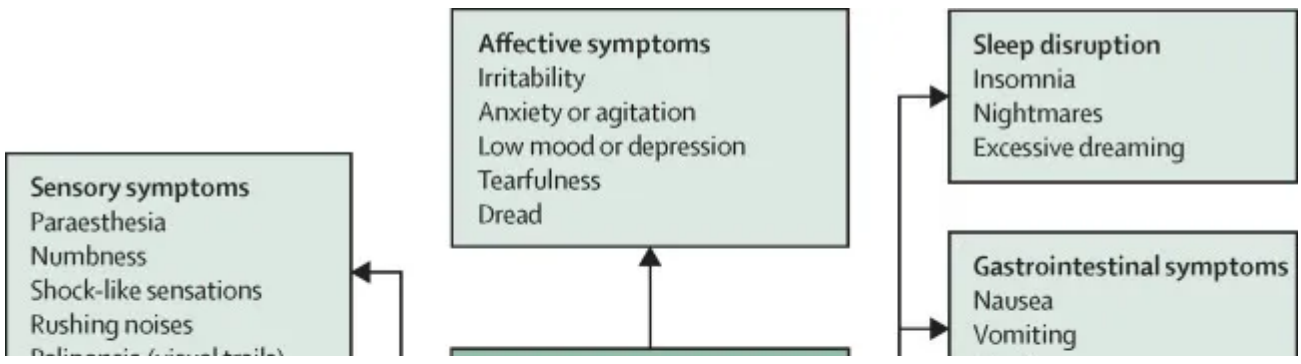
Harvard professor Clifford Woolf first identified the mechanism central sensitizati in the 1980s through a series of electrophysiological and reflex experiments in rats, and later expanded on the concept high-profile 2011 review in *PAIN*. It took until 2 for the International Association for the Study of Pain to formalize central sensitization into a diagnostic category relevant to chronic pain. Alongside nociceptive pain (from tissue damage) and neuropathic pain (from nerve damage), th added nociplastic pain, or pain arising from altered central nociceptive processing without evidence of tissue or nerve damage driving it. The concept was laid out for broad clinical audience in Lancet in 2021, and it is influencing how the the field understands fibromyalgia, chronic low back pain, tension-type headache, IBS, and t long list of conditions that used to get filed under "medically unexplained" (see abo list).

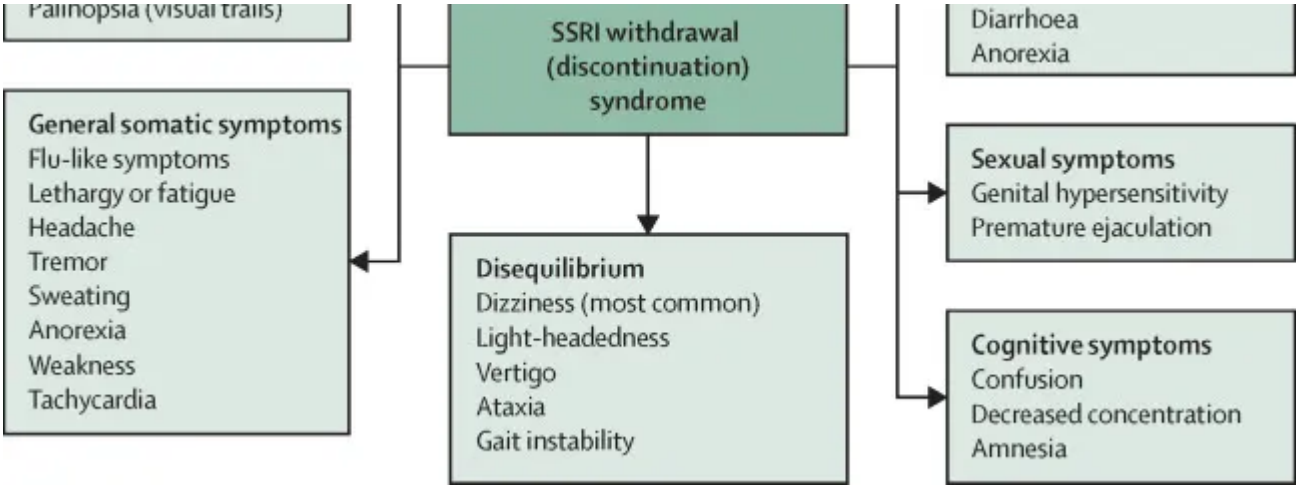
Central sensitization works as follows: Severe bodily or mental stress and/or trauma either single events or repeated events, or perhaps some other unknown cause, indu an adaptive state of hyperarousal and hypervigilance in the CNS, involving increase activity in nociceptive facilitatory pathways, poor endogenous analgesia (the brain's descending inhibitory system loses its brakes), activated glia in the CNS, altered sensory processing, and disrupted resting-state connectivity in the default mode

network. Layered on top of this is a threat-appraisal loop — fear, prior experience, catastrophic beliefs like "pain equals damage," environmental context, and emotion state all feed into how much danger the brain assigns an incoming signal, which creates more muscle tension, more sympathetic arousal, more stimulatory input to dorsal horn, more sensitization, which then produces more pain, which confirms th danger appraisal, tightening the loop further. None of this requires ongoing tissue damage and the loop sustains itself. It's a defense mechanism that protects a body c mind that has been traumatized from further injury, which makes sense in a dark sc of way, since our brain is wired to maximize survival, not how good we feel.

Protracted Antidepressant Withdrawal: Another Cluster of Symptoms of Central Sensitization

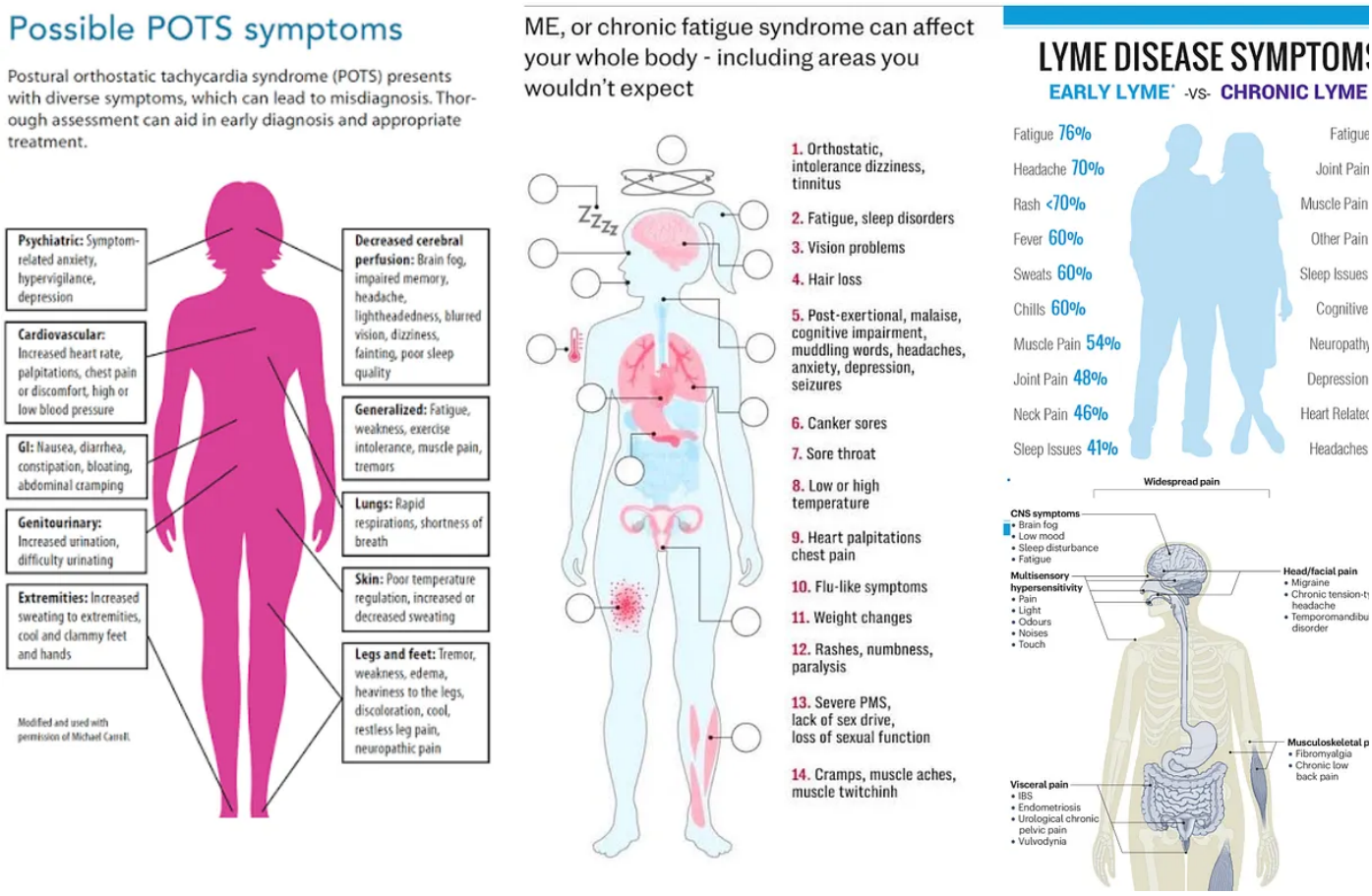
Symptoms of protracted withdrawal are non-specific and are drawn from a pool of symptoms common to all of these medically unexplained conditions. Moreover, exposure to antidepressants is neither *necessary nor sufficient* to induce symptoms th resemble symptoms of protracted withdrawal. Every organ system is fair game (see below figure), as is the case other medically unexplained syndromes. You could argu that serotonin, as a fundamental neurotransmitter that mediates numerous domain human perception and behavior, should induce withdrawal that also spans multiple symptomatic domains, but protracted SRI withdrawal usually presents in entirely different ways in two individuals without any specific "serotonin fingerprint" like w see in the dopaminergic tardive dyskinesia associated with prolonged antipsychotic use.





SSRI withdrawal symptoms. Source: [Horowitz and Taylor, 2019]

Notice any similarities?



Protracted SRI symptoms do not appear to be reliably distinguishable from

benzodiazepine-induced neurologic dysfunction, or withdrawal from non-serotone antidepressants (maybe data will eventually suggest otherwise, but such comparisor are very difficult to make with statistical rigor).

We can see that the seminal 2021 Lancet article on nociplastic pain/central sensitization maps perfectly on protracted withdrawal:

"Caring for patients with nociplastic pain is challenging; the pain complaint is often difficu to describe, there are associated subjective symptoms, and pathognomonic clinical findings biomarkers are absent. Nociplastic pain conditions are frustrating for both health-care professionals and patients, with physicians uncertain regarding diagnosis and patients resentful that their symptoms are doubted."

It's quite possible we've been thinking about antidepressant withdrawal the wrong way. Acute antidepressant withdrawal is one of many triggers that can lead to centr sensitization, but is itself completely distinct from protracted withdrawal as it's currently defined. **In protracted withdrawal patients who do not improve, or worse with antidepressant reinstatement, I propose that the true diagnosis may be centr sensitization.**

The stress-diathesis model suggests that people may carry different biological vulnerability to central sensitization and a different threshold of "hits" required to reveal that underlying diathesis and manifest overt symptoms of CS. For individuals with highly vulnerable genetics, a single week of severe antidepressant withdrawal may be enough to trigger CS. For others, several nervous system insults are required a hostile household growing up, then an abusive partner, followed by a life-threatening hospitalization, before experiencing acute antidepressant withdrawal, which breaks the glass and leads to the manifestation of CS symptoms. For some very high-functioning individuals with no prior "hits" and extremely high in conscientiousnes the psychological distress of suddenly being incapacitated by debilitating antidepressant withdrawal symptoms (and pushing through anyway in the name of

discipline and dutifulness) might be a powerful enough hit to shatter the glass and manifest CS. In such a case, the antidepressant is the trigger that sets off the CS cascade, but is simply one of many possible triggers. A process has manifested that operates independently of the antidepressant, of serotonin, and its treatment may h little to do with it (e.g. reinstatement).

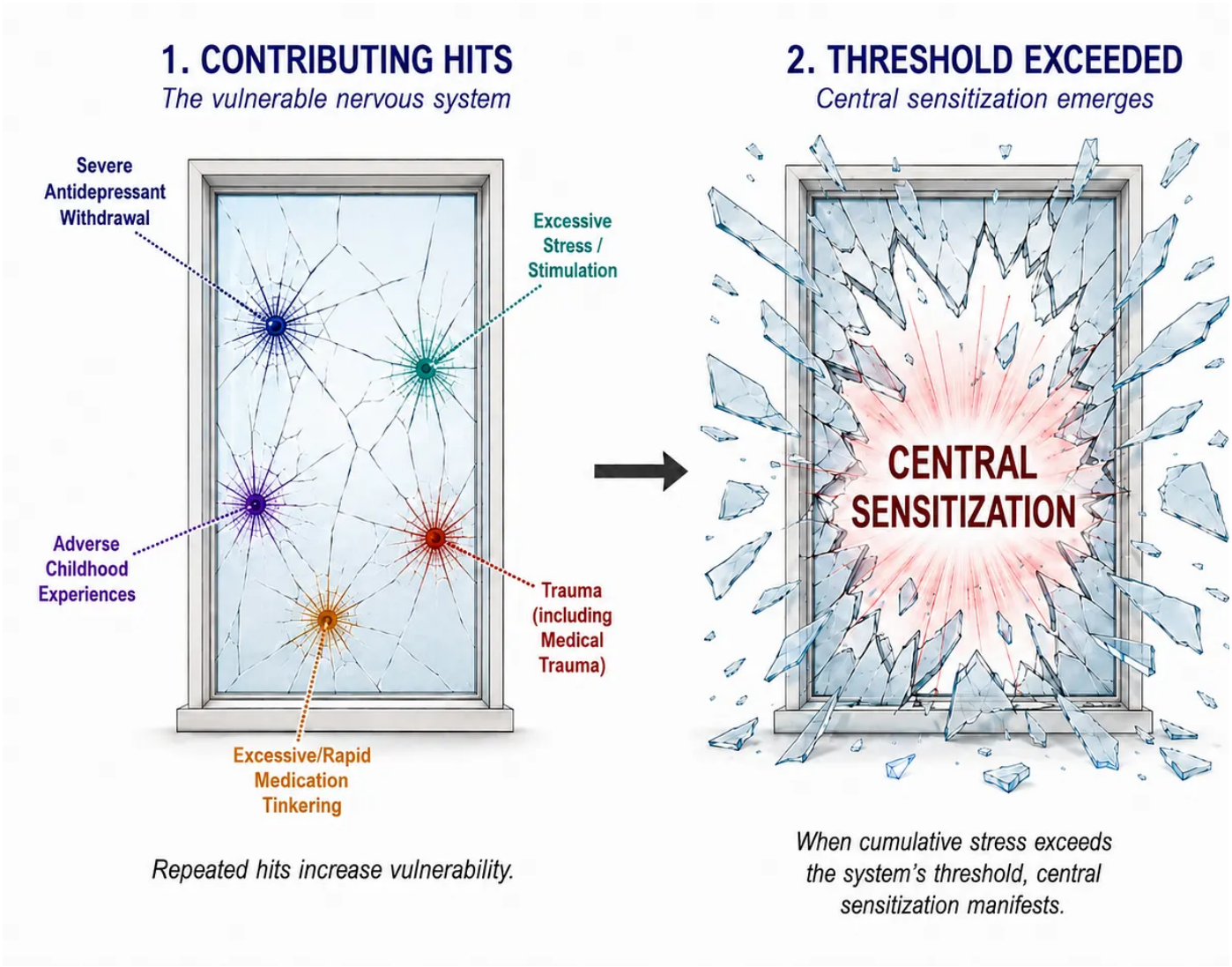


Figure. A model of central sensitization, with antidepressant withdrawal conceptualized a "hit" that contributes to central sensitization (note: biological predisposition to central sensitization is represented by the thickness of the glass

A few notes: This theory does not suggest that patients with "protracted withdrawa *making their symptoms up.* Symptoms of central sensitization are real and not feignec

We also need to destigmatize, even deplatform, the concept of "psychosomatic." Th nervous system is the interface of mind and body. Conditions that originate in the central nervous system are just as real and debilitating as somatic conditions with currently identifiable biological markers. Stress and trauma have clear effects on th body, and on their own can induce symptoms of a heart attack or mimic a seizure. A central sensitization theory of protracted withdrawal also does not *blame the patient* Patients with central sensitization often have had no control over adversarial experiences, traumatic events and bad medical advice, despite advocating for themselves the best they can. Identifying a contributing factor isn't the same as assigning blame to a patient: we don't consider it blame when a cardiologist counse patient on diet, exercise, or smoking cessation as contributors to their heart disease The same logic extends central sensitization.

If confirmed, the CS theory of protracted withdrawal has major clinical implication for treatment and recovery. It would also great news, suggesting no actual "injury" irreversible damage has occurred in most (hopefully all) patients experiencing these debilitating symptoms. However, a differential is possible: Maybe 90% of protracted withdrawal cases are central sensitization, while 10% reflect TD-esque damage to th serotonin system. Maybe both coexist.

In the next piece, we'll turn to recovery. If protracted withdrawal is best understood through the lens of central sensitization, this has profound implications for treatme

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Great read, Bryan. Looking forward to the next piece on recovery/treatment of CS.

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Fantastic read. Thank you!

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