What is the impact of nicotine on the Post-COVID-19 syndrome - a severe impairment of acetylcholine-orchestrated neuromodulation: A case series

Marco Leitzke (marco.leitzke@gmx.de)
Helios Clinics Germany https://orcid.org/0000-0001-5155-1978

Research Article

Keywords: Post-COVID-19 syndrome, neuromodulation, long haul COVID, nicotinic acetylcholine receptors, nicotine

Posted Date: September 29th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2063399/v1

Abstract

Following SARS-CoV-2 infection, many individuals suffer from post-COVID-19 syndrome. It makes them unable to proceed with ordinary everyday activities due to weakness, memory lapses, pain, dyspnea, and other unspecific physical complaints. Several investigators have demonstrated that the SARS-CoV-2-related spike glycoprotein (SGP) not only attaches to angiotensin-converting enzyme-2 (ACE-2) receptors but also shows DNA sections highly affine to nicotinic acetylcholine receptors (nAChRs). The nAChR is the principal structure of cholinergic neuromodulation and is responsible for coordinated neuronal network interactions. Nonintrinsic viral nAChR attachment substantially compromises integrative interneuronal communication. This explains the cognitive, neuromuscular, and mood impairment and the vegetative symptoms characterizing post-COVID-19 syndrome. The agonist ligand nicotine shows an up to 30-fold higher affinity for nACHRs than acetylcholine (ACh). We hypothesize that this molecule could extrude the virus from nAChR attachment and pave the way for unimpaired cholinergic signal transmission. Treating several individuals suffering from post-COVID-19 syndrome with a nicotine patch application, we observed an immediately substantial improvement of the symptoms up to complete remission after several days.

Introduction

Post-COVID-19 syndrome

The coronavirus SARS-CoV-2-evoked pandemic calamity demanded approximately 6 million victims within 30 months[1]. Unprecedented scientific efforts led to a better understanding of the viral structure, transmission paths, and pathologic patterns and helped to create sufficiently protective vaccines. However, the virus always seems to be one step ahead. It presents genetic variants of SARS-CoV-2[2–7] causing higher contagiousness[7], compromising the sufficiency of vaccines[4], promoting escape from natural immunity [4,7], or revealing new pathology patterns[8]. Thus, the fifth wave of rising infection rates is underway[9,10], and the medical care capacity in most countries is challenged anew[11]. This, during the third and fourth waves, in some areas, is even harder than during the previous waves[12].

Meanwhile, we are becoming increasingly aware that after convalescence from acute COVID-19, the suffering in many cases is not over yet[13].

Symptoms such as chronic fatigue[9,14,15], dizziness[9,16], low-grade fever[15], anosmia[17], memory lapses[15], ageusia[17], muscle weakness[15], diarrhea and bouts of vomiting[15], concentration and sleep difficulties[9,15], mood disorders[15], headache[9,15], cognitive impairment[18], motor deficits, new onset of diabetes[15,19,20] and hypertension[15], dyspnea[9,15,18] and exercise intolerance[16,18] are summarized as post-COVID-19 syndrome[14]. (see Table 1)

The occurrence of the mentioned symptoms weeks or months after the acute phase of SARS-CoV-2[15] infection is independent of the severity of the initial disease course[21,22] or baseline chronic medical conditions[21,23]. Its incidence is estimated to be 35% (outpatients)[21] and 87% (inpatients)[24] among all individuals experiencing SARS-CoV-2 infection. In addition, the endurance of the symptoms is unpredictable[15,22,25], and after six months, an average of 14 persistent symptoms are reported by subjects suffering from long-haul COVID[26].

These facts underline the enormous meaning of the post-COVID-19 syndrome to global societies regarding public health, political, sociopolitical, and financial burden to respective systems[18,27–29]. Not to neglect the individual somatic and psychological misery of each suffering patient. Thus, we should be aware of this inevitable aftershock to health care systems[13,18], which is to be expected from this chronic phase of COVID-19[30,31].

We will see many more infected patients recovering from the acute phase of COVID-19 but in a large proportion needing therapy and rehab capacity[18,22,27] to cure the symptoms of the chronic phase[22], the post-COVID-19 syndrome[32].

Is it just the ACE2 receptor?

For the acute infection phase, physicians lack a causal therapeutic strategy to face viral assault on human organ systems and must be confined to symptomatic therapeutic approaches. These, in the severe courses of SARS-CoV-2 infections, are rather underwhelming[48,49]. Unfortunately, the situation is comparably cloudy regarding post-COVID-19 syndrome[13,26]. The cause of its widespread symptomatology is speculated to be ongoing systemic inflammation[16,26], peripheral organ dysfunction[16], such as cerebrovascular changes[9] and direct virus-related encephalitis[16], myalgic encephalomyelitis/chronic fatigue syndrome (ME/CSF)[50], persistent brainstem dysfunction[23], and psychosomatic disorders[39]. This makes therapeutic approaches to long-haul COVID likewise speculative[51,52], and their effectiveness is rather dissatisfying[29].

Recently, our group described the crucial meaning of autonomic balance for the severity of COVID-19 courses[53,54] and highlighted the essential importance of nicotinic acetylcholine receptors (nAChRs) for the limiting regulation of cytokine liberation and virus replication at the transcriptional level, restricting nuclear factor kappa-light-chain-enhancer of activated B cells (nf-κB) action along the cholinergic anti-inflammatory pathway (CAP)[53,54]. Analyzing the amino-acid (aa) sequence alignment of the motifs found in toxins from snakes of the *Ophiophagus* (cobra) and *Bungarus* genera in the G-ectodomains of three *rabies lyssavirus* (formerly rabies virus) (RABV) strains[55] or muscarinic toxin-like protein and cobratoxin (naja siamensis)[28] and comparing it to the motifs in spike glycoprotein (SGP) from SARS-CoV-2[28,55] revealed profound similarities between the highly nAChR affine toxins and SARS-CoV-2 specific proteins[28,55]. Therefore, Changeux et al. (2020) recently proposed the ´nicotine hypothesis´, which implicates the propensity of SARS-CoV-2 not only to bind to ACE2-receptors (ACE2R) but also to nicotinic

AChRs[55]. Viral competition with acetylcholine for nAChR binding to enter the human body may lead to primary neurological infection[55,56]. Furthermore, it showed that among the severe and fatal cases of COVID-19, the proportion of nicotine consumers was significantly lower[57]. Since nicotine might at least protect nAChRs from viral attachment, therapeutic nicotine application was proposed to manage acute COVID-19 infections[55]. This argument is convincingly supported by the cohort study of Cox et al. (2020), which included 8.28 million participants (19.486 confirmed COVID-19 cases) and showed lower odds for COVID-19 infection and COVID-19-related ICU stay in association with smoking[58]. Farsalinos et al. (2020) examined and identified a “toxin-like” aa sequence in the receptor binding domain of the spike glycoprotein (SGP) of SARS-CoV-2 (*aa 375–390*), showing significant sequence homology with the neurotoxin homolog NL1, one of the many snake venom toxins interacting with nAChRs[59]. Additionally, they performed computational molecular modeling and docking experiments using 3D structures of the SARS-CoV-2 SGP and the extracellular domain of the nAChR α9 subunit[59]. Thus, they could show the primary interaction between the *aa 381–386* sequence of the SARS-CoV-2 SGP and the *aa 189–192* sequence of the extracellular domain of the nAChR α9 subunit[59], the core of the “toxin-binding site” of nAChRs[59]. Likewise, a similar interaction could be demonstrated between the ligand binding domain of the pentameric α7 nicotinic acetylcholine receptor (α7nAChR) chimera and the SARS-CoV-2 SGP[59]. The authors concluded that their findings strongly support the hypothesis declaring a dysregulation of the nicotinic cholinergic system is a considerable part of the pathophysiology of COVID-19[59]. They emphasized that nicotinic cholinergic agonists may act protectively to nAChRs and thus have therapeutic value in COVID-19 patients[59].

The pivotal neuromodulational role of nicotinic acetylcholine receptors

Within the central nervous system (CNS), acetylcholine (ACh) is mainly released from projection neurons (PN), which innervate distal areas and local interneurons interspersed with their cellular targets. PN are found in several nuclei, including the medial habenula, pedunculopontine, laterodorsal tegmental areas, the basal forebrain complex, and the medial septum (reviewed in [60]). They promote extensive and diffuse innervation of numerous neurons in the CNS. Their signaling is carried out by ACh coupling to pre- and postsynaptic as well as axonal and cell body-located AChRs on a massive number of targeted neurons throughout the brain (reviewed in [60]). Regulating the velocity and amount of transmitter release into the synaptic cleft improves the signal-to-noise ratio (reviewed in [60])(see Fig. 1). It orchestrates fine-tuned, synchronized response behavior of central and autonomic nuclear regions of the brain to internal and external stimuli (reviewed in [60])(see Fig. 1). Moreover, they are involved in synaptic plasticity, neuronal development, and learning processes in general (reviewed in [60]).

AChRs are distinguishable into metabotropic muscarinic (mAChRs)[61,62] and ionotropic nicotinic acetylcholine receptors (nAChRs)[63,64]. In addition to their different propensity binding to muscarine or nicotine[62], they differ in their signal properties, which most of all show up in great differences in the

signal transmission velocity[62]. Signal transduction of mAChRs is realized slowly via coupling to G-proteins either activating phospholipase C (PLC), inhibiting adenylate cyclase[65], or noncanonically[65], altering pathways involving phospholipase A2, phospholipase D, and tyrosine kinase as well as calcium channels[65]. The excitatory or inhibitory manner of the mAChR effect depends on the targeted cell type to which muscarinic cholinergic signaling is applied[65]. This diversity of mAChRs in terms of their several modes of action, together with the high degree of homology at the orthosteric ACh-binding site[65], made the development of specifically acting ligands, therapeutically influencing muscarinic AChR-related signaling pathways almost impossible until recent times [61,65].

In contrast, nAChR activation leads to fast and nonselective opening of membrane-bound, excitatory cation channels[62]. These pentameric nAChRs[63] with allosteric configuration[66] are essential to the interneuronal communication within the CNS and the autonomic nervous system (ANS)[60]. Even though neuromodulators commonly act in a metabotropic fashion, ionotropic nAChRs were shown to act neuromodulatory largely as well[67]. They consist of a varying, either homomeric or heteromeric, combination out of nine (α2-α10) α- and three (β2-β4) β-subunits[63,68,69] and are located at presynaptic or preterminal membrane sections where they modulate transmitter release. In addition, nAChRs are found on dendrites or neuronal cell bodies, where they generate postsynaptic effects[63]. In the CNS, nAChR neuromodulation realizes the regulation of transmitter release, cell excitability, and integrative adaptation of neuronal activity[63]. Stimulation of nAChRs can increase the release of several neurotransmitters, such as glutamate, gamma-aminobutyric acid (GABA), and dopamine (DA) (reviewed in[60]). Thus, networking and coordination of essential physiological functions such as arousal, sleep, fatigue, anxiety, nutritional behavior, cognition, and central processing of pain[63,68,70–72] are regulated. nAChRs play a significant role in the synchronization of neuronal activity[60,67].

Gotti et al. (2006) described the α4β2 nAChR subtype as the best-characterized nAChR in animal (rat) brains[63]. They stated this nicotinic AChR to be the primary neuromodulatory nAChR subtype in several cerebral subregions, such as the cortex, striatum, superior colliculus, lateral geniculate nucleus, and cerebellum[63]. This was demonstrated not least in the detectable loss of high-affinity nAChRs in the CNS of α4β2 subunit knockout mice[73] and underlines the central role of nAChRs in the entire neuromodulatory network.

Nicotine effect on nicotinic acetylcholine receptors

The chronic application of nicotine in animal and in vitro models yielded an upregulation[74] of respective central binding sites. In contrast, the chronic increase in the natural ligand ACh via the application of a cholinesterase inhibitor led to a consecutive decrease in the central density of nAChRs[75]. These changes occur quickly after nicotine exposure, making it clear that cholinergic signaling adapts quickly to nicotine and can effectively improve compromised cholinergic neurotransmission. These effects were mainly

seen in α4β2-type receptors with the aforementioned prominent meaning to nicotinic cholinergic neuromodulation[63]. Notably, nAChR upregulation is not accompanied by desensitization but rather an increased ratio of high-affinity nAChRs (from 25% baseline up to 70% under nicotine exposure) compared to low-affinity nAChRs[74]. In addition, the opening frequency of the α4β2 cation channels increases up to three times under chronic nicotine exposure[74]. Thus, nicotine exposure leads to functional upregulation of human α4β2 nAChRs[74]. Clinically, nicotine application to animals improves vigilance, locomotor activity, cognition, respiratory function, cortical blood flow, electroencephalogram (EEG) activity, pain resilience, and gastrointestinal and cardiovascular regulation[69]. French et al. (1999) demonstrated a long-lasting (up to 72 hours after nicotine exposure) increase in neurotrophic nerve growth factor (NGF) mRNA after nicotine administration to the hippocampus, suggesting long-term neuroprotective effects of nicotine[76]. Altogether, nicotine works as a ligand with high affinity and profound intrinsic activity on nAChRs[63], substantially improving the responsiveness[74] and activity[69] of these core receptors of neuromodulation. In addition to the prescription of transcutaneous nicotine application as a substitute for weaning smokers, the transcutaneous application of this substance has been investigated in clinical trials evaluating its therapeutic effects on neurologic or gastrointestinal disorders in nonsmoking patients for several weeks[77–80]. These investigations showed no substantial side effects[77–79]. Using very high dosages (up to 107 mg/day), almost every patient with more than 90 mg/day showed frequent nausea and vomiting[80]. Nonetheless, all individuals in this trial investigating the ameliorative effects of nicotine on Parkinson's disease (PD) showed improved motor scores under reduced dopaminergic treatment[80]. In contrast to the well-known addictive potential of chronically inhalation nicotine usage, none of the trials showed nicotine dependency after withdrawal of transcutaneous nicotine application at the end of the investigations[77–80].

The competition of SARS-CoV-2, acetylcholine, and nicotine at the nicotinic acetylcholine receptor

In terms of the central role of nAChRs in interneuronal communication and their involvement in almost every synaptic signal transmission, the possibility that SARS-CoV-2 binds to these nAChRs on a large scale in a nonintrinsic way is a plausible explanation for the widespread symptoms of long-haul COVID-19. By competitively inducing a diminished effect of its natural ligand (ACh), the viral blockade of these receptors leads to a sharp deterioration of cholinergic neuromodulation. Thus, most long-term COVID-associated deficiencies (see Table 1) can be attributed to neuromodulatory deterioration.

Referring to the abovementioned results of Changeux et al. (2020)[55], Oliveira et al. (2021) investigated the possible binding of SARS-CoV-2 SGP to nAChRs using molecular simulations of validated detailed atomic structures of nAChRs and the spike protein[81]. Examining the Y674-R685 loop of the viral SGP and its binding to three different nAChR types (i.e., α4β2, α7, and the muscle-like nAChR αβγδ from Tetronarce californica), their results predict an apparent nAChR affinity of SARS-CoV-2-related spike protein due to a PRRA (proline, arginine, arginine, alanine) motif in the spike binding region. Notably, this is not found in other SARS-like coronaviruses[81]. Using principal component analysis (PCA), the molecular mechanics

Poisson-Boltzmann surface area (MM-PBSA) approach[82], and in silico alanine-scanning mutagenesis[83], the authors calculated AChR subtype-specific binding-related conformational behavior of the protein, such as subtype-specific but uniformly stable complex formation between nAChR and SGP[81]. These results confirm the data from Farsalinos et al. (2020), which showed hydrogen bonding and shape-related interaction of the extracellular domain of α9AChRs and SARS-CoV-2 SGP, as well as SGP coupling to the ligand binding domain of a pentameric α7 nAChR chimera using in silico experiments[59].

The affinity of natural or synthetic ligands to several nAChRs varies depending on the distinctive nAChR composition from the α- or β-subunits[63]. Despite these subtype-specific differences between the agonist ligands, every binding site shows significantly higher inhibition constants (K_i) for the natural agonist (ACh) compared to nicotine (reviewed in [63]). In the case of α7-α7 subunit interfaces, this indicates an up to 30-fold higher affinity[84] of nicotine to respective α7 subunits containing nAChRs compared to the physiological ligand ACh[63].

The far higher affinity of nicotine to the nAChRs in comparison to ACh and the apparent capability of SARS-CoV-2 to displace ACh from its specific receptors suggest the assumption that nicotine might counteract the viral blockade of nAChRs and displace the virus for his part from the nAChR binding (see Fig. 2).

Material

We investigated one female (32 years old) and three male (19, 41, and 52 years old) individuals who suffered from numerous symptoms indicative of post-COVID-19 syndrome following a polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection with a relatively mild course. The patients described weakness, dyspnea, sleep disturbances, dizziness, complete ageusia and anosmia, and various other symptoms (see Tables 3, 4, 5, and 6). Except for the youngest, the patients could not continue their daily activities compared to the period before the SARS-CoV-2 infection. Since these multiple nonspecific symptoms have not improved over a specific time without signs of acute COVID-19 infection, they visited our outpatient clinic.

Methods

After meticulously explaining the hypothesis described above, the expected effects of nicotine, and clarification of possible side effects, the patients were advised to apply a standard nicotine patch. Since all included individuals were nicotine-naïve persons, they were instructed to use the lowest available dosage (7.5 mg/24 hrs) and to place the patch once daily in the morning. All patients followed these instructions, except for the 41-year-old patient. He bought the patches mistakenly at a dosage higher (15 mg/24 hrs) than the recommended dosage. In all cases, the patients were asked to register their symptoms four days before applying the nicotine patch (see Figures 3, 4, 5, and 6) and to score the severity of their complaints from 0 to 5 daily (see Table 2).

Results

Case 1

The 19-year-old otherwise healthy patient was diagnosed with SARS-CoV-2 infection by a positive PCR test on March 26, 2021. After a relatively mild course of the acute infectious disease with symptoms such as mild fever, sore throat, and feeling of weakness, these resolved entirely within ten days. Approximately three weeks after the detection of the infection, the patient noticed a sudden loss of sense of smell and taste and general fatigue. These complaints persisted over the next several months with minimal undulation in symptom severity. On presentation to our outpatient clinic in November 2021, we counseled the nicotine-naïve patient about the apparent expression of a post-COVID-19 syndrome. We informed him about the problematic diagnostic and therapeutic approach to the described symptoms. The patient consented to the off-label use of percutaneous nicotine application and began 24 hourly applications of a nicotine patch (7.5 mg/24 h for seven days) on 23 November 2021.

For the days before nicotine application, weakness was scored in the range of the two highest possible levels (levels 4 to 5). Anosmia and ageusia were reported consistently at the highest possible level (5). Recovery from weakness was most rapid, with a daily reduction in symptom severity by one level after nicotine exposure to remain at level 2 for three days from day three and at level 1 for three days from day 6. Finally, from day 9, the patient felt free from weakness (see Fig. 3). The loss of taste was reduced by one level on the first day, dropped to level 3 on the 3rd day, and returned to level 2 on the 10th day and to level 1 on the 13th day. From day 16, the patient described the complete restoration of the sense of taste. A similarly protracted symptom reduction was seen with anosmia. Beginning on day 3, the patient experienced a decline from level 5 to level 4, regressing to level 3 on day 7, to level 2 on day ten, and to level 1 beginning on day 13. From day 16, the patient reported being able to smell to the same extent as before his SARS-CoV-2 infection. All symptoms did not recur until an interview approximately six months after that. With the onset of nicotine administration, the patient experienced diarrhea and chest tightness for 2 and 3 days, respectively, terminating spontaneously and considered mild (level 1) by the patient. We interpreted these symptoms as classic nicotine side effects. They did not require further therapy.

Case 2

The 31-year-old female patient presented to our outpatient clinic on 17.12.2020, having survived an acute SARS-CoV-2 infection confirmed by a positive PCR test on 21.11.2020 with a moderate course (fever, reduction in smell and taste, loss of appetite, headache, and pain in the limbs, reduced memory, lack of drive, neck, limb and back pain, and rhinitis). The acute infection phase lasted until 5.12.2020, and a negative PCR test confirmed freedom from infection. From that time onwards, she had numerous symptoms, such as chronic fatigue (level 4), loss of smell and taste (level 1), marked difficulty concentrating (level 4), headache (level 4), and considerable exercise intolerance (level 4). Information, education, informed consent, and nicotine therapy were given to the otherwise healthy, nicotine-naïve patient as described above (7.5 mg/24 h for six days). From day two, after the initiation of nicotine therapy, the patient reported a reduction in fatigue of one level per day, which was completely reversed by

day 4. From the 6th day onwards, the patient experienced a recurrence of fatigue to a lesser extent (level 3), which only entirely and permanently abated from the 13th day (level 2), 20th day (level 1), and 23rd day (level 0). The reduction in retentiveness was perceived as very high (level 4) before and at the beginning of the application, dropped significantly from the 3rd day after nicotine administration (level 2), and was no longer perceptible from the 4th day. In the same course, the impaired ability to concentrate was reduced until the concentration performance perceived before SARS-CoV-2 was regained from the 4th day after nicotine therapy.

Similarly, the markedly impaired exercise intolerance (level 4) dropped significantly on day 3 (level 1), becoming unreproducible on day 4, but rose again slightly on day 5 (level 2) and day 6 (level 3), and fell continuously from day eight onwards. From the 24th day after nicotine application, the patient reported full recovery of her physical performance. Starting on day 2, the patient experienced a very unpleasant feeling of tightness in the thoracic region, which was said to be undiminished (stages 3–5) until day 13 after the start of nicotine therapy and to decrease continuously from then on (day 14, level 3; day 19, level 2; day 22, level 1) until complete remission on day 23. We attributed this symptom, which began directly with the start of nicotine administration, to the active substance nicotine in the sense of a side effect. The patient considered these symptoms to be associated with nicotine. She decided to stop therapy on the 6th day and not continue until the 7th day, as we had recommended. This was due to the otherwise perfect symptom remission until the 4th day of nicotine administration (all symptoms, level 0). In a new telephone interview after approximately six months, the patient confirmed that there had been no recurrence of symptoms.

Case 3

A 41-year-old male patient visited our outpatient clinic on 20.12.2022, having been ill from a SARS-CoV-2 infection confirmed on 13.11. 2020 with a moderate course (weakness, fever, chills, headache, coughing attacks, loss of sense of smell and taste, shortness of breath, exercise intolerance, permanent fatigue, pronounced feeling of weakness). At the time of presentation, he was suffering from a variety of persistent symptoms (chronic fatigue - level 3, dyspnoea - level 3, anosmia - level 5, loss of taste - level 5, muscle weakness - level 4, difficulty sleeping - level 1, headache - level 2). The nicotine-naïve patient agreed to off-label use of nicotine patches in the manner described. Unfortunately, the patient misleadingly did not paste the dose we recommended, but twice the dose (15 mg/24 h), which led to intolerable vomiting (level 5) and diarrhea (level 5) within the next 7 hours, so that the patient discontinued the therapy after 10 hours. Despite the cessation of nicotine use, chronic fatigue decreased significantly on day two after nicotine use (level 2), continued to decline on day 3 (level 1), and was no longer detectable on day 4. As in the cases described above, the courses of anosmia and tastelessness showed a rather protracted, continuously declining course. The reduction of these two symptoms co-occurred in the presented case. On the 11th day after nicotine application, there was a slight reduction (level 4), dropping to level 3 on the 12th and 13th days. After a decrease to level 2 on the 14th day, the patient could fully perceive all smell and taste qualities on the 15th day. The mild sleep problems (level 1) had already permanently disappeared on the 1st day of application of the nicotine patch (level 0).

Regarding the feeling of weakness, the patient described a daily reduction by one level until reaching level 1 on the 3rd day, which lasted for another day to be permanently eliminated from the 5th day onwards (level 0). The residual headache reported by the patient with level 2 was entirely resolved by day two after nicotine administration (level 0). This patient also said no recurrence of the described symptoms after a new presentation at an interval of 6 months.

Case 4

A 52-year-old male patient presented to our outpatient clinic on 1.4.2022. He stated that he had been suffering from persistent complaints (chronic fatigue – level 2, shortness of breath - level 2, difficulty concentrating, difficulty sleeping – level 3, mood swings - level 2, chest tightness – level 2, palpitations - level 2) since a SARS-CoV-2 infection proven by a positive PCR test on 3.3.2022. After excluding persistent acute SARS-CoV-2 infection by a negative PCR test, we informed the patient of the apparent presence of post-COVID-19 syndrome. The nicotine-naïve and otherwise unrestrictedly healthy patient agreed to a therapy trial using a nicotine patch (7.5 mg/24 h). Without consultation and contrary to our recommendations, the patient increased the nicotine dose to double on the 3rd day of therapy and stopped the application on the 4th day after almost complete symptom remission. He stated that he had not experienced any side effects of the nicotine application, which is why he doubted the effectiveness (too low a dose) and therefore had two nicotine patches (7.5 mg/24) starting on day 3.

Chronic fatigue increased slightly on the 2nd day of nicotine application (level 3) and then decreased significantly on the 5th day after the start of therapy (level 1). On the 6th day, the fatigue was permanently terminated. The patient's breathlessness was reduced on the 5th day (level 1) and was no longer noticed from the 7th day (level 0). The patient reported that the concentration difficulties had already ended on the day of the 1st nicotine use (level 0). Difficulty sleeping and mood swings persisted until the 4th day (level 2) and were no longer detectable from the 5th day onwards (level 0). The perceived chest tightness (level 2) was reduced on day 5 (level 1) and was no longer detectable on the following day (level 0). The intermittent palpitations (level 1), perceived as mild, had not occurred for two days at the beginning of nicotine usage. On day 3 of therapy, the patient again noticed episodes of palpitations (level 2), which were felt at this level for two days. On day 3 of nicotine administration, this discomfort (level 1) was reduced and permanently abolished on day 4. We interpreted this recurrence of palpitations as a classic substance side effect of nicotine that stopped spontaneously and did not require further therapy. In an interview three months after the intervention, the patient confirmed that he had not noticed any recurrence of the symptoms that had brought him to us.

Discussion

All the cases we presented showed significant alleviation of symptoms immediately after the nicotine patch application or in rapid succession after treatment. There were clear differences in the pattern and the time course of symptom relief. The course of symptom improvement in the cases we presented was independent of their different lengths of existence before nicotine therapy. Notably, in all cases, signs of exhaustion, such as fatigue, weakness, breathlessness, and exercise intolerance, improved equally rapidly

after nicotine exposure (at the latest, by the 6th day). In cases with impairment or loss of the sense of taste and smell, improvement was observed in rather lengthy courses until the complete restoration of these senses over 13 to 16 days. The perceived tightness in the chest and palpitations were described as clear (level 2) during palpitations and ended on the 2nd day after their occurrence (day three after the start of nicotine administration). Regarding chest tightness, which was almost exclusively perceived as mild to very strong, the patient stated that she had not felt any reduction in performance, so a coronary vascular genesis seems unrealistic from the author's point of view. The patient documented recovery from this side effect until the 22nd day after starting nicotine therapy. The amount of virally blocked AChR can vary greatly among individuals, which certainly influences the course of the reduction of symptoms and may require individualized nicotine doses and application intervals. All cases described were observed in nonsmokers. We observed only severe side effects in the patient who had mistakenly applied double the dose recommended by us. Severe nausea with sweating and repeated vomiting are classic side effects of nicotine, which is why this patient discontinued the therapy. However, with continuous nicotine abstinence from then on, all symptoms previously complained of by the patient decreased until restitutio ad integrum on the 15th day after nicotine application. From the author's point of view, this course tends to support the underlying hypothesis since the displacement of SARS-CoV-2 from nAChR binding should follow a certain dose-response relationship. In the case of the patient who had independently doubled the recommended dose from day 3, we suspect that the previous administration of the recommended dose may have led to a habituation reaction that helped avoid later side effects. The release of the SARS-CoV-2 virus from nAChR receptor binding could lead to short viremia with signs of acute SARS-CoV-2 infection at the beginning of nicotine therapy. This viral load should have been shielded after a short time by the humoral component of the immune system by SARS-CoV-2 antibodies formed during the acute phase of infection. Transcutaneous administration of nicotine ensures constant serum levels without relevant peak levels. Thus, we did not see any development of nicotine dependence in the context of nicotine patch therapy. This is also not to be expected from the author's point of view. The amazing similarity between the large number of symptoms of post-COVID-19 syndrome and the long-known central and peripheral symptoms of central anticholinergic syndrome (CAS)[85] encourages the author to believe that long-haul COVID must be a profound cholinergic signal transmission disorder. This is caused by a significantly higher affinity of SARS-CoV-2 to the nAChR compared to the natural ligand ACh[81] and its displacement from AChRs with subsequent blockade of the intrinsic activity of ACh on the nAChR. The presented cases only describe patients with no concomitant morbidities other than post-COVID-19 syndrome. Therefore, the uncritical use of nicotine patches in patients with relevant cardiovascular or respiratory diseases or already existing medication is not advisable. It is probably safer for this group of patients to apply nicotine under inpatient conditions. The presentation of only four individual case descriptions we have made undoubtedly does not allow any general conclusions about the therapeutic effect of transcutaneous nicotine administration in post-COVID-19 syndrome. This requires double-blinded, randomized surveys, which appear easy to carry out due to the minimal therapeutic intervention. Due to the lack of blinding, the author believes that the psychosomatic component, which other authors suspect to be a central component of long-haul COVID[86], cannot be safely ruled out as part of the therapeutic effect. On the other hand, the patients reported no

relapse of symptoms in a later telephone consultation (3–6 months). The studies by Changeux et al. (2020) and Alexandris et al. (2021) show the structurally and functionally high affinity of the corresponding SARS-CoV-2 SGP sections to the nAChR without making a quantitative comparison to the dissociation constants (K_i) of ACh and nicotine[55,87]. Therefore, the displacement of ACh from nAChR binding by SARS-CoV-2 and the removal of this blockade by nicotine remain speculative. The assumption of this constellation is based solely on the known, much higher affinity of nicotine for nAChR in comparison to ACh. Investigations that follow such a quantitative approach would be necessary to objectify the hypothesis put forward by the author. We see the high burden on health care systems, the expected high incidence of post-COVID-19 syndrome associated with the current extraordinarily long courses of therapy, and their unpredictable results. Compared with the low therapeutic effort of a nicotine patch and the easily controllable side effects of a well-known substance, this seems to justify carrying out larger double-blinded randomized investigations based on the described hypothesis. This is particularly so since all previous attempts at explaining etiopathogenesis and the therapeutic efforts based on them are purely theoretical considerations.

Conclusions

Post-COVID-19 syndrome is well explained in its pathogenesis and clinical manifestation with cholinergic neuromodulation disorder due to partial or complete blockage of nicotinic acetylcholine receptors by the SARS-CoV-2 virus. In all the cases we studied, transcutaneous nicotine use led to an immediate improvement in symptoms and rapid restitutio ad integrum. The course of symptom improvement was as individual as the clinical picture of the post-COVID-19 syndrome itself. The ease of implementation and the excellent controllability of the only minor side effects make randomized, double-blinded studies seem easily feasible. The therapeutic access to this complex clinical picture using nicotine patches looks far superior to the time-consuming, personnel- and cost-intensive, and often disappointing rehabilitation measures for patients at all these levels.

Abbreviations

aa *amino acid*

ACE-2 *angiotensin-converting enzyme-2*

ACE2R *angiotensin-converting enzyme-2 receptor*

ACh *acetylcholine*

ANS *autonomic nervous system*

CAS *central anticholinergic syndrome*

CNS *central nervous system*

COVID-19 coronavirus disease 2019

DA *dopamine*

EEG *electroencephalogram*

gamma-aminobutyric acid *gamma-aminobutyric acid*

ICU *intensive care unit*

K_i *inhibition constant*

mAChRs *muscarinic acetylcholine receptors*

MM-PBSA *molecular mechanics Poisson-Boltzmann surface area*

myalgic encephalomyelitis/chronic fatigue syndrome myalgic encephalomyelitis/chronic fatigue syndrome

nAChRs *nicotinic acetylcholine receptors - main receptor type for cholinergic neuromodulation*

neurotrophic nerve growth factor *neurotrophic nerve growth factor*

nf-κB *nuclear factor kappa-light-chain-enhancer of activated B cells*

PCR *polymerase chain reaction*

PD *Parkinson's disease*

PN *projection neurons*

principal component analysis *principal component analysis*

proline, arginine, arginine, alanine *proline, arginine, arginine, alanine*

RABV *rabies virus*

SARS-CoV-2 severe acute respiratory syndrome coronavirus type 2

SGP *SARS-CoV-2-related spike glycoprotein*

Declarations

Conflict of interests

The author reports no financial and no nonfinancial conflict of interest.

Funding

The author received no financial support for this article's research, authorship, and/or publication.

Acknowledgments

I thank Mr. Frank Jabin for his persistent and accurate work in creating the images.

Ethics and consent

The ethics committee of our hospital approved the implementation of the treatments classified as rescue therapy and their publication as a case report series.

Consent

All included patients consented to the off-label use of the substance used after detailed information and publication of the results.

Availability of data

All data are available on request from the corresponding author.

Authors contributions

M.L. recruited the patients, collected and analysed the data, wrote and reviewed the manuscript.

References

1. COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. Lancet 399, 1513–1536 (2022).
2. Weisblum, Y. et al. Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. Elife 9, e61312 (2020).
3. Tang, J. W., Tambyah, P. A. & Hui, D. S. Emergence of a new SARS-CoV-2 variant in the UK. Journal of Infection 82, e27–e28 (2021).
4. Harvey, W. T. et al. SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol 19, 409–424 (2021).
5. Mohiuddin, M. & Kasahara, K. Investigating the aggressiveness of the COVID-19 Omicron variant and suggestions for possible treatment options. Respiratory Medicine 191, 106716 (2022).
6. Vaughan, A. Omicron emerges. New Scientist 252, 7 (2021).
7. Karim, S. S. A. & Karim, Q. A. Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic. The Lancet 398, 2126–2128 (2021).

8. Abdelnabi, R. et al. Comparing infectivity and virulence of emerging SARS-CoV-2 variants in Syrian hamsters. EBioMedicine 68, 103403 (2021).
9. Baker, H. A., Safavynia, S. A. & Evered, L. A. The 'third wave': impending cognitive and functional decline in COVID-19 survivors. British Journal of Anaesthesia 126, 44–47 (2021).
10. Chu, D. K. W. et al. Introduction of ORF3a-Q57H SARS-CoV-2 Variant Causing Fourth Epidemic Wave of COVID-19, Hong Kong, China. Emerg Infect Dis 27, 1492–1495 (2021).
11. Pinho, R. D. N. L. et al. Mental Health and Burnout Syndrome Among Postgraduate Students in Medical and Multidisciplinary Residencies During the COVID-19 Pandemic in Brazil: Protocol for a Prospective Cohort Study. JMIR Res Protoc 10, e24298 (2021).
12. Graichen, H. What is the difference between the first and the second/third wave of Covid-19? - German perspective. J Orthop (2021) doi:10.1016/j.jor.2021.01.011.
13. Rimmer, A. Covid-19: Impact of long term symptoms will be profound, warns BMA. BMJ m3218 (2020) doi:10.1136/bmj.m3218.
14. Lamprecht, B. Gibt es ein Post-COVID-Syndrom? Pneumologe 17, 398–405 (2020).
15. Yelin, D. et al. Long-term consequences of COVID-19: research needs. The Lancet Infectious Diseases 20, 1115–1117 (2020).
16. Heneka, M. T., Golenbock, D., Latz, E., Morgan, D. & Brown, R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alz Res Therapy 12, 69 (2020).
17. Lee, Y., Min, P., Lee, S. & Kim, S.-W. Prevalence and Duration of Acute Loss of Smell or Taste in COVID-19 Patients. J Korean Med Sci 35, e174 (2020).
18. Stam, H., Stucki, G. & Bickenbach, J. Covid-19 and Post Intensive Care Syndrome: A Call for Action. J Rehabil Med 52, jrm00044 (2020).
19. Draulans, D. 'Finally, a virus got me.' Scientist who fought Ebola and HIV reflects on facing death from COVID-19. Science (2020) doi:10.1126/science.abc7042.
20. Rubino, F. et al. New-Onset Diabetes in Covid-19. N Engl J Med 383, 789–790 (2020).
21. Tenforde, M. W. et al. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020. MMWR Morb. Mortal. Wkly. Rep. 69, 993–998 (2020).
22. Barker-Davies, R. M. et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. Br J Sports Med 54, 949–959 (2020).
23. Yong, S. J. Persistent Brainstem Dysfunction in Long-COVID: A Hypothesis. ACS Chem. Neurosci. acschemneuro.0c00793 (2021) doi:10.1021/acschemneuro.0c00793.
24. Carfì, A., Bernabei, R., Landi, F., & for the Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. JAMA 324, 603 (2020).
25. Sawadogo, S. A., Dighero-Kemp, B., Ouédraogo, D.-D., Hensley, L. & Sakandé, J. How NETosis could drive "Post-COVID-19 syndrome" among survivors. Immunology Letters 228, 35–37 (2020).

26. Carod Artal, F. J. Síndrome post-COVID-19: epidemiología, criterios diagnósticos y mecanismos patogénicos implicados. RevNeurol 72, 384 (2021).
27. Klitzman, R. L. Needs to Prepare for “Post-COVID-19 Syndrome”. The American Journal of Bioethics 20, 4–6 (2020).
28. Farsalinos, K. et al. Editorial: Nicotine and SARS-CoV-2: COVID-19 may be a disease of the nicotinic cholinergic system. Toxicology Reports 7, 658–663 (2020).
29. Scordo, K. A., Richmond, M. M. & Munro, N. Post–COVID-19 Syndrome: Theoretical Basis, Identification, and Management. AACN Advanced Critical Care 32, 188–194 (2021).
30. Higgins, V., Sohaei, D., Diamandis, E. P. & Prassas, I. COVID-19: from an acute to chronic disease? Potential long-term health consequences. Critical Reviews in Clinical Laboratory Sciences 58, 297–310 (2021).
31. Phillips, S. & Williams, M. A. Confronting Our Next National Health Disaster — Long-Haul Covid. N Engl J Med 385, 577–579 (2021).
32. Nath, A. Long-Haul COVID. Neurology 95, 559–560 (2020).
33. Goërtz, Y. M. J. et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ Open Res 6, 00542–02020 (2020).
34. Sher, L. Post-COVID syndrome and suicide risk. QJM: An International Journal of Medicine hcab007 (2021) doi:10.1093/qjmed/hcab007.
35. Vink, M. & Vink-Niese, A. Could Cognitive Behavioural Therapy Be an Effective Treatment for Long COVID and Post COVID-19 Fatigue Syndrome? Lessons from the Qure Study for Q-Fever Fatigue Syndrome. Healthcare 8, 552 (2020).
36. Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. The Lancet 397, 220–232 (2021).
37. Mendelson, M. et al. Long-COVID: An evolving problem with an extensive impact. S Afr Med J 111, 10 (2020).
38. Ortelli, P. et al. Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom. Journal of the Neurological Sciences 420, 117271 (2021).
39. Mardani, M. Post COVID Syndrome. Arch Clin Infect Dis 15, (2020).
40. Görlinger, K., Dirkmann, D., Gandhi, A. & Simioni, P. COVID-19–Associated Coagulopathy and Inflammatory Response: What Do We Know Already and What Are the Knowledge Gaps? Anesthesia & Analgesia 131, 1324–1333 (2020).
41. Dani, M. et al. Autonomic dysfunction in ‘long COVID’: rationale, physiology and management strategies. Clin Med 21, e63–e67 (2021).
42. Alonso-Lana, S., Marquié, M., Ruiz, A. & Boada, M. Cognitive and Neuropsychiatric Manifestations of COVID-19 and Effects on Elderly Individuals With Dementia. Front. Aging Neurosci. 12, 588872 (2020).

43. Liu, J. W. T. W., de Luca, R. D., Mello Neto, H. O. & Barcellos, I. Post-COVID-19 Syndrome? New daily persistent headache in the aftermath of COVID-19. Arq. Neuro-Psiquiatr. 78, 753–754 (2020).
44. Staats, P., Giannakopoulos, G., Blake, J., Liebler, E. & Levy, R. M. The Use of Non-invasive Vagus Nerve Stimulation to Treat Respiratory Symptoms Associated With COVID -19: A Theoretical Hypothesis and Early Clinical Experience. Neuromodulation: Technology at the Neural Interface ner.13172 (2020) doi:10.1111/ner.13172.
45. Puntmann, V. O. et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol 5, 1265 (2020).
46. Novak, P. Post COVID-19 syndrome associated with orthostatic cerebral hypoperfusion syndrome, small fiber neuropathy and benefit of immunotherapy: a case report. eNeurologicalSci 21, 100276 (2020).
47. Rábano-Suárez, P. et al. Generalized myoclonus in COVID-19. Neurology 95, e767–e772 (2020).
48. Iyer, M. et al. COVID-19: an update on diagnostic and therapeutic approaches. BMB Rep 53, 191–205 (2020).
49. Jeong, G. U., Song, H., Yoon, G. Y., Kim, D. & Kwon, Y.-C. Therapeutic Strategies Against COVID-19 and Structural Characterization of SARS-CoV-2: A Review. Front. Microbiol. 11, 1723 (2020).
50. Wong, T. L. & Weitzer, D. J. Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)—A Systemic Review and Comparison of Clinical Presentation and Symptomatology. Medicina 57, 418 (2021).
51. Crook, H., Raza, S., Nowell, J., Young, M. & Edison, P. Long covid—mechanisms, risk factors, and management. BMJ n1648 (2021) doi:10.1136/bmj.n1648.
52. Tirelli, U., Taibi, R. & Chirumbolo, S. Post COVID syndrome: a new challenge for medicine. European Review for Medical and Pharmacological Sciences 25, 4422–4425 (2021).
53. Leitzke, M., Stefanovic, D., Meyer, J.-J., Schimpf, S. & Schönknecht, P. Autonomic balance determines the severity of COVID-19 courses. Bioelectron Med 6, 22 (2020).
54. Leitzke, M. & Schönknecht, P. The Viral Accelerated NF-κB Pathway Probably Drives COVID-19-associated Coagulopathy via Excessive Transcription of Tissue Factor and Plasminogen Activator Inhibitor 1 – Case Report. Arch Clin Biomed Res 05, (2021).
55. Changeux, J.-P., Amoura, Z., Rey, F. A. & Miyara, M. A nicotinic hypothesis for Covid-19 with preventive and therapeutic implications. Comptes Rendus. Biologies 343, 33–39 (2020).
56. Steardo, L., Steardo, L., Zorec, R. & Verkhratsky, A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiol 229, (2020).
57. Miyara, M. et al. Low rate of daily smokers in patients with symptomatic COVID-19. http://medrxiv.org/lookup/doi/10.1101/2020.06.10.20127514 (2020) doi:10.1101/2020.06.10.20127514.
58. Hippisley-Cox, J. et al. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. Heart 106, 1503 (2020).

59. Farsalinos, K. et al. Nicotinic Cholinergic System and COVID-19: In Silico Identification of an Interaction between SARS-CoV-2 and Nicotinic Receptors with Potential Therapeutic Targeting Implications. IJMS 21, 5807 (2020).
60. Picciotto, M. R., Higley, M. J. & Mineur, Y. S. Acetylcholine as a Neuromodulator: Cholinergic Signaling Shapes Nervous System Function and Behavior. Neuron 76, 116–129 (2012).
61. Wess, J. Novel insights into muscarinic acetylcholine receptor function using gene targeting technology. Trends in Pharmacological Sciences 24, 414–420 (2003).
62. Jones, S. V. P. et al. Muscarinic Acetylcholine Receptors. in Molecular Biology of G-Protein-Coupled Receptors (ed. Brann, M. R.) 170–197 (Birkhäuser Boston, 1992). doi:10.1007/978-1-4684-6772-7_8.
63. Gotti, C., Zoli, M. & Clementi, F. Brain nicotinic acetylcholine receptors: native subtypes and their relevance. Trends in Pharmacological Sciences 27, 482–491 (2006).
64. Hurst, R., Rollema, H. & Bertrand, D. Nicotinic acetylcholine receptors: From basic science to therapeutics. Pharmacology & Therapeutics 137, 22–54 (2013).
65. Scarr, E. Muscarinic Receptors: Their Roles in Disorders of the Central Nervous System and Potential as Therapeutic Targets. CNS Neuroscience & Therapeutics 18, 369–379 (2012).
66. Spurny, R. et al. Molecular blueprint of allosteric binding sites in a homologue of the agonist-binding domain of the α7 nicotinic acetylcholine receptor. Proc Natl Acad Sci USA 112, E2543–E2552 (2015).
67. Picciotto, M. R. Nicotine as a modulator of behavior: beyond the inverted U. Trends in Pharmacological Sciences 24, 493–499 (2003).
68. Gotti, C. & Clementi, F. Neuronal nicotinic receptors: from structure to pathology. Progress in Neurobiology 74, 363–396 (2004).
69. Lloyd, G. K. & Williams, M. Neuronal Nicotinic Acetylcholine Receptors as Novel Drug Targets. J Pharmacol Exp Ther 292, 461 (2000).
70. Hogg, R. C., Raggenbass, M. & Bertrand, D. Nicotinic acetylcholine receptors: from structure to brain function. in Reviews of Physiology, Biochemistry and Pharmacology vol. 147 1–46 (Springer Berlin Heidelberg, 2003).
71. Dajas-Bailador, F. & Wonnacott, S. Nicotinic acetylcholine receptors and the regulation of neuronal signalling. Trends in Pharmacological Sciences 25, 317–324 (2004).
72. Hogg, R. & Bertrand, D. Nicotinic Acetylcholine Receptors as Drug Targets. CDTCNSND 3, 123–130 (2004).
73. Picciotto, M. R. et al. Neuronal nicotinic acetylcholine receptor subunit knockout mice: physiological and behavioral phenotypes and possible clinical implications. Pharmacology & Therapeutics 92, 89–108 (2001).
74. Buisson, B. & Bertrand, D. Chronic Exposure to Nicotine Upregulates the Human α4β2 Nicotinic Acetylcholine Receptor Function. J. Neurosci. 21, 1819–1829 (2001).
75. Schwartz, R. & Kellar, K. Nicotinic cholinergic receptor binding sites in the brain: regulation in vivo. Science 220, 214–216 (1983).

76. French, S. J., Humby, T., Horner, C. H., Sofroniew, M. V. & Rattray, M. Hippocampal neurotrophin and trk receptor mRNA levels are altered by local administration of nicotine, carbachol and pilocarpine. Molecular Brain Research 67, 124–136 (1999).
77. Newhouse, P. et al. Nicotine treatment of mild cognitive impairment: A 6-month double-blind pilot clinical trial. Neurology 78, 91–101 (2012).
78. Sandborn, W. J. Transdermal Nicotine for Mildly to Moderately Active Ulcerative Colitis: A Randomized, Double-Blind, Placebo-Controlled Trial. Ann Intern Med 126, 364 (1997).
79. Pullan, R. D. et al. Transdermal Nicotine for Active Ulcerative Colitis. N Engl J Med 330, 811–815 (1994).
80. Villafane, G. et al. Chronic high dose transdermal nicotine in Parkinson's disease: an open trial: Chronic high dose transdermal nicotine in Parkinson's disease. European Journal of Neurology 14, 1313–1316 (2007).
81. Oliveira, A. S. F. et al. A potential interaction between the SARS-CoV-2 spike protein and nicotinic acetylcholine receptors. Biophysical Journal 120, 983–993 (2021).
82. Homeyer, N. & Gohlke, H. Free Energy Calculations by the Molecular Mechanics Poisson–Boltzmann Surface Area Method. Mol. Inf. 31, 114–122 (2012).
83. Anand, P., Nagarajan, D., Mukherjee, S. & Chandra, N. ABS–Scan: In silico alanine scanning mutagenesis for binding site residues in protein–ligand complex. F1000Res 3, 214 (2014).
84. Gotti, C. et al. Pharmacology and Biophysical Properties of α7 and α7 - α8 α-Bungarotoxin Receptor Subtypes Immunopurified from the Chick Optic Lobe. European Journal of Neuroscience 6, 1281–1291 (1994).
85. Heck, M. & Fresenius, M. Zentrales anticholinerges Syndrom. in Repetitorium Anaesthesiologie 609–612 (Springer Berlin Heidelberg, 2001). doi:10.1007/978-3-662-12917-3_47.
86. Stengel, A., Malek, N., Zipfel, S. & Goepel, S. Long Haulers—What Is the Evidence for Post-COVID Fatigue? Front. Psychiatry 12, 677934 (2021).
87. Alexandris, N. et al. Nicotinic cholinergic system and COVID-19: In silico evaluation of nicotinic acetylcholine receptor agonists as potential therapeutic interventions. Toxicology Reports 8, 73–83 (2021).

Tables

Tables 1 to 6 are available in the Supplementary Files section

Figures

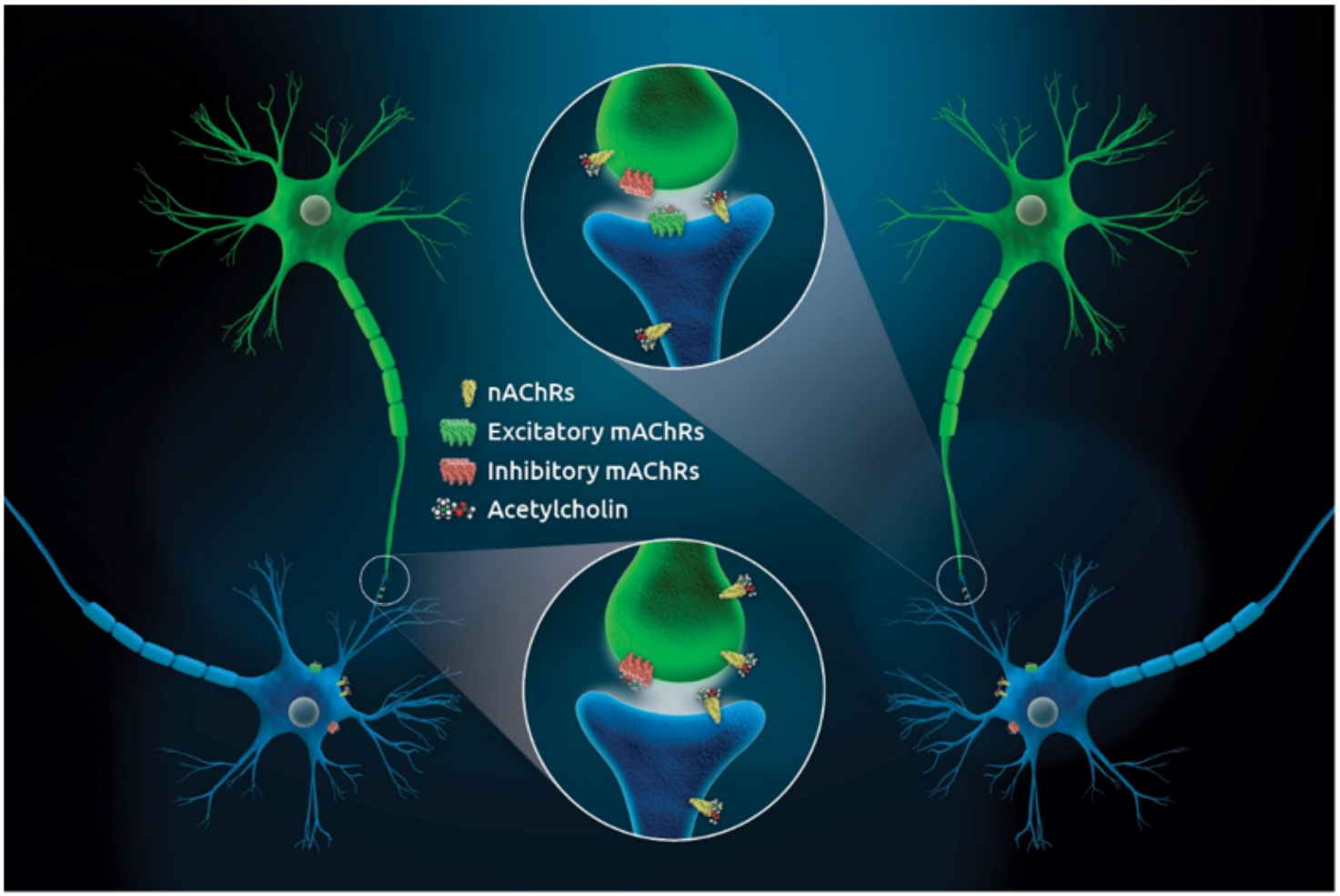

Figure 1

(**cholinergic neuromodulation**): AChRs are located at the membranes of neural cell bodies, as well as in pre- or postsynaptic sites and at the axonal membranes. ACh binding regulates the velocity and amount of transmitter release and cell excitability and orchestrates network operation between several core groups and synchronized response behavior to internal and external stimulation. Cholinergic neuromodulationaction is indispensable for neural plasticity, neuronal development, and learning processes. Thus, numerous physiological functions (sleep, arousal, fatigue, anxiety, nutritional behavior, cognition, and central pain processing) are interactively regulated by cholinergic neuromodulation. The two subtypes of AChRs bind despite ACh either to nicotine (nAChrs) or muscarine (mAChRs). While mAChRs act slowly and promote excitatory or inhibitory transmission effects via numerous canonical and noncanonical pathways, nAChRs consist of a homomeric (α) or heteromeric (α/β) configuration of 5 subunits forming calcium channels with a fast reaction to agonistic stimulation. These allosteric nAChRs are the principal structures of central and autonomic neuromodulation and underlie remarkable plasticity in terms of count, binding sites, and affinity in dependency on agonist stimulation.

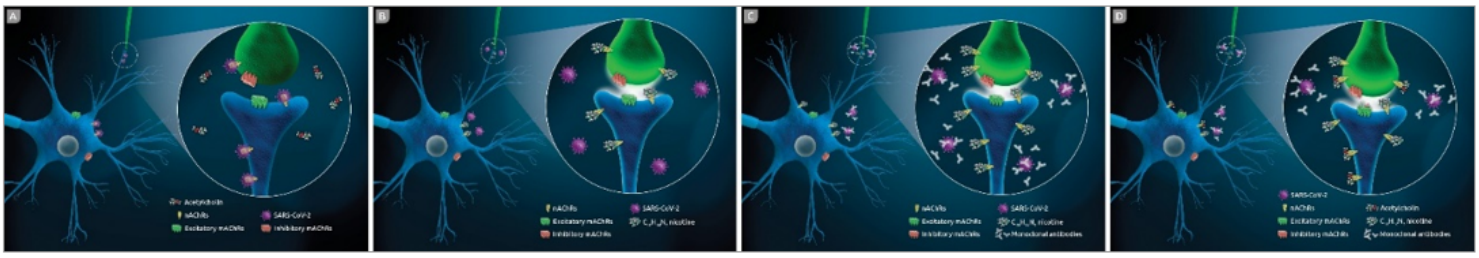

Figure 2

(**nAChR competition of ACh, SARS-CoV-2, and nicotine**): Membrane-bound neuromodulational nAChRs are attached by SARS-CoV-2 viruses in a nonintrinsic fashion, displacing the natural ligand (ACh) and substantially compromising neuromodulatory cholinergic signaling (A). Due to the high affinity of nicotine for nAChRs, the virus is extruded from the attachment to nAChRs from nicotine on its part, acting in a profound intrinsic fashion at the nAChRs and thus neutralizes the blockade of cholinergic neuromodulational signal transmission (B). Since long-haul COVID patients have preformedSARS-CoV-2-specific antibodies, the released viruses are captured by these antibodies, thus preventing reinfection with SARS-CoV-2 due to the re-emergence of the virus within the bloodstream (C). In addition, both the high intrinsic activity of nicotine at nAChR and the nicotinic upregulation of nAChRs lead to the re-establishment of ACh-borne neuromodulation (D).

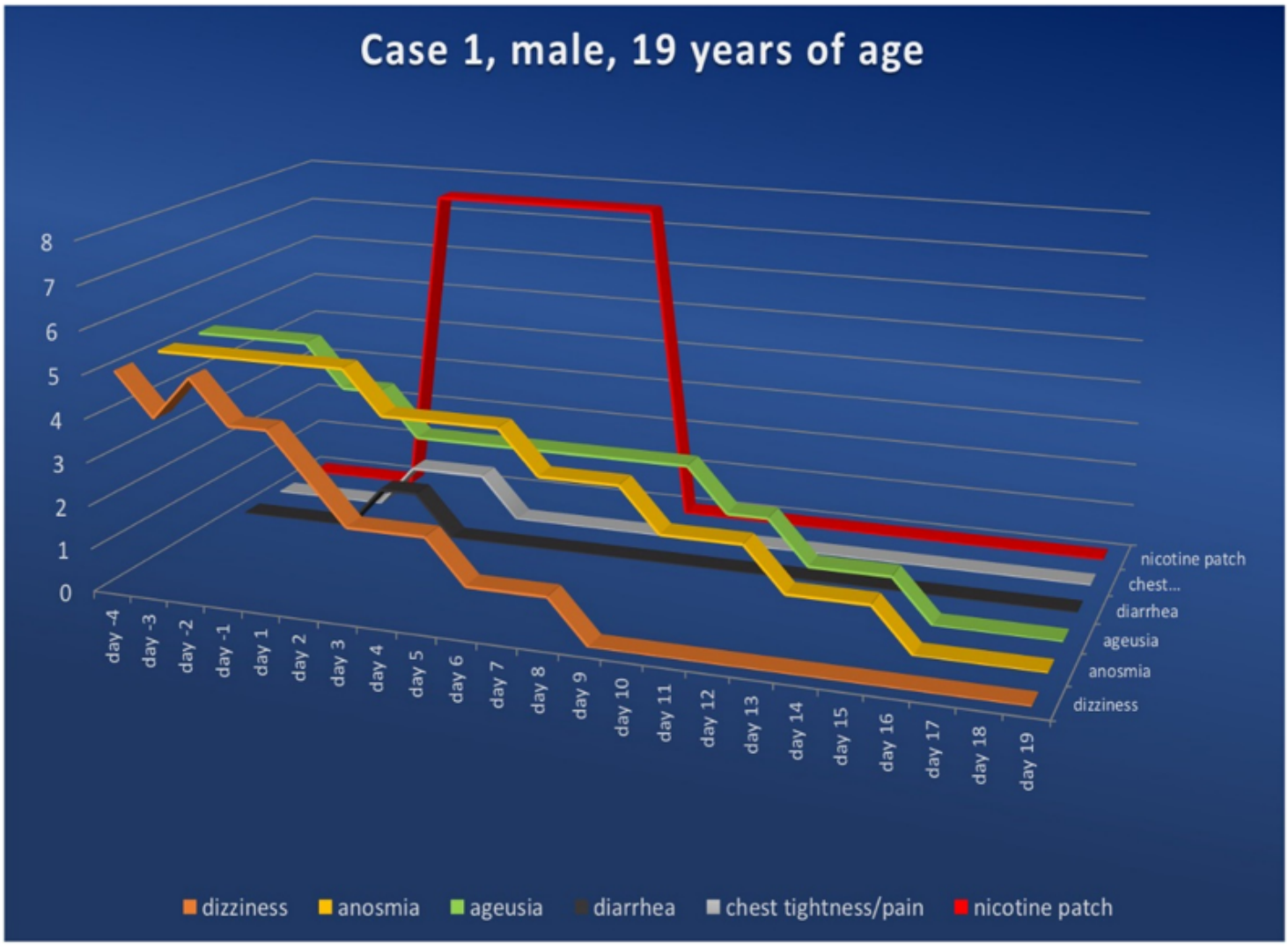

Figure 3

Symptom score of case 1 ranging from the 4th day before to the 26th after nicotine administration (4th symptom-free day). It clearly shows that with the beginning of nicotine treatment, the symptom scores in all complained symptoms fall continuously. The numerical value in the ordinate gives the value of the symptom score in the case of symptoms and the case of nicotine (red), the amount delivered per 24 h.

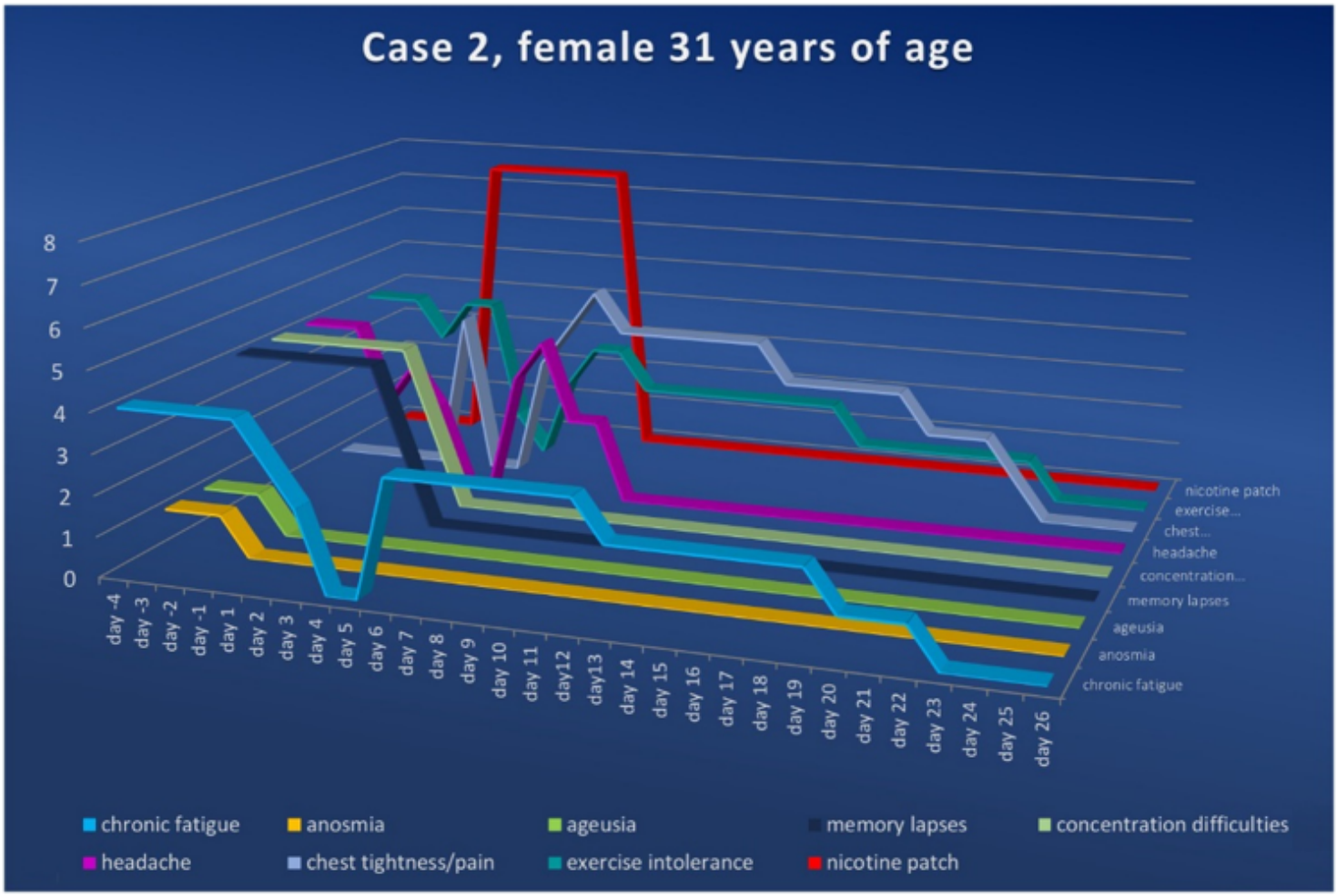

Figure 4

Symptom score of case 2 ranging from the 4th day before to the 26th after nicotine administration (4th symptom-free day). It clearly shows that with the beginning of nicotine treatment, the symptom scores in all complained symptoms fall continuously. The numerical value in the ordinate gives the value of the symptom score in the case of symptoms and the case of nicotine (red), the amount delivered per 24 h.

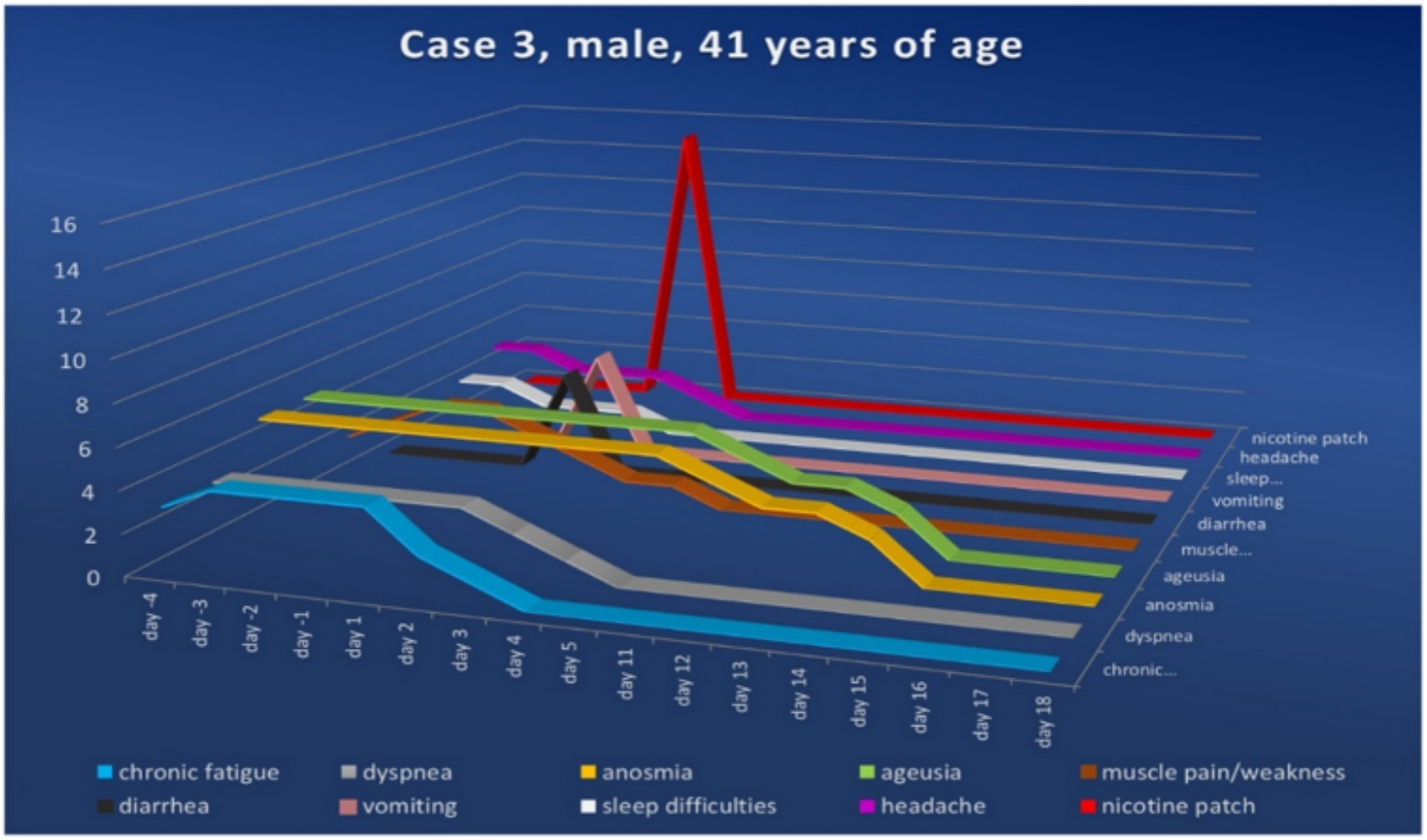

Figure 5

Symptom score of case 3 ranging from the 4th day before to the 18th after nicotine administration (4th symptom-free day). It clearly shows that with the beginning of nicotine treatment, the symptom scores in all complained symptoms fall continuously. However, the mistakenly applied high dosage of nicotine with severe side effects of the substance (vomiting) and the cessation of nicotine after 10 hours led to total symptom regredience until the 16th day after nicotine exposure. The numerical value in the ordinate gives the value of the symptom score in the case of symptoms and the case of nicotine (red), the amount delivered per 24 h.

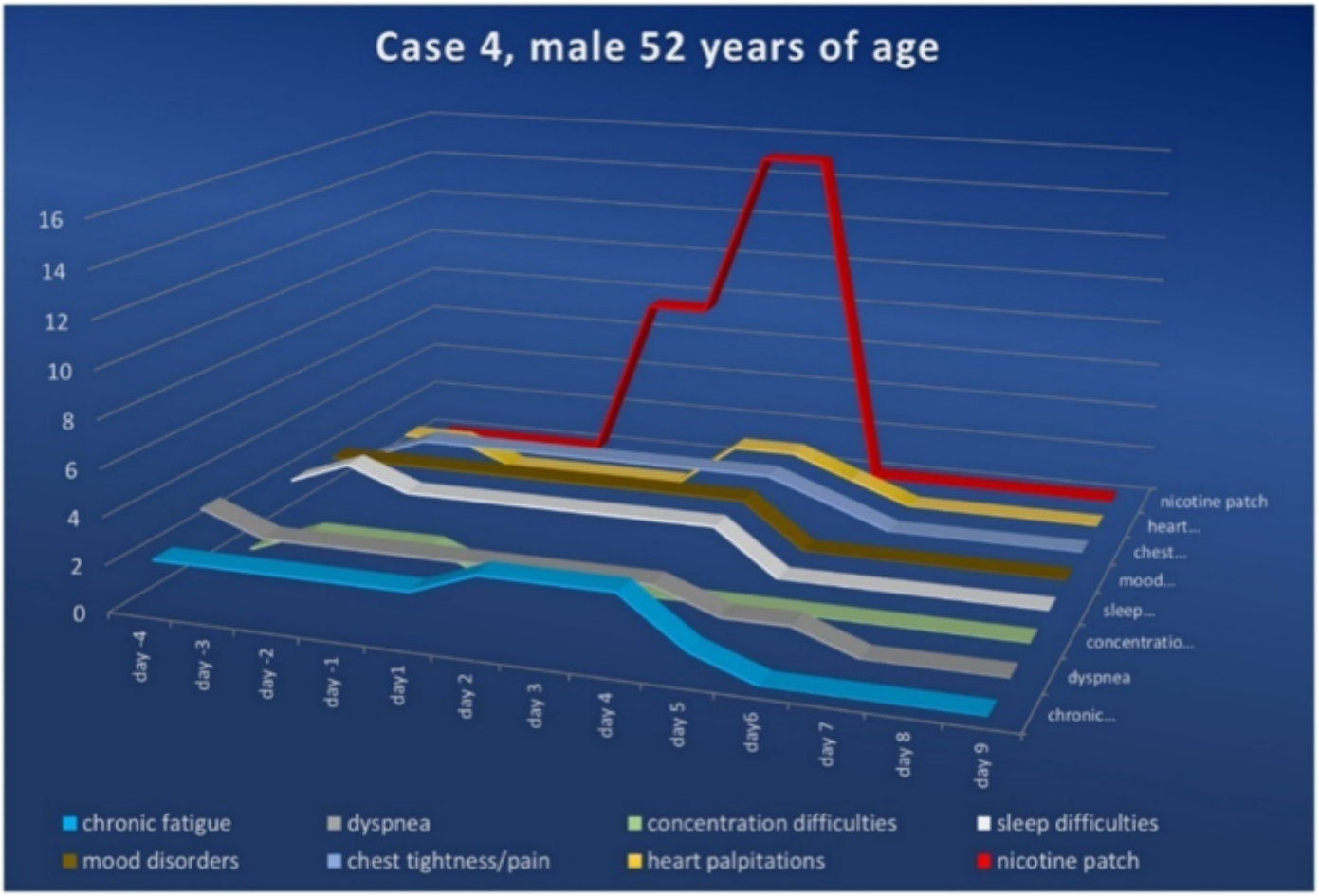

Figure 6

Symptom score of case 4 ranging from the 4th day before to the 10th after nicotine administration (4th symptom-free day). It clearly shows that with the beginning of nicotine treatment, the symptom scores in all complained symptoms fall continuously. The numerical value in the ordinate gives the value of the symptom score in the case of symptoms and the case of nicotine (red), the amount delivered per 24 h.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx