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ORIGINAL RESEARCH

Consequences of dysregulation of two essential homeostatic systems - the renin-angiotensin-aldosterone system and the nicotinic cholinergic nervous system - caused by SARS-CoV-2 spikes (review/analysis)

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ABSTRACT

OPEN ACCESS

There is no doubt that spike-inducing Covid-19 vaccines are associated with a complex and diverse range of side effects, which have significant health consequences for those affected. The known causes, primarily the activation of the renin-angiotensin-aldosterone system, as well as other induced and manipulated spike effects, are not sufficient enough to provide a plausible explanation for unusual clusters or the occurrence of rare side effects. This study aimed to investigate various adverse drug reactions that have not been observed, or have only rarely been observed, when using conventional vaccines. The analysis focused on the most extensive 'reaction groups' following vaccination with the spike-inducing vaccines Tozinameran and Elasomeran: nervous system disorders, psychiatric disorders, musculoskeletal disorders, and general disorders. The data were retrieved from the EudraVigilance Web Reports and were interpreted based on an analysis of original research papers and review articles published in scientific journals. Among the most common adverse reactions from the aforementioned reaction groups were headaches (248,567 reports associated with Tozinameran, 90,948 reports following Elasomeran), fatigue (211,056 and 77,531 respectively), myalgia (156,735 and 62,034 respectively), asthenia (53,968 and 15,303 respectively), muscular weakness (10,882 and 3,328 respectively), anxiety/ fear (8,009 and 2,054 respectively), memory impairment/amnesia (6,475 and 2,132 respectively), depression/depressive mood (5,395 and 1,517 respectively), brain fog (3,685 and 992 respectively) and muscle twitching (3,605 and 908 respectively).

Recent findings suggest that further pathophysiological spike effects, which can significantly impair the body's ability to maintain homeostasis, must be taken into account as possible causes. This involves an impairment of the cholinergic nervous system, which normally acts as a counter-regulatory mechanism, thereby promoting or exacerbating the undesirable activation of the renin-angiotensin-aldosterone system. Impairment of the cholinergic nervous system is caused by neurotoxin-like structures in the spike glycoprotein, which can trigger the inhibition of nicotinic-cholinergic receptors. Consequently, this can result in exacerbated inflammatory processes throughout the body, including the central nervous system. It may also result in activation of the sympathetic nervous system, thrombogenesis, pathological neuropsychiatric and musculoskeletal reactions, and an imbalance in the autonomic nervous system. Taken together, these factors may help to explain why there has been an increase in the incidence of adverse inflammatory and immunological reactions, cardiovascular reactions, coagulopathies, and neuropsychiatric and musculoskeletal disorders. However, in concrete terms, it depends on the organ-specific expression of counteracting regulators, on opposing regulatory effects, dose-dependent effects and time-dependent effects within the regulatory systems, as well as on comorbidities, age, gender, drug interactions and genetic predispositions.

Therapeutic intervention should be aimed at restoring and stabilising homeostasis. There are two main options for achieving this. Angiotensin receptor blockers are the preferred choice for inhibiting the renin-angiotensin-aldosterone system activation, specifically for counteracting the effects of the main effector, Angiotensin II. To activate and restore impaired cholinergic functions, particularly the cholinergic anti-inflammatory pathway, acetylcholine analogues, acetylcholinesterase inhibitors (e.g. donepezil and rivastigmine), and vagus nerve stimulation may be considered.

Keywords: Spike-inducing Covid-19 vaccine, adverse reactions, activation of RAAS, inhibition of nAChR, cholinergic dysregulation, fatigue, brain fog, impairment of cognition, memory impairment, anxiety, headache, myalgia, impairment of muscular function, LongCovid, PostVacc, disturbance of homeostasis

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Introduction

Active vaccines are designed to trigger a specific immune response in the recipient, providing protection against future infections. This response is aimed at neutralising the antigens of the pathogens. Vaccines are generally very well tolerated.

The SARS-CoV-2 virus, which causes COVID-19, contains the spike glycoprotein as its most important antigen. This trimeric fusion protein consists of two subunits. The S1 subunit is responsible for the initial attachment of the virus to the ACE2 receptor on the surface of host cells. This process is mediated by the amino acid sequence 437–508 of the receptor-binding domain (RBD)[1]. The S2 subunit then mediates fusion between the viral and host cell membranes. Neutralising antibodies target the antigenic receptor-binding domain (RBD) of the S1 subunit. Non-neutralised S1 proteins can become systemically and pharmacologically active. The decision to use the viral spike glycoprotein as an antigen for producing spike-inducing (mRNA and vector vaccines) respectively spike-based (inducing and protein-based) COVID-19 vaccines was not without consequences.

In a first for vaccine development, spike-inducing mRNA and vector vaccines require the recipient to produce the antigens within their own body. Consequently, these vaccines are generally classified as 'prodrugs', the efficacy of which depends on a variety of factors. In contrast to the galenically necessary components or specific characteristics of the finished vaccines, such as modified mRNA and pro-inflammatory lipid nanoparticles that transport it, as well as other viral components, adjuvants and so on, which are injected into the body in defined quantities with each vaccination and do not replicate, the extent and duration of induced spike antigen production, its dependence on individual conditions and the occurrence of expression errors have not yet been systematically investigated and therefore remain unknown. Since the start of the mass vaccination campaigns, this has signalled not only uncertainties regarding antigenic efficacy, but also a high potential for side effects.

In principle, a causal link between the spike proteins and persistent organ dysfunction requires the long-term presence of a viral reservoir or spike antigens, which has been demonstrated for up to approximately two years[2-5]. Furthermore, neuroinvasion and the presence of replication-competent SARS-CoV-2 viruses and the detection of pathologically active spikes in the central nervous system (CNS) can be considered proven[4, 6-9].

The injection of a bolus of 30–100 µg of mRNA molecules (equivalent to 13–40 $x10^{18}$ mRNA molecules) within a few seconds, each of which is estimated to be capable of producing 10–100 spike proteins[10,11], into a human organism containing only 28–36 $x10^{12}$ cells illustrates the fatal effect of the sudden influx of foreign proteins. Furthermore, the use of modified mRNA (incorporation of N1-methylpseudouridine[11]) and optimisation of the spike antigen (proline substitution[12,13]), with the stated objectives of prolonging spike production and stabilising the prefusion configuration, may have exacerbated adverse side effects[14].

Both the SARS-CoV-2 virus and the vaccine's spike antigens interact with the renin-angiotensin-aldosterone system (RAAS) in the human body, which plays a fundamental role in maintaining homeostasis. In addition to direct, spike-related consequences and synergistic effects, the impairment of the protective angiotensin-converting enzyme 2 (ACE2), including the resulting amplified, complex reactions mediated by angiotensin II, is a major cause of a wide range of extrapulmonary organ dysfunctions associated with SARS-CoV-2 infection, as well as numerous, sometimes serious, side effects of spike-based COVID-19 vaccines[15-17,20].

So far, there have been no plausible explanations for some of the manifestations of SARS-CoV-2, nor for certain adverse reactions to the novel spike-based vaccines that have not been observed with conventional vaccines. These reactions include neuropsychiatric disorders, cognitive impairment, 'brain fog', memory lapses and loss, neuroinflammation, unusual muscle function disturbances, and autonomic symptoms[19-21,105]. The same applies to disorders with delayed onset and long-lasting effects, such as post-COVID/long-COVID syndrome and post-vaccination syndrome.

Recently, another key interaction partner of the spikes has been identified. This is the nicotinic acetylcholine receptor (nAChR) of the cholinergic nervous system. Their involvement in the complex mechanism of action of the spikes makes it possible, for the first time, to rationally assess numerous unusual side effects associated with spike-based COVID-19 vaccines.

This analysis aims to explain the additional, often exacerbating, effects of cholinergic dysfunction. Several typical examples of adverse drug reactions associated with spike-inducing vaccines are analysed and discussed in the context of the scientific literature. The associated consequences are outlined.

Methods

This analysis evaluates and interprets a number of selected characteristic adverse reactions that have been reported anonymously to the EMA's publicly accessible Eudra-Vigilance database since the start of the Covid-19 vaccination campaign.

Based on the general trend in reported adverse reactions, the primary objective was to determine the number of characteristic cases of unusual adverse reactions in the following reaction groups: the nervous system, psychiatric disorders, musculoskeletal disorders and general disorders following spike-inducing vaccination with Tozinameran (T) and Elasomeran (E).

Data were retrieved from WebReports of EudraVigilance[22]. The EudraVigilance database of the European Medicines Agency (EMA) records reports of suspected adverse drug reactions submitted electronically by national medicines regulatory authorities and marketing authorisation holders. The stated purpose of this system is to assess benefits and risks and to monitor safety following authorisation within the European Economic Area. The data is available to the general public and provides an overview of the nature, frequency and outcome of suspected adverse reactions without going into detail. Given the professionalism of those submitting reports and the effort they put into their work, it can be assumed that the data collected is relevant.

Reported adverse drug reactions are generally classified into 27 ‘reaction groups’, most of which are organ- or system-related, and provide an overview of the potential for harm.

Seventeen organ-related reaction groups were ranked in descending order according to their frequency and analysed globally. However, the following reaction groups were not analysed: congenital, familial and genetic disorders, endocrine disorders, hepatobiliary disorders, injury, poisoning and procedural complications, investigations, neoplasms benign, malignant and unspecified, pregnancy, puerperium and perinatal conditions, produkt issues, social circumstances, surgical and medical procedures.

The ‘reaction’ is based on the MedDRA dictionary of terms for side effects (also known as ADRs). All evaluated adverse events correspond to the search terms of the EudraVigilance based on clinical characterisation. The

total number of individual cases of a particular reaction observed, as well as the number of fatal outcomes, were taken from Table 6, which contains the relevant information.

The following suspected reactions were selected from the 'nervous system disorders' reaction group: headache, memory impairment, brain fog, altered state of consciousness, anosmia/hyposmia, amnesia, cognitive disorders, involuntary muscle contractions, mental impairment, motor dysfunction, dementia, Alzheimer's dementia, myoclonus and myasthenia. The following suspected reactions were selected from the reaction group 'psychiatric disorders' category: anxiety, fear, depression/symptoms of depression, mental disorders, mood altered, affective disorder and schizophrenia. The following were selected from the 'musculoskeletal and connective tissue disorders' reaction group: myalgia, muscular weakness, muscle twitching, polymyalgia rheumatica, rhabdomyolysis, myokymia. Fatigue, chronic fatigue syndrome and asthenia were selected from the 'general disorders' reaction group.

The EudraVigilance database is updated weekly and the data is constantly growing. The cut-off date for Tozinameran (T) and Elasomeran (E) side effects was 19 October 2025 (all suspected adverse drug reactions and associated deaths, as well as adverse drug reactions from 17 organ-related reaction groups and examples of suspected adverse drug reactions from the reaction groups 'General disorders' and 'Musculoskeletal disorders') or 5 October 2025 (examples of suspected adverse drug reactions and associated deaths from the reaction groups 'nervous system disorders' and 'psychiatric disorders'). The total number of deaths was evaluated by summing the fatal outcomes in all 27 defined reaction groups (Table 6 of the EudraVigilance system).

The frequency and percentage were used to quantitatively describe the adverse drug experiences.

Data interpretation is based on an analysis of original research papers and review articles published in scientific journals.

Results

1. GENERAL TRENDS

The data set for the most widely used Covid-19 vaccines, Tozinameran (T) and Elasomeran (E), is extremely extensive and has continued to grow since the initial research (13 February 2022)[20] to a total of 2,946,202 and 960,112 suspected adverse reactions respectively (see Table 1). Women reported adverse reactions twice as often as men; on average, 2.3–2.46 adverse reactions were reported by those affected.

The incidence of fatal adverse reactions fell slightly compared with 2022 (Tozinameran from 2.34% to 2.01%, Elasomeran from 4.75% to 3.42%). Adverse reactions associated with Elasomeran appear to be slightly more likely to be fatal.

Table1: Overview of reported suspected adverse reactions of Tozinameran and Elasomeran in European countries (as of 19 October 2025, EudraVigilance/EMA[22])

	Tozinameran	including fatal cases (n)/*percentage*	Elasomeran	including fatal cases (n)/*percentage*
all individually reported cases	1,274,607	25,671 *2.01 %*	389,614	13,342 *3.42%*
women	887,315 69.6%		267, 690 68.7%	
men	363,353 28.5%		116,312 29.9%	
not specified	23,939 1.9%		5,612 1.4%	
all reported adverse reactions	2,946,202		960,112	
ADR/case	2.3		2.46	

n: number; ADR: adverse drug reaction

Over a period of 4 years and 10 months, up to 19 October 2025 (see Table 2), a total of 447,753 ADRs of the ‚nervous system' associated with a Tozinameran (approx. 15% of all adverse reactions or approx. 35% of all those affected by adverse reactions) and 154,395 cases associated with an Elasomeran vaccination (approx. 16% of all adverse reactions or approx. 39.6% of all those affected by adverse reactions) were reported. This makes nervous system disorders the second most common category after 'general disorders and administration site conditions'. The high number of adverse neurological symptoms has been known since February 2022[22]; by 19 October 2025, it had continued to rise (to approximately 154% in association with Tozinameran vaccination and to 161% for Elasomeran). These adverse reactions were comparatively severe, as indicated by the proportion of fatal outcomes, ranging from 9.7% (E: n = 1,290) to 10.8% (T: n = 2,765) of all vaccine-associated deaths; this death rate is almost on a par with that resulting from adverse cardiac reactions (11.3–14.5% fatal cases).

The third most commonly reported ADRs were musculoskeletal and connective tissue disorders (326,268 cases associated with T – accounting for 25.6% of those affected – and 117,736 cases associated with E – accounting for 30.2% of those affected). By 19 October 2025, the number of these musculoskeletal ADRs associated with a Tozinameran vaccination had risen to approximately 156% and for Elasomeran to 168% compared with an analysis from 2022[20]. The percentage of fatal outcomes in this category was 1.4% (n=368) for T and 1.97% (n=263) for E.

The frequency of reports of cardiovascular adverse reactions documented in the 'reaction groups' 'cardiac disorders' and 'vascular disorders', ranked 9th (3.48% of all adverse events) and 11th (2.23% of all adverse events) for T, and 8th (3.45% of all adverse events) and 11th (1.98% of all adverse events) for E. The frequencies currently identified confirm previous analyses (up to 13 February 2022[20]) and demonstrated a significant increase in these adverse events by 19 October 2025 (to 148–170%). Heart disease was fatal in approximately 14.5% of cases associated with T and in 11.25% of cases associated with E.

55,319 suspected cases of psychiatric adverse reactions associated with Tozinameran vaccination (approximately 1.9% of all adverse reactions or 4.3% of those affected by adverse reactions) and 16,476 cases associated with Elasomeran (approx. 1.7% of all adverse reactions or 4.2% of those affected by adverse reactions), as well as the number of fatal adverse reactions in this category (1.13% and 1.57% respectively), are alarming.

The number of reported suspected adverse reactions affecting other organ systems, such as the digestive system, the reproductive organs, the skin, the respiratory tract or chest, the blood and lymphatic system, the sensory organs, the immune system, the metabolism, the kidneys or urinary tract, and infections, is extremely diverse and comparatively common (n=11,272-200,955 for T and n=4,966-72,294 for E); they require separate analysis.

Table 2: Frequency of suspected Tozinameran (T) and Elasomeran (E) ADRs across 17 organ-related reaction groups (out of a total of 27 according to EudraVigilance/EMA; 19 October 2025[22])

reaction group	reported suspected ADRs following vaccination with T (n)/ % of all ADRs	including fatal cases (n)/ *percentage of all deaths*	reported suspected ADRs following vaccination with E (n)/ % of all ADRs	including fatal cases (n)/ *percentage of all deaths*
general disorders and administration site conditions	746,005 *25.3%*	6,721 *26.18%*	250,006 *26.04%*	4,190 *31.4%*
nervous system disorders	447,753 *15.2%*	2,765 *10.8%*	154,395 *16.08%*	1,290 *9.67%*
musculoskeletal and connective tissue disorders	326,268 *11.07%*	368 *1.4%*	117,736 *12.26%*	263 *1.97%*
gastrointestinal disorders	200,955 *6.82%*	991 *3.86%*	72,294 *7.53%*	516 *3.87%*
infections and infestations	199,681 *6.78%*	2,631 *10.25%*	42,867 *4.46%*	1,208 *9.05%*
reproductive system and breast disorders	132,663 *4.5%*	11 *0.04%*	30,941 *3.2%*	12 *0.09%*
skin and subcutaneous tissue disorders	131,069 *4.45%*	230 *0.9%*	51,004 *5.31%*	125 *0.94%*
respiratory, thoracic and mediastinal disorders	120,561 *4.09%*	2,707 *10.5%*	38,093 *3.97%*	1,397 *10.5%*
cardiac disorders	102,514 *3.48%*	3,714 *14.47%*	33,086 *3.45%*	1,501 *11.25%*
blood and lymphatic system disorders	87,560 *2.97%*	387 *1.51%*	25,301 *2.64%*	168 *1.25%*
vascular disorders	65,587 *2.23%*	1,179 *4.59%*	19,049 *1.98%*	528 *3.96%*
psychiatric disorders	55,319 *1.88%*	291 *1.13%*	16,476 *1.72%*	210 *1.57%*
eye disorders	44,198 *1.5%*	73 *0.28%*	12,870 *1.34%*	48 *0.36%*

ear and labyrinth disorders	38,041 *1.29%*	28 *0.11%*	11,251 *1.17%*	9 *0.07%*
immune system disorders	22,181 *0.75%*	175 *0.68%*	6,270 *0.65%*	41 *0.31%*
metabolism and nutrition disorders	19,588 *0.66%*	449 *1.75%*	7,606 *0.79%*	312 *2.3%*
renal and urinary disorders	11,272 *0.38%*	401 *1.56%*	4,966 *0.52%*	259 *1.9%*

ADR: adverse drug reaction

2. EXAMPLES OF TYPICAL SUSPECTED ADVERSE REACTIONS

Suspected adverse reactions associated with vaccination with Tozinameran (T) and Elasomeran (E) are not only very common but also incredibly diverse. Due to the sheer volume of reports (approx. 1–3 million for E and T respectively), only a few suspected side effects from the organ-related 'reaction groups' – nervous system, musculoskeletal system, psychiatric disorders and general complaints – could be examined as examples.

Headaches were the predominant symptom in the nervous system reaction group (see Table 3). Approximately one in five (19.5–23%) reported headaches. Even though headaches can be a common occurrence in everyday life, the reporting of 248,567 and 90,948 cases respectively in connection with the vaccinations should not be trivialised, given their significance as a warning sign.

Some strikingly unusual symptoms associated with vaccinations (see Tables 3 and 4), such as anxiety/fear symptoms (T: n=8,009; E: n=2,054), memory problems (T: n=6,475; E: n=2,132) or depression/mood disorders (T: n=5,520; E: n=1,550), brain fog (T: n=3,685; E: n=992), disturbances of consciousness (T: n=3,519; E: n=833), or cognitive disorders (T: n=1,541; E: n=537), dementia and Alzheimer's symptoms (T: n=410; E: n=197) or individual cases of schizophrenia (T: n=49; E: n=19) prompted a report to the authorities.

The symptoms of anxiety, depression, memory impairment, brain fog or altered consciousness occurred more frequently than the anosmia or hyposmia characteristic of Covid-19 (3,195 cases following the T vaccine and 913 post-vaccination cases following the E vaccine).

Table 3: Examples of typical suspected adverse reactions in the nervous system reaction group associated with Tozinameran (T) or Elasomeran (E) vaccination (reported to EudraVigilance up to 5 October 2025[22])

individuals with suspected ADRs	frequency associated with a Tozinameran vaccination (n)/percentage		frequency associated with an Elasomeran vaccination (n)/percentage	
all those affected		1,274,459		389,581
all those affected with nervous system disorders	447,682	33.13%	154,377	39.93%
including fatal cases	*2,764* *0.62%*		*1,290* *0.84%*	
anyone who suffers from headaches	248,567 55.5%	19.5%	90,948 58.9%	23.345%
including fatal cases	*201* *0.08%*		*123* *0.135%*	
anyone who suffers from memory impairment	4,596 1.027%	0.36%	1,396 0.9%	0.358%
including fatal cases	*14* *0.30%*		*6* *0.43%*	
anyone who suffers from 'brain fog'	3,685 0.82%	0.289%	992 0.64%	0.255%
including fatal cases	*1* *0.027%*		*1* *0.1%*	
anyone who suffers from altered states of consciousness	3,519 0.786%	0.276%	833 0.54%	0.21%
including fatal cases	*168* *4.77%*		*68* *8.16%*	
all those with anosmia/hyposmia	3,195 0.714%	0.25%	913 0.59%	0.234%
including fatal cases	*4* *0.125%*		*8* *0.88%*	
all cases of amnesia, amnestic disorders	1,879 0.42%	0.15%	736 0.48%	0.19%
including fatal cases	*4* *0.21%*		*6* *0.82%*	
all those with cognitive disorders	1,541 0.34%	0.12%	537 0.35%	0.138%
including fatal cases	*20* *1.3%*		*11* *2.05%*	
all cases with involuntary muscle contractions	829 0.185%	0.065%	212 0.137%	0.054%
including fatal cases	*2* *0.24%*		*1* *0.47%*	
anyone with a mental impairment	726 0.16%	0.057%	308 0.199%	0.079%
including fatal cases	*4* *0.55%*		*3* *0.97%*	
anyone suffering from motor dysfunction	632 0.14%	0.05%	375 0.243%	0.096%
including fatal cases	*5* *0.79%*		*3* *0.8%*	
all those with dementia, Alzheimer's dementia	410 0.09%	0.03%	197 0.128%	0.05%
including fatal cases	*34* *8.29%*		*30* *15.23%*	
all with myoclonus	351 0.078%	0.0275%	90 0.058%	0.023%
including fatal cases	*3* *0.85%*		*2* *2.22%*	
all those with myasthenia gravis/crisis	344 0.077%	0.027%	184 0.12%	0.047%
including fatal cases	*2* *0.58%*		*1* *0.54%*	

ADR: adverse drug reaction; n: all reported cases; %: in relation to those affected by ADRs

Although cases of dementia, Alzheimer's disease and schizophrenia were reported relatively rarely, the high proportion of fatal outcomes among these diagnoses is striking (8.3–approx. 21%).

For patients diagnosed with 'altered consciousness', this condition proved fatal in 4.8% (T) to 8.2% (E) of cases. Between 1% and approx. 2% of cases resulted in death in connection with the diagnosis of 'cognitive disorder' (T: n=20; E: n=11), mental (E: n=3) or affective disorder (T: n=2). The remaining recorded adverse effects resulted in death in less than 1% of cases.

Table 4: Examples of typical suspected adverse reactions in the reaction group psychiatric disorders associated with Tozinameran (T) or Elasomeran (E) vaccination (reported to EudraVigilance up to 5 October 2025[22])

individuals with suspected ADRs	frequency associated with a Tozinameran vaccination (n)/percentage			frequency associated with an Elasomeran vaccination (n)/percentage		
all those affected			1,274,459			389,581
all those affected with psychiatric disorders	55,296		4.34%	16,471		4.23%
including fatal cases	*291*	*0.53%*		*210*	*1.27%*	
anyone experiencing symptoms of anxiety or fear	8,009	4.48%	0.628%	2,054	12.47%	0.531%
including fatal cases	*24*	*0.299%*		*9*	*0.44%*	
anyone experiencing symptoms of depression or depressive mood	5,395	9.76%	0.42%	1,517	9.21%	0.39%
including fatal cases	*10*	*0.185%*		*4*	*0.264%*	
anyone experiencing symptoms of mental disorders	707	1.28%	0.055%	149	0.9%	0.038%
including fatal cases	*1*	*0.14%*		*2*	*1.34%*	
anyone experiencing symptoms of altered mood	558	1.01%	0.044%	110	0.668%	0.028%
including fatal cases	*1*	*0.18%*		*0*	*0%*	
anyone experiencing symptoms of affective disorders	125	0.23%	0.0098%	33	0.2%	0.0085%
including fatal cases	*2*	*1.6%*		*0*	*0%*	
everyone who suffers from schizophrenia	49	0.089%	0.0038%	19	0.115%	0.0049%
including fatal cases	*1*	*2.04%*		*4*	*21.05%*	

ADR: adverse drug reaction; n: all reported cases; %: in relation to those affected by ADRs

figures in italics: fatal cases, as a percentage of the corresponding adverse reaction

The high number of reports of musculoskeletal adverse reactions is striking (see Table 5). Myalgia was reported by 156,735 people in connection with T and 62,034 in connection with E (12.3% to approx. 16% of all those affected by ADRs). Muscular weakness was reported by 10,882 (in connection with T) and 3,328 people (in connection with E). Muscle twitching affected 3,605 (following T) and 908 people (following E). The rare phenomenon of myokymia increased significantly compared to its first mention in 2022[20]; it occurred in 130 people following T and in 21 people following E.

Rhabdomyolysis, as a potential ADR linked to the vaccine spike protein, was already known in 2022. The number of cases rose to 333 following T (a 162% increase) and to 167 following E (a 131% increase). Polymyalgia rheumatica was reported 1,487 times following T and 365 times following E.

Table 5: Examples of typical suspected adverse reactions in the reaction group 'musculoskeletal and connective tissue disorders' and 'general disorders and administration site conditions' associated with Tozinameran (T) or Elasomeran (E) vaccination (reported to EudraVigilance up to 19 October 2025[22])

individuals with suspected ADRs	frequency associated with a Tozinameran vaccination (n)/percentage			frequency associated with an Elasomeran vaccination (n)/percentage		
all those affected			1,274,607			389,614
all those affected with musculoskeletal and connective tissue disorders	326,268		25.6%	117,736		30.2%
including fatal cases	*368*	*0.11%*		*263*	*0.22%*	
everyone who suffers from myalgia	156,735	48.0%	12.3%	62,034	52.69%	15.92%
including fatal cases	*86*	*0.05%*		*44*	*0.07%*	
everyone who suffers from muscular weakness	10,882	3.34%	0.85%	3,328	2.83%	0.85%
including fatal cases	*37*	*0.34%*		*31*	*0.93%*	
everyone who suffers from muscle twitching	3,605	1.1%	0.28%	908	0.77%	0.23%
including fatal cases	*4*	*0.11%*		*2*	*0.22%*	
everyone who suffers from polymyalgia rheumatica	1,487	0.46%	0.12%	365	0.31%	0.09%
including fatal cases	*0*			*0*		
everyone who suffers from rhabdomyolysis	333	0.1%	0.03%	167	0.14%	0.043%
including fatal cases	*18*	*5.4%*		*7*	*4.2%*	
everyone who suffers from myokymia	130	0.04%	0.01%	21	0.018%	0.005%
including fatal cases	*0*			*0*		
all those affected with general disorders	746,005		58.53%	250,006		64.17%
including fatal cases	*6,721*	*0.9%*		*4,190*	*1.68%*	

everyone who suffers from fatigue	211,059	28.3%	16.6%	77,531 31%	19.9%
including fatal cases	*283*	*0,13%*		*205* *0,26%*	
everyone who suffers from asthenia	53,968	7.24%	4.24%	15,303 6.12%	3.93%
including fatal cases	*280*	*0.52%*		*237* *1.55%*	
everyone who suffers from chronic fatigue syndrome	2,172	0.29%	0.17%	526 0.21%	0.14%
including fatal cases	*0*			*0*	

ADR: adverse drug reaction; n: all reported cases; %: in relation to those affected by ADRs
figures in italics: fatal cases, as a percentage of the corresponding adverse reaction

Unusual muscular disorders (involuntary muscle contractions, motor dysfunction, myoclonus, myasthenia; total: n=2,156 for T; n=861 for E) were also found in the nervous system reaction group (see Table 3).

Among the musculoskeletal adverse reactions with fatal outcomes, rhabdomyolysis occurred particularly frequently, in 4.2% (n = 7 after E) to 5.4% (n = 18 after T) of cases. A diagnosis of myoclonus led to death in a maximum of 2.2% of cases (see Table 3). For other musculoskeletal adverse effects, fatal outcomes were reported in less than 1% of cases.

The phenomenon of fatigue, asthenia and chronic fatigue syndrome is attracting increasing attention. It was reported a total of 267,199 times in connection with T and 93,360 times in connection with E (see Table 5). Fatal adverse drug reactions accounted for up to 1.55% (n = 237 according to E).

Due to a lack of data, it was not possible to establish a correlation between the frequency of adverse reactions and vaccination rates.

Discussion

The effects of the SARS-CoV-2 spike protein are considerably more diverse and complex than was previously assumed. This is demonstrated by the data on the two most widely used spike-inducing vaccines, Tozinameran (T) and Elasomeran (E), in European countries (see Table 1). As of 19 October 2025, there were 2,946,202 adverse reaction reports for Tozinameran (T) and 960,112 for Elasomeran (E).

In order to understand the nature and severity of adverse reactions, it is important to be aware of the pathophysiological effects of spikes and to consider the specific characteristics of COVID-19 vaccines, as outlined in the introduction.

THE PATHOPHYSIOLOGICAL EFFECTS OF THE SPIKE PROTEIN

Our understanding of the effects of the spike glycoprotein has grown enormously in just a few years. The pathophysiologically significant effects of the spike-based (spike-inducing and protein-based) COVID-19 vaccines essentially comprise three core competencies (see Fig. 1). The **primary function** of the spike protein is to stimulate protection against infection through its antigenic efficacy. This requires a separate, up-to-date analysis and is not the subject of this analysis.

The antigenicity is inseparably linked to the **second core function** of the spike protein: the interaction between the receptor-binding domain (RBD) of the viral spike S1 subunit (amino acid sequence 437–508)[1] and its receptor,

the host organism's angiotensin-converting enzyme 2 (ACE2). ACE2 has been shown to be essential for the regulation of blood pressure and cardiovascular, renal and pulmonary functions for more than 20 years[23]. If ACE2 loses its function or is downregulated due to spike attachement or binding, it loses its ability to break down angiotensin II (Ang II), which is the most important effector in the renin-angiotensin-aldosterone system (RAAS). This leads to an increase in Ang II, which can be harmful by disrupting the homeostatic regulation of the RAAS in the cardiovascular system. Vasoconstriction, tissue ischaemia, endothelial dysfunction, increased sympathetic tone, heightened oxidative stress and/or effects on blood coagulation, which are triggered by Ang II/AT_1R, can cause acute rises in blood pressure, angina pectoris, myocardial infarction, heart failure, impaired cardiac electrical conduction, thromboembolism and stroke. Defence and repair mechanisms may also be impaired, and hyperinflammatory states and immunological dysfunction may develop.

Fig. 1: Spike-Core-Competencies

	SARS-CoV2-spikes	vaccine-spikes
• **antigenicity**	+	+
• **attachment to/ downregulation of ACE2**	+	+
replication requirement	+	−
• **inhibition of nAChRs**	+	+
additional effects	+	+

ACE2 – Angiotensin-Conversion-Enzyme 2; nAChR – nicotinic acetylcholine receptor; JK Lehmann, 2026

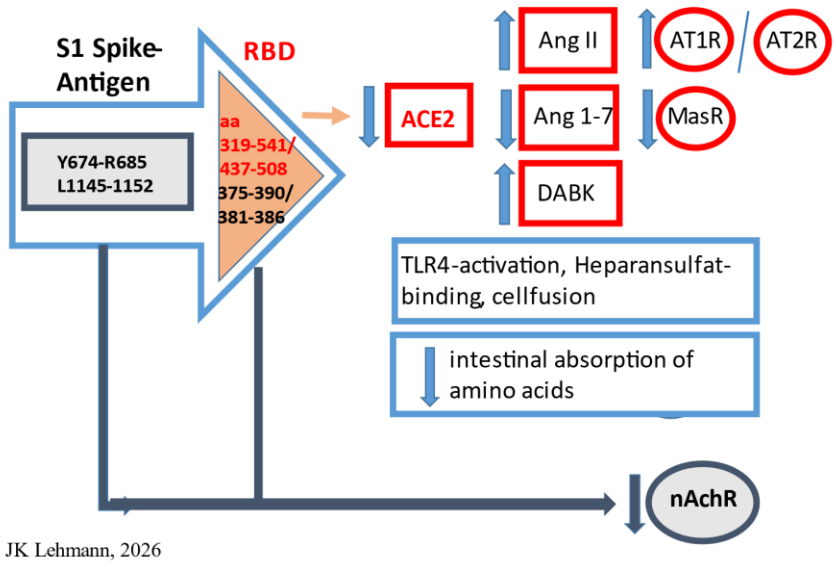
For a long time, the role of Ang II in triggering autoimmune reactions was overlooked. However, successes achieved with ACE inhibitors, ARBs and renin inhibitors in experimentally induced autoimmune processes have attracted attention[24]. Nevertheless, RAAS activation was not considered a significant factor in many vaccine-induced autoimmune diseases. On the contrary, it has been suggested that viral proteins, including spike proteins, share similarities with essential immune system proteins, which could increase the risk of triggering autoimmune diseases[11].

The second most important angiotensin II receptor is the AT_2R. It has protective effects that are the opposite of those of the AT_1R. These include vasodilation, improved cerebral blood flow, increased glucose uptake, reduction of inflammation and inflammatory cytokines, stimulation of neurite growth and differentiation of various cells, and antiproliferation[25]. The extent to which the effects of the AT_1R can be counterbalanced by those of the AT_2R when Ang II activity increases is unclear, but this does appear to be a distinct possibility. The specific AT_1R blockade achieved by angiotensin receptor blockers (ARBs), which has been used successfully in clinical practice for decades, is likely to be enhanced by unsuppressed AT_2R activation. Unfortunately, this fact is not addressed in current hypertension guidelines[26].

The particular vulnerability of older people and those with chronic illnesses, who were originally prioritised for the vaccine, may be due to the characteristics of ageing cells, which accumulate inflammatory factors, chemokines, bioactive lipids and procoagulant factors. These factors are collectively known as SASP factors and can create conditions that lead to feared outcomes such as cytokine storms, acute respiratory distress syndrome, myocarditis, T-cell depletion, blood clotting disorders, chronic diseases, delirium, and multi-organ failure. It has thus been demonstrated that senescent human endothelial cells exhibit a significantly exaggerated inflammatory response when exposed to the SARS-CoV-2 spike S1 protein or PAMP-(pathogen-associated molecular pattern) lipopolysaccharides. In animal experiments, an impaired immune response and increased mortality were also observed. This suggests that senescent cells promote SARS-CoV-2 pathogenesis by increasing the expression of SASP factors. This weakens the viral defence and increases the expression of viral entry proteins in neighbouring non-senescent cells. Senescent cells can also trigger and exacerbate systemic inflammatory responses through S1 spike interaction, and accelerate the ageing process[27].

Further harmful synergistic effects come into play, as shown in Fig. 2.

Fig. 2: Pathophysiological spike effects



RBD: receptor binding domain; ACE2: angiotensin-conversion-enzyme 2; Ang II: angiotensin II; AT1R/AT2R: angiotensin$_1$receptor/angiotensin$_2$receptor; Ang 1-7: angiotensin 1-7; MasR: Mas-receptor; DABK: des-Arg9-Bradykinin; TLR4: toll like receptor 4; nAChR: nicotinic acetylcholine receptor; down arrow: inhibition; up arrow: activation.

The bradykinin system is closely linked to the RAAS. A loss of function in ACE2 leads to an inhibition of the breakdown of its bioactive pro-inflammatory metabolite des-Arg9-BK (DABK). This can result in inflammation, thereby amplifying the effects of Ang II. Dry cough, bronchospasm, increased vascular permeability, angioedema (EudraVigilance WebReports regarding facial oedema and facial swelling up to 19 October 2025 for T: 13,414 cases[22]), hypokalaemia triggering arrhythmia and sudden cardiac death or hypotension are typical bradykinin-associated effects[28], which have also been reported as side effects of spike-based vaccines.

Further direct effects of the spike protein (e.g. cell fusion, TLR4 binding, heparan sulphate binding) amplify the inflammatory and neuroinflammatory effects of Ang II. Free Spike proteins react with platelets, facilitate the release of coagulation factors and can thus trigger coagulopathies[29]. Intracerebroventricular spike infusions caused reversible cognitive deficits in mice via TLR4 activation, including hippocampal microgliosis, neuroinflammation and loss of synapses. Given the proven presence of spikes in the central nervous system, this finding could add an important aspect to research into the underlying causes of Long Covid and/or post-vaccination conditions[30]. In the gut, ACE2 plays a role in regulating the uptake of amino acids and glucose, as well as influencing the gut microbiome, innate immunity, and intestinal inflammatory processes. In the absence of ACE2, or when its function is impaired, the uptake of amino acids, such as the essential amino acid tryptophan, decreases. As a serotonin precursor, tryptophan plays a key role in preventing depressive states. Furthermore, Ang II is involved in serotonin synthesis and release[18, 29]. Low serotonin concentrations are not only suspected to cause depression, but also to play a role in the development of Long Covid or Post-Vaccination Syndrome.

The existence of the RAAS in the central nervous system (CNS) has been known since around 1971[31], and it functions autonomously when the blood-brain barrier is intact. However, systemically circulating Ang II can also directly affect the central nervous system via the periventricular organs, which lack a tight blood-brain barrier. The central nervous system's counterpart to peripheral cardiovascular reactions is vasoconstriction and ischaemia, which can lead to strokes, microinfarcts, vascular occlusions, vasculitis, thromboses and embolisms[16].

Elevated Angiotensin II levels have been associated with depressive states, anxiety, and neuroinflammation[32], which are symptoms that have frequently been reported following the administration of the SARS-CoV-2 vaccine[21]. In animal experiments, chronically elevated Ang II has been shown to impair cognitive function, reduce synaptic plasticity and promote neuroinflammation[33]. Ang II exacerbated the accumulation of beta-amyloid[34].

The effects of angiotensin on the central nervous system are mediated by AT_1, AT_2, AT_4, prorenin and Mas receptors. Notably, AT_2R and AT_4R expression is distributed in a manner that largely overlaps with that of nicotinic-cholinergic acetylcholine receptors (nAChRs) in the brain. The efficacy of AT_2R are in many cases similar to those of AT_4R and include the modulation of neuronal excitability, neurite growth and migration, and trigger an increase in cerebral blood flow, resulting in demonstrable improvements in cognitive function and neuronal regeneration. For this reason, it is believed that the AT_2R plays an important role in maintaining the normal function of the human brain. Some findings suggest that a mutation-induced reduction in AT_2R expression appears to be linked to significant intellectual impairment, seizures or autism. Ang IV and AT_4R are also thought to play important roles in learning and memory processes[25].

The enzyme ACE2, which breaks down Ang I and Ang II, is widely distributed in the brain, particularly in regions that regulate cardiovascular functions, but also in the motor cortex and the raphe nuclei[23]; the highest levels of activity were found in the hypothalamus. Interestingly, the regions where vagal afferents terminate and vagal efferents originate are also those in which ACE2 is expressed[35]. The close interconnection between the cholinergic and RAA systems is supported by the fact that cholinergic interneurons, which primarily contribute to cholinergic tone in the dorsolateral striatum, exhibit higher levels of AT_1R, MasR and AT_4R expression than non-cholinergic interneurons, alongside generally pronounced local ACE2 expression[36].

Overexpression of ACE2 exerts tissue-protective effects[23]. Upon activation of its Mas receptor, the converted product Ang 1-7 exhibits functions that are the opposite of those of Ang II (modulates noradrenaline effects, reduces sympathetic tone, modulates baroreflex sensitivity, stimulates prostaglandin and NO release, supports

metabolic bradykinin effects, inhibits smooth muscle cell growth, and possesses stress-reducing and neuroprotective properties), thereby counterbalancing, as in the periphery, the consequences of ACE/Ang II/AT_1R activation. This limits potential RAAS overactivity. However, in certain brain regions (e.g. the rostral or caudal ventrolateral medulla), both Ang II and Ang 1-7 can trigger similar unidirectional responses[23,37].

Counterregulatory mechanisms are important for maintaining homeostasis. Ang II/AT_1R and ACE2 influence each other, suggesting that ACE2 expression is not only modulated by the classical RAAS, but that this enzyme can also, in turn, alter the function of the RAAS. Studies have demonstrated that AT_1R downregulation is caused by overexpression, while ACE2 deficiency causes upregulation[23,37].

In recent years, our understanding of the adverse effects of SARS-CoV-2 spike S1 proteins has expanded to include evidence of parasympathetic nervous system impairment, specifically affecting nicotinic acetylcholine receptors (nAChRs). Since around 2020, it has been suspected that the spike glycoprotein binds to nAChRs, thereby disrupting their anti-inflammatory cholinergic effects. Inhibiting nAChRs or dysregulating the cholinergic nervous system is another **significant core competence of the spike protein**.

One of the key factors behind the interest in nAChRs was the observation that there were fewer smokers than expected among those diagnosed with or hospitalised for Covid-19[38-41]. Based on the assumption that SARS-CoV-2 viruses act as blockers of nicotinic acetylcholine receptors, Changeux and other[39,42] proposed that COVID-19 is a nicotinic-cholinergic disorder and that nicotine could potentially be used as a preventive and therapeutic agent. Interest in nAChRs grew when it became known that low concentrations of nicotine increased ACE2 in human bronchial epithelial cells and that this effect was mediated by α7-nAChR[43].

The documented severity of the disease in smokers[44-46, 136, 137], the increased risk of infection due to the overexpression of the spike-binding receptor ACE2[35, 43, 47-49], the fact that increased ACE2 expression translates into increased competence for SARS-CoV-2 replication and cytopathic effect, as demonstrated by Maggi[48], and the finding that there is a dose-dependent relationship between cigarette smoke and ACE2 expression[50], were all disregarded. Nor were the known health risks associated with nicotine taken into account[51].

AN OVERVIEW OF THE NOCOTINIC-CHOLINERGIC NERVOUS SYSTEM

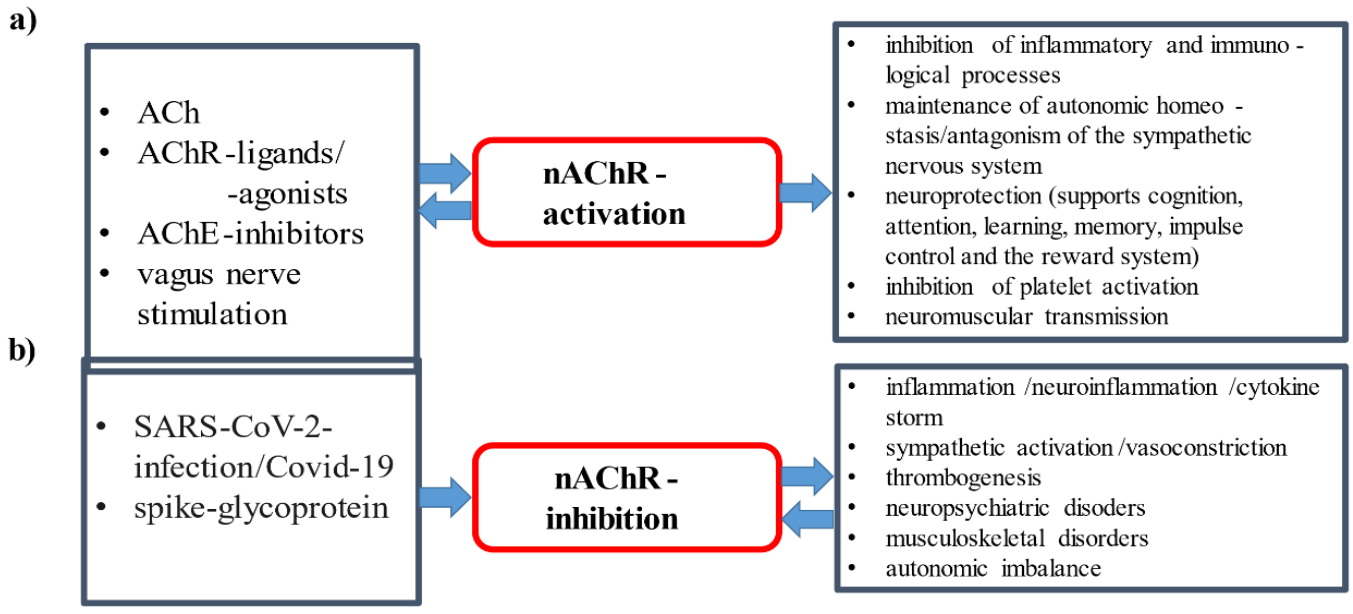
Nicotinic acetylcholine receptors (nAChRs) are membrane proteins consisting of five transmembrane subunits (pentamers) formed by homo- or heteromeric polypeptide combinations. It is well known that the structurally and functionally highly diverse, ligand-gated nAChRs modulate higher central nervous system activities such as cognition, attention, alertness, learning and memory; they are responsible for neuroprotection/neurodegeneration and neuronal plasticity; and they are involved in reward systems/addiction as well as motivational processes[52,53]. They influence inflammatory processes throughout the body via the cholinergic anti-inflammatory pathway (CAP). They are also involved in neuromuscular and ganglionic signal transmission and the maintenance of peripheral autonomic homeostasis (see Fig. 3. a). They are active at the presynaptic level (neurotransmitter release), the postsynaptic level (involved in fast excitatory transmission) and at the non-synaptic level (modulation of various neurotransmitter systems, influencing neuronal excitability). In the brain, they are involved in the release of acetylcholine, dopamine, noradrenaline, glutamate, serotonin and 4-aminobutyrate in a subtype- and regional-specific manner[52].

Heteropentameric α4β2 receptors with high affinity for nicotine are predominant in the brain (in the cortex, hippocampus, cerebellum, raphe nuclei, substantia nigra, thalamus, amygdala, hypothalamus, striatum, nucleus

interpeduncularis and olfactory bulb); the highest concentration is found in the dorsal anterior cingulate gyrus and the anterior insula[54-56]. They are involved in cognitive processes, attention, concentration, the reduction or suppression of disturbing factors and the ability to focus on what is relevant. They also influence mood, memory, reward, recall and nicotine dependence[56-58]. Individual differences in the availability of these receptors influence the control of disturbances[56]; damage to the receptors impairs learning and attention. The receptor is up-regulated by low but physiologically relevant concentrations of nicotine and can produce long-term neuroprotective effects[59,60].

The human homopentameric, low-affinity nicotinic and rapidly desensitised α7-nAChR consists of five identical α7 subunits, each of which possesses an extracellular (agonist-binding), a transmembrane (surrounding the ion channel) and an intracellular domain, and is activated by endogenous acetylcholine or exogenous ligands such as nicotine [61]. It is also widely distributed in the CNS[58]. The highest concentrations have been reported in the cortex, hippocampus and limbic regions, with lower concentrations found in the thalamus and basal ganglia[62]. α7-nACh receptors have also been detected in the reticular nucleus, the lateral and medial geniculate nuclei, the pineal gland, the cerebellum, the interpeduncular nucleus, the substantia nigra, the hypothalamus, the amygdala and the olfactory bulb[54]. These receptors are predominantly expressed presynaptically and play a key modulatory role in the release of various neurotransmitters[1]. The α7-nAChR contributes to perception, sensory processing and attention, and is thought to be involved in the pathogenesis of neuropsychiatric disorders, particularly schizophrenia and Alzheimer's disease. This receptor also plays a central role in brain development and is involved in learning, synaptic plasticity, memory, locomotion, attention and anxiety[63].

Fig. 3: Overview of cholinergic reactions



a: Responses to nicotinic acetylcholine receptor (AChR) activation triggered by acetylcholine (ACh), AChR ligands/agonists, acetylcholinesterase (AChE) inhibitors, vagus nerve stimulation.
b: Responses following nAChR inhibition caused by spikes or SARS-CoV-2 infection/COVID-19
JK Lehmann, 2026

Knowledge and understanding of the relationships between microstructural, layer-specific features of the brain and macroanatomical structural units, connective pathways, and physiological or pathophysiological functions are far from being fully understood in the cholinergic nervous system. The regions of particular receptor density are known, and it is also known that cholinergic axons, originating in the basal forebrain,

project throughout the cortex; they form a dense network of presynaptic varicosities in all cortical layers. However, the majority of these varicosities are not classically associated with postsynaptic structures, which is why it has been suggested that cholinergic neurotransmission could also occur via diffuse release into the extracellular space as so-called 'volume' transmission. The slow response to nicotine, mediated by the high-affinity, extrasynaptically localised, non-α7 receptor, and the fast nicotine response, mediated by the low-affinity α7 receptor, could be related to 'volume transmission' and classical synaptic transmission, respectively. Both types of receptor are likely to exert different influences on cortical activity. For instance, the slow excitation triggered by non-α7 receptors could promote modulatory signalling pathways that develop over longer periods of time[53] and are significant for the pathogenesis of Long Covid and post-vaccination symptoms.

At the neuromuscular junction, the activation of presynaptic α7-nAChRs (a component of terminal Schwann cells, TSCs) by high concentrations of ACh triggers a reduction in ACh levels via a negative feedback mechanism. This activation is also controlled by butyrylcholinesterase (BChE), which is present in TSCs; ACh modulates its own release[64].

The α7-nACh receptors also play a significant role in non-neuronal cells. They are an essential part of the anti-inflammatory signalling pathway and thus act as a link between the nervous and immune systems. These receptors are found in macrophages, monocytes, B and T lymphocytes, neutrophils, dendritic cells, bronchial/ alveolar epithelial and endothelial cells, adipocytes, keratinocytes, as well as astrocytes and microglia, which are not only the primary sites of attack for SARS-CoV-2 but are also involved in the anti-inflammatory cholinergic circuit[1,11,57].

Blockade of endothelial nAChRs reduces NO production and promotes vasoconstriction and thrombogenesis, which can cause further organ damage[65]. Activation of α7-nACh receptors suppresses the production of pro-inflammatory cytokines[49]; inhibition leads to hyperinflammatory synergies, which could be particularly noticeable in the lungs, as the cholinergic anti-inflammatory signalling pathway is especially active there. SARS-CoV-2-induced nAChR dysregulation could also disrupt the balance with the sympathetic nervous system and promote the adrenergic-mediated cytokine storm[11]. The use of cholinergic agonists to enhance the impaired cholinergic nervous system or of beta-blockers to inhibit the activated sympathetic nervous system could be beneficial for patients with COVID-19[66].

Human platelets express α7-nACh receptors[67]; a deficiency increases inflammatory processes and platelet activity[35]. It has been demonstrated that acetylcholine acts as an endogenous inhibitor of platelet activation[68]. A deficiency in ACh or a dysfunction of the n-cholinergic system is therefore also implicated in the severity of thrombotic and vascular complications of Covid-19[35].

The impairment of the muscle αβγδε subunit receptor could be the cause of reports of muscle weakness, pain, joint discomfort, etc.[57]. More than just isolated cases of myasthenia gravis (new onset) and the exacerbation of an existing condition have been documented in connection with both SARS-CoV-2 infections and vaccination[69-78], regardless of vaccine type, mostly in temporal association with, but not exclusively, the second dose. The authors generally attributed the neuromuscular transmission disorder to an autoimmune aetiology (autoantibodies impairing nAChR function), molecular mimicry, genetic predisposition or exacerbation of a latent condition. The obvious interaction between spikes and cholinergic muscle receptors was not included in the causality.

Since around 2000, it has been known that the cholinergic nervous system rapidly and reflexively attenuates inflammatory and immunological processes via nicotinic acetylcholine receptors (nAChR); the release of TNF

by macrophages is inhibited and systemic inflammatory responses are reduced[79,80]. In 2001, it was demonstrated for the first time[81] that, as a cholinergic agonist, nicotine selectively suppresses the cytokine response of alveolar macrophages, including TNF-α, following bacterial infection in vitro, thereby supporting bacterial replication. Soon afterwards (in 2002), Tracey[82] discovered that vagal stimulation triggers an anti-inflammatory effect via nicotinic acetylcholine receptors (α7-nAChR). The activation of α7-nACh receptors by cholinergic agonists, such as nicotine, suppresses the production of pro-inflammatory cytokines and reduces the production of TNF. Pre-treatment with nicotine or a selective α7-nAChR agonist reduced the dysfunction caused by experimentally induced renal ischaemia/reperfusion in a dose-dependent manner, blocking or reducing neutrophil infiltration and TNF production. The renoprotective anti-inflammatory effect persisted even after vagotomy, suggesting that it was mediated via local cholinergic receptors[83]. Inhibiting this receptor reduces vagal control over TNF, resulting in an unrestricted innate immune response to invasive or infectious stimuli.

This established the concept of a neural inflammatory circuit (see also Fig. 3. a), which, in a manner analogous to the central regulation of heart rate and blood pressure, modulates cellular immune function extremely rapidly, maintains immune homeostasis and minimises inflammatory damage to tissues and organs[84-86]. The loss of parasympathetic tone and/or the blockade of nAChR (see Fig. 3. b) promotes dysautonomia and exacerbates inflammatory reactions, particularly in the nervous system, mediated by the activation of microglia and mast cells[87]. The integrity of the cholinergic anti-inflammatory pathway (CAP) appears to offer protection against the effects of Ang II, such as hypertension and renal fibrosis. For instance, an nAChR agonist has been shown to reduce blood pressure in vivo in rats infused with Ang II, while also inhibiting the expression of pro-inflammatory cytokines. Conversely, a CAP deficit appears to promote the pathogenesis of end-organ damage[88].

It is also worth noting that impaired vagus nerve function is present in some of the major lifestyle-related diseases, including diabetes mellitus and obesity, which often lead to extremely serious complications in patients who also are infected with Covid-19. This supports the hypothesis that the potentiation of nicotinic receptor dysregulation by SARS-CoV-2 spikes promotes hyperinflammatory states[39].

Oka et al. (2023)[89] found clear evidence of inflammatory processes in the brains of mice, accompanied by a reduction in acetylcholine levels and a disruption of the cholinergic anti-inflammatory regulatory circuit; these changes occurred following the expression of the S1 protein in the nasal cavities of the experimental animals, alongside damage to olfactory bulb cells. The amygdala, which is involved in the pathogenesis of Long Covid, was most severely affected. In the lungs, a correlation between cytokine production and S1 mRNA expression was demonstrated. The cholinesterase inhibitor donepezil was able to reverse the disrupted processes and some associated behavioural changes (fatigue, depressive symptoms).

TOXIN-LIKE STRUCTURES IN THE SARS-CoV-2 SPIKE PROTEIN (see also Fig. 2)

SARS-CoV-2 spikes contain various sequence motifs that resemble those of known nicotinic acetylcholine receptor (nAChR) antagonists (e.g. the highly toxic snake venom α-bungarotoxin; [57,90]). These spike structures can interact with nAChRs[35, 39, 49] and compete with their natural ligands or other agonists, such as nicotine.

The following interactions were investigated

a) the amino acid sequence aa 375–390 of the spike RBD protein with various n-cholinergic receptors,
b) the neurotoxin-like protein fragment Y674–R685 of the S protein with α7-nAChR, and
c) the segment L1145–L1152 with L411–V418 of the α7-nAChR.

a: A few months after the initial assumption that the nicotinic-cholinergic nervous system appeared to be involved in the pathophysiology of severe COVID-19 cases (spring 2020) computer simulation succeeded in identifying a toxin-like peptide fragment (aa 375–390) as part of the receptor-binding domain (RBD, aa 319–541) of the spike glycoprotein. This is not identical to the ACE2 receptor-binding motif (aa 437–508). The most significant interaction described was that between aa 381–386 of the spike glycoprotein and aa 189–192/195 (core toxin-binding site) of the extracellular domain of the α9-nAChR subunit. A similar interaction has been observed between α7-nAChR and the spike glycoprotein[1, 91]. This interaction is similar to that between the highly toxic, n-cholinergic antagonist snake venom alpha-bungarotoxin and the α9-nAChR. These findings thus also provide an explanation for the disruption of the cholinergic anti-inflammatory signalling pathway by Spike-S1 activity, for the numerous undesirable effects including the cytokine storm, and for the anticipated anti-inflammatory efficacy of nicotine as well as other nicotinic agonists that can competitively displace S1 at the receptor. Farley[92] demonstrated in vitro that isolated, recombinant Spike S1 protein causes a dose-dependent inhibition of α7-nACh receptors.

b: Molecular computer simulations have demonstrated that the neurotoxin-like Y674-R685 spike region, which exhibits structural homology with known α7-nAChR antagonists, is susceptible to interactions. This region is located in the spike head region between S1 and S2, immediately before the furin cleavage site (S686)[57,90]. It contains a sequence of four amino acids (proline, arginine, arginine, alanine = PRRA) that is specific to SARS-CoV-2 spikes and is responsible for binding also to other receptors, such as neuropilin-1. It can be assumed that this Y674-R685 region of the SARS-CoV-2-specific spike protein generally has an affinity for nAChRs. Stable complexes were obtained with all three nAChR subtypes investigated (α7-nAChR, α4β2 and muscle-like *αβγδε* receptor). The Y674-R685 spike region acts as an antagonist at α4β2 and αβγδε receptor complexes. Interestingly, there was some evidence suggesting a gating function for the α7-nAChR, which, via the anti-inflammatory cholinergic signalling pathway, could be relevant to COVID-19 or spike pathology.

Based on the results of molecular dynamics simulations, experimental evidence of a functional interaction between human α7-nACh receptors and a synthetic Y674-R685 peptide has been provided[61]. The allosterically mediated functional interaction with α7-nAChR is particularly interesting because nicotine also utilises this receptor and regulates the expression of ACE2. The S-fragment exerts a dual effect. In the pM concentration range, Y674-R685 activated the α7-nAChR agonistically, but only when a positive allosteric modulator (PAM) was present at the same time. At increasing concentrations (IC_{50} in the low micromolar range for α4β2 nAChRs), additional non-competitive inhibition by the S-fragment was observed. The significance of these findings was highlighted in view of the presence of free S and S1 proteins in bodily fluids.

Shortly afterwards, Lykhmus et al.[93] succeeded in demonstrating reduced α7-nACh receptors in the mouse brain, an increase in the concentration of neuroinflammatory substances such as IL-1β and TNF-α in the brain, and an impairment of episodic memory caused by this neurotoxin-like spike protein fragment (674–685), effects that could be partially reversed by choline.

O'Brien[49] confirmed that low concentrations of the spike peptide potentiated ACh-induced reactions at α7-nAChR, which switched to inhibition at higher concentrations. The results were interpreted as allosteric-modulatory effector properties rather than competitive displacement behaviour against acetylcholine, choline or nicotine. It was hypothesised that, due to the activation of cholinergic anti-inflammatory responses, rapid and only minimally restricted viral replication might be facilitated at the beginning of a COVID-19 infection.

There is concern that tobacco use or nicotine could exert a potentiating influence and impair physiological, immunological and inflammatory responses.

c: Tillman[86] found that spike proteins caused a specific, marked functional downregulation of α7-nAChR in various cell populations, including neuronal cells, presumably triggered by a competitive mechanism. The specific nature of the spike-α7-nAChR interaction under investigation may be due to the L1145-L1152 segment, which is common to all SARS-CoV-2 variants and mRNA vaccines and is homologous to the L411-V418 region of the receptor. The authors assume that all cells producing spike proteins also exhibit reduced α7-nAChR activity, the extent of which depends on the cell type.

There has also been discussion about whether a prion-like domain exists within the S1-RBD (amino acids 473–510). This domain appears to be unique to SARS-CoV-2 viruses, and is thought to be responsible for both the virus's prion potential and its 10–20 times higher affinity for the ACE2 receptor[94].

IMPAIRMENT OF HOMEOSTASIS CAUSED BY SPIKE EFFECTS (examples)

The physiological function of the cholinergic nervous system is to counteract the angiotensinergic/adrenergic system. If the cholinergic nervous system becomes ineffective, the harmful effects of the angiotensinergic/adrenergic system prevail unchecked, disrupting or causing homeostasis to spiral out of control.

In light of the findings cited in this paper concerning spike-induced RAAS activation, the dysregulation of the cholinergic nervous system through the inhibition of nicotinic acetylcholine receptors (nAChRs), and other spike-related effects, a harmful pathogenetic synergy emerges that helps to explain disorders of the cardiovascular and coagulation systems, the nervous system, neuromuscular disorders, and, above all, inflammatory-immunological disorders (see Table 6).

Table 6: General, systemic spike effects (simplified overview)

Spike-Effects	Inflammatory/immunological reactions	Cardiovascular reactions	Coagulopathies	Disorders of the nervous system	Neuromuscular disorders
RAAS-activation Ang II-increase/ AT1R-activation	✚	✚	✚	✚	✚
DABK - increase	✚	✚			
TLR 4 - dysregulation	✚	✚		✚	
Heparansulfat–binding	✚		✚		
Cell- fusion	✚		✚		
Reduktion of aminoacid-resorption				✚	
Cholinergic Dysregulation / nAChR - inhibition	✚	✚	✚	✚	✚

JK Lehmann, 2026

Ang II-angiotensinII; AT1R - angiotensin1receptor; RAAS-renin-angiotensinaldosteronesystem; DABK- bradykininmetabolitedes-Arg9-BK; TLR 4 - Toll likereceptor4; nAChR – nicotinicacetylcholinereceptor

Approximately 15% (T) to 16% (E) of all adverse reaction reports concerned the nervous system, and 1.7% (E) to 1.9% (T) concerned psychiatric disorders (see Table 2). The frequency of fatal nervous system disorders (ranging from 9.7% for E to 10.8% for T) highlights the severity of these symptoms. However, the number of fatal psychiatric disorders (1.13% and 1.57% respectively) is also alarming.

The extent to which this data has been incorporated into national statistics on causes of death is not known. Notably, a comprehensive annual survey of causes of death in the general population in Germany revealed a consistent increase in deaths from nervous system diseases and psychiatric disorders between 2019 and 2023, with a sharp rise in 2022, the second year of vaccination[95].

The timing of the beginning of symptoms and their severity are unknown, as these characteristics were not recorded. Analysis of individual cases (n = 13)[96] revealed that 0–10 days elapsed between vaccination and the beginning of a neuropsychiatric adverse reaction. In another study, a median of three days elapsed between vaccination and the onset of PostVac syndrome (predominantly nervous system disorders), with a high self-assessed symptom severity score of 80 out of 100 reported[97].

In 2025, Thorp[21] analysed the incidence of adverse neuropsychiatric symptoms associated with the Covid-19 vaccine. Over a period of four years, these significantly exceeded the side effects reported for influenza vaccines and for all vaccines (excluding Covid-19 vaccines) recorded by the CDC/FDA Vaccine Adverse Event Reporting System (VAERS) over the past 35 years. Notable was the increase in cognitive impairment and in neuropsychiatric morbidity and mortality. A large-scale, population-based study in Seoul conducted in 2024[98] found that, within three months of receiving a SARS-CoV-2 vaccine, the incidence of depression, anxiety, dissociative, stress-related, and somatoform disorders, as well as sleep disorders, was significantly higher among vaccinated individuals than among unvaccinated individuals. Possible explanations put forward included pro-inflammatory and immunological effects, TLR4-mediated cognitive dysfunction and a reduction in cerebral blood flow due to the presence of the spike protein.

Under the rubric ‘nervous system’, **headaches** are clearly the most common symptom (248,567 reports associated with T, or 19.5% of all reported cases; 90,948 reports associated with E, or approximately 23% of all reported cases; see Table 3). A study launched at the start of the vaccination campaign has already provided revealing details[99]. 90.3% of respondents had never experienced headaches in connection with other vaccinations. More than half of the recipients experienced headaches associated with the vaccination within 10 hours, on average after 18 hours. The headaches were mostly felt on both sides of the forehead and were predominantly dull and pressing in nature (40–50%). Less frequently, they were throbbing or pulsating in nature (approx. 14%), and in some cases, stabbing in nature (13.8%). Around 40% of patients complained of severe to very severe headaches. Patients with a history of migraines reported more intense and longer-lasting symptoms. The frequency of occurrence, which has also been confirmed by other authors[20,97], should have prompted serious consideration of headaches in connection with vaccination in itself. Furthermore, the causal mechanism should be considered to be spike-induced, Ang II- and/or adrenergic-triggered temporary vasoconstriction (reversible cerebral vasoconstriction syndrome, RCVS), as this can have serious consequences such as stroke and increased case fatality rate. The first case reports of typical ‘thunderclap’ headaches have been published[19,100-102]; evidence of a vasoconstrictive aetiology was provided by the detection of cortical ischaemia and the response to nimodipine[19]. Losartan (an angiotensin receptor blocker) also proved effective for both treatment and prevention[100]. The fact that vasoactive drugs accounted for approximately 41% of RCVS risk factors suggests

a vasoconstrictive aetiology. It has also been hypothesised that virus-induced endothelial dysfunction, in conjunction with an overactive RAAS, acts as a trigger for cerebral vasoconstriction[103]. Immune reactions involving systemic inflammation and impaired cerebral autoregulation were also considered to be causative factors, as were direct, endothelium-damaging spike effects[102].

Reports of **anxiety** (T: n=8,009; E: n=2,054) and **depression/mood disorders** (T: n=5,520; E: n=1,550) were far less common, but still alarmingly frequent (see Table 4). These phenomena had not been previously observed with other, conventional vaccines. Kim et al.[98] observed a significantly higher incidence of anxiety, depression, and other neuropsychiatric disorders in individuals vaccinated against Covid-19. An analysis of VAERS data[21] identified 14,917 cases of anxiety within four years of the start of vaccination, with 61 resulting in suicide.

A comprehensive review article[32] successfully demonstrated the crucial role of the RAAS in emotional disorders. It is now proven that elevated Ang II concentrations trigger anxiety- or depression-like behaviour, while increased AT_2R, ACE2 and Ang 1-7 activities have an anxiolytic effect, as did ACEIs and, in particular, ARBs. The efficacy of Ang II is most likely based on the release of inflammatory cytokines and increased oxidative stress. RAAS blockers have anti-inflammatory, antioxidant and anti-stress effects. Clinical successes have been achieved in patients with anxiety disorders, depressive symptoms or reduced quality of life. Spike-induced persistent impairment of tryptophan resorption, as well as Ang II-induced alterations in serotonin synthesis and/or release, can ultimately lead to a serotonin deficiency in the brain and contribute to the development of depressive states. These findings provide a plausible explanation for the unusually high incidence of anxiety and depression following spike-based COVID-19 vaccination. Additionally, the inhibition of α7-nACh receptors by spikes promotes inflammatory processes, resulting in a harmful synergistic effect with the pro-inflammatory effects of Ang II. Furthermore, the reported incidence is significantly higher than that of anosmia/hyposmia, which characterises Covid-19 disease (3,195 cases following T-vaccination and 913 cases following E-vaccination). A causal link with the spike-inducing vaccination is evident.

Reports of **memory impairment/amnesia** (T: n=6,475; E: n=2,132), **altered consciousness** (T: n=3,519; E: n=833; see Table 3), and **cognitive impairment** (T: n=1,541; E: n=537) are unusual and distressing for those affected. However they are not uncommon in connection with the vaccination against SARS-CoV-2. These symptoms affected approximately 45% of individuals experiencing post-vaccination syndrome[97]. The frequency of fatal cases presenting with the symptom of 'altered consciousness' (4.8–8.2%) is not easily explained and requires further investigation.

The closely related phenomenon of **'brain fog'** involves subjective disturbances of consciousness or cognitive impairment. It appears to be a typical consequence of SARS-CoV-2 infection, long Covid and spike-inducing vaccines, as well as being a characteristic feature of post-vaccination syndrome. By October 2025, 'brain fog' had been reported 3,685 times in connection with T and 992 times in connection with E (see Table 3). Thorp[21] reports 1,223 cases over a four-year period (an average of 25.5 per month), which significantly exceeds the number of reports of all vaccine side effects - excluding those from the COVID-19 vaccine -over the past 35 years (an average of 0.6 per month). Among PostVac patients, brain fog was one of the most common complaints, ranging from 63% to 76.44% [97, 104]. In Germany, 36 cases of brain fog (16.4% of 220) had been recorded by 2021[20].

When looking for an explanation for acute cognitive impairment and transient memory problems that occurred suddenly, ACE2 impairment with vasoconstrictive and hypoxic consequences was identified relatively quickly

amidst several less likely alternatives[105]. Hypoxaemic damage, endothelial dysfunction with disruption of the blood-brain barrier, or an intracerebral cytokine storm have been suggested as causes of Covid-19-induced central nervous system disorders, with neurodegenerative consequences attributed to ACE2 downregulation and neuroinflammation[106]. In the same year, it was demonstrated that the S1 subunit of the SARS-CoV-2 spike protein in particular can induce direct neuronal damage, endolysosomal dysfunction and neurite dystrophy[107]. On the other hand, improved blood flow and increased AT_2R activity have been shown to reduce cognitive deficits.

Over the past few decades, our understanding of the key role played by acetylcholine and nAChRs in complex brain functions such as cognition and consciousness has grown. Research has shown that a cholinergic deficit, particularly in the prefrontal cortex, can disrupt these processes. Conversely, n-cholinergic agonists such as nicotine have been found to enhance memory function[62]. It has long been known that the cholinergic nervous system enhances learning behaviour [108,109]. Low doses of nicotine (0.25 mg/kg) have been shown to accelerate the acquisition of a conditioned shuttle-box response and increase the stability of the reflex in rats[110]. This finding has been replicated at an almost identical dose (0.2 mg/kg) and confirmed with other nicotinic agonists (Levin, 1997; cited in[111]).

By contrast, spike-induced TLR4 activation promotes cognitive impairment[98], thereby exacerbating the harmful effects of Ang II and reducing nAChR activity (see also Table 6).

Genetic characteristics and changes in receptor activity over time, including desensitisation, broaden the range of responses[62].

Dementia and Alzheimer's symptoms (T: n=410; E: n=197; see Table 3) were reported to the European authority significantly less frequently. However, the extent to which these symptoms proved fatal- namely in 8.3% (T) to 15.2% (E)- was both worrying and unexplained. The low number of reports may be due to people being unaware of, or unable to conceive, such a link, which is why they did not report it. Given the data from the VAERS database[21], which showed a 112-fold higher incidence for Covid-19 vaccines than for all recorded vaccines excluding Covid-19 vaccines, and given the modes of causation, under-reporting of these symptoms appears plausible.

A review from 2012[112] cited numerous findings demonstrating that chronic activation of the RAAS, increased Ang II levels and elevated AT_1R activity led to neuronal cell damage, neuroinflammation and cognitive impairment in Alzheimer's disease models. Other factors involved were the induction of cerebral remodelling, a reduction in cerebral blood flow, increased oxidative stress and astrocyte ageing in the brain. In contrast, protective AT_2R activation could counteract neuronal damage and cognitive impairment.

In the same year, it was demonstrated for the first time that hypertensive patients treated with ARBs were 32–35% less likely to develop Alzheimer's disease, regardless of their blood pressure levels, and showed fewer amyloid deposits in post-mortem brain tissue than those treated with other antihypertensive drugs, particularly ACEIs, or those who were untreated[113]. Subsequent autopsy findings (n = 756)[114] did show a significant reduction in arteriolosclerosis (6–24%), as well as a decrease in various neuropathological factors. However, they did not reveal a clear difference in Alzheimer's markers between antihypertensive drugs that were misleadingly described as Ang II-stimulating (!), such as ARBs, and a mixture of so-called Ang II-inhibiting antihypertensives without ARBs. Following an extensive analysis of hypertension studies, Belachew[115] found a 13% lower risk of dementia

from any cause and a 12% lower risk of Alzheimer's dementia for AT_2R-activating antihypertensive drugs compared with inhibitory agents (e.g. ACE inhibitors, beta-blockers, non-dihydropyridine calcium channel blockers). The results of a subsequent large-scale case-control study confirmed that at least one year of treatment with (misleadingly termed!) Ang II-stimulating antihypertensive drugs, such as ARBs and other anthypertensive medication, is sufficient to significantly reduce the risk of developing dementia[116]. It is clear that ARBs (AT_1R blockers) possess neuroprotective properties.

The second, major cause of Alzheimer's disease is a cholinergic forebrain deficit, which is triggered by the accumulation of misfolded Aβ and tau in certain brain regions and leads to the loss of the cholinergic phenotype, involving impaired nAChR function in the early stages of the disease[117]. However, there is also a growing body of evidence regarding the consequences of high-affinity beta-amyloid binding to neuronal α7-nAChRs[58], which can lead to neuronal damage and even cell death. Selective α7-nAChR agonists have been shown to alleviate cognitive impairment in Alzheimer's disease and schizophrenia[53,58,117].

There have been few reports of **schizophrenia** occurring in connection with spike-inducing vaccination (see Table 4). In principle, the same reasons for under-reporting apply here as for dementia/Alzheimer's dementia – a lack of awareness and the inability to conceive of a possible link with the vaccination. However, the fatality rate of 2–21% is worth noting and highlights the significance of this disease for the safety profile of spike-inducing vaccines. The VAERS data also show relatively few cases of schizophrenia; however, compared with all reports of vaccine side effects (excluding Covid-19 vaccinations), these were recorded approximately 14 times more frequently per month following Covid-19 vaccinations. In contrast, a reduced incidence of schizophrenia was reported within 3 months of vaccination[98]. The extent to which methodological factors (short observation period, diagnostic criteria, etc.) may have influenced this result is unknown.

The nature of the condition and its symptoms are extremely complex, necessitating a targeted analysis. Regarding angiotensinergic and/or cholinergic aetiology, only limited hypotheses can be formulated. The central RAAS appears to play an important role in the pathogenesis of schizophrenia by influencing neurotransmitters or their receptor activity – such as dopamine/dopamine D_2 receptor activity, GABA, glutamate and others – and also by triggering neuroinflammation[118-120]. It is well known that spikes, by increasing Ang II concentrations, promote neuroinflammatory processes and are exacerbated in this regard by the inhibition of anti-inflammatory, n-cholinergic effects (see Fig. 3. b). This could potentially suggest a link between spike efficacy and schizophrenia.

Schizophrenics are thought to have a reduced number of α7-nAChR receptors in the hippocampus, which may impair the filtering function for incoming stimuli. Low concentrations of α7-nAChR mRNA in lymphocytes are considered biological markers of schizophrenia[58]. Improvements in sensory deficits following nicotine treatment and improved cognition following treatment with varenicline and other n-cholinergic agonists were cited[117].

Reports of **musculoskeletal side effects** (myalgia, muscular weakness, motor dysfunction, muscle twitching, involuntary muscle contractions, myoclonus, myokymia, rhabdomyolysis, myasthenia gravis; see Tables 5 and 3) must under no circumstances be overlooked, given their frequency (the third most common type of side effect) and the burden of suffering they cause (cumulative deaths: 263 following E vaccination; 368 following T vaccination).

Myalgia ranks highest within the reaction group (T: n = 156,735; E: n = 62,034; corresponding to 12.3 to approximately 16% of all those affected by side effects). Earlier studies arrived at very similar prevalence figures[20]. 55% of those suffering from post-vaccination symptoms reported myalgia[97]. Healthcare workers reported myalgia in 36.4% of cases three weeks after vaccination with various Covid-19 vaccines[121]. The frequency of reports of arthralgia/myalgia is roughly in line with the frequency associated with Covid-19 (15.5–19% to 62.5%)[122], which suggests a common aetiology. Possible causes include ACE2-mediated, directly damaging effects of the spike protein on the muscles, a reduced blood supply due to endothelial dysfunction and/or spike-induced inflammatory reactions, such as myositis. Myalgia may also be part of a multifocal motor neuropathy (MMN); if antibodies are present, an immunological aetiology should be considered[20]. Spike-induced cholinergic dysfunction could exacerbate inflammatory reactions.

Muscular weakness and motor dysfunction (T: n=11,514; E: n=3,703) were frequently reported; the reporting rate roughly doubled between the start of data collection and February 2022[20]. These ADRs may be concomitant symptoms of other conditions, such as rhabdomyolysis or myasthenia gravis, or they may be part of the symptomatology of fatigue/asthenia. Catabolic, proteolytic effects of Ang II are known to be a causative factor[123]. Other possible mechanisms include impaired blood supply due to vasoconstrictive effects of Ang II, impaired cholinergic nerve transmission, an autoimmune aetiology, or inflammatory potentiation involving fibre proteolysis and reduced protein synthesis[122]. A dysfunction of the muscular cholinergic αβγδε subunit receptor is also considered a possible cause of muscle weakness, pain or joint problems[57].

The symptom **muscle twitching/involuntary muscle contractions/myoclonus** was reported less frequently (combined: n=4,785; E: n=1,210); **myokymia** was mentioned even less frequently (T: n=130; E: n=21). The occurrence of these phenomena has been known for some time[20]. An analysis of a small series of patients (n = 21) with motor-neurological abnormalities requiring clinical treatment revealed that vaccinated individuals exhibited functional neurological deficits significantly more frequently than patients with Covid-19 (58% vs. 22%)[124]. In addition to non-specific neurological damage caused by systemic hypoxaemia or immunological dysfunction, the proposed causal mechanisms also included RAAS dysfunction and the unmasking of pre-existing symptoms due to a loss of stress compensation, which is pathophysiologically plausible. Furthermore, the nature of the symptoms suggests neuromuscular and central nervous system disorders involving cholinergic transmission.

Myasthenia gravis (MG) is the prototypical antibody-mediated autoimmune disorder. Circulating antibodies target antigens on the postsynaptic membrane of the neuromuscular junction. In 85% of cases, these antigens are nAChRs[75].

Myasthenia gravis cases were recorded 344 times following vaccination with T and 184 times following E in the Eudravigilance WebReports. New cases associated with vaccination were rarely published [73, 74, 76, 77, 125, 126]. An increase was observed not only since the outbreak of Covid-19, but also in connection with vaccination; those who developed myasthenia for the first time had a higher vaccination rate (88.14%)[78]. Neuromuscular disorders, including myasthenia (8.5%), were identified as significant side effects of the COVID-19 vaccination. Fourteen out of the 22 individuals received an mRNA vaccine. Symptoms developed approximately 6 days (median) after vaccination. Antibodies against AChR were present in 80% of cases[127]. A deterioration in the condition of unstable patients is possible[75].

Autoimmune processes, formation of antibodies against the AChR, the muscle-specific tyrosine kinase, or the low-density lipoprotein receptor-associated protein 4 (LRP4), direct neurotoxic effects and/or disruption of immune homeostasis as well as triggering a pre-existing subclinical condition - are all being considered as potential causes. Vaccine-induced antibodies may cross-react with proteins at the neuromuscular junction. The fact that vaccine spikes can bind to nAChRs, thereby influencing neuromuscular transmission and also contributing to hyperstimulation of the immune system, has rarely been discussed[126]. In any case, the therapeutic efficacy of acetylcholinesterase inhibitors was convincing.

Polymyalgia rheumatica (PMR), characterised as an autoimmune condition, accounted for a comparatively small number of reports in European countries up to October 2025, representing 0.09% (365 cases following vaccination with E) and 0.12% (1,487 cases following vaccination with T) of all those affected by adverse reactions. Analysis of VAERS data revealed a significantly higher rate following Covid-19 vaccination (2,227 cases over 61 months) compared with flu vaccination (233 cases over 433 months) or compared with all other vaccinations (526 cases over 433 months[128]). Despite a few negative findings[129], the large number of cited, supporting studies suggests a link with vaccination. The authors describe macrophage and dendritic cell infiltration, accompanied by immune dysregulation and increased cytokine production, as a possible cause. Persistent spike protein production could also be a factor, as well as subclinical infections. Macrophages and dendritic cells are equipped with α7-nACh receptors and thus qualify as part of the cholinergic anti-inflammatory signalling pathway CAP. As explained, spikes can inhibit α7-nAChR function and thereby trigger inflammatory reactions, which are exacerbated in conjunction with RAAS activation.

Reports of **rhabdomyolysis** have risen since 2022 from 332[20] to a total of 500 cases (T and E), with a significant proportion of fatal outcomes (4.2–5.4%). The first case was published in 2021[130]. With regard to causes, the authors generally discussed trauma, infections, extreme fluctuations in body temperature, myotoxic drugs, genetic or metabolic disorders, tissue hypoxia/ischaemia and/or inflammatory muscle diseases. In connection with the COVID-19 vaccination, cytokine-mediated direct muscle damage was considered, which may be mediated by Ang II, exacerbated by the harmful effects of nAChR inhibition.

The most frequently documented set of symptoms among the vaccine reactions discussed to date comprises **fatigue/chronic fatigue syndrome and asthenia** (267,199 cases in connection with T and 93,360 following E). These symptoms of fatigue, which severely impair quality of life, are already known to be associated with Covid-19 and are the most significant symptom of long Covid[131]. However, fatigue is increasingly being observed in connection with the Covid-19 vaccination, as well as with Post-Covid-19 Vaccination Syndrome (PCVS) and Post-Acute Covid-19 Vaccination Syndrome (PACVS), which are not yet well understood and are also known as LongVac. The prevalence is alarming. 69% of a representative post-vaccination population experienced excessive fatigue[97]. Halma[104] found a prevalence of around 77%. Purpura[132] found a fatigue prevalence of around 93% among PACVS sufferers.

In 2013, van Elzakker[133] proposed the hypothesis that an infection of the vagus nerve could lead to this disorder. While the vagus nerve normally signals the body to rest when it detects a bacterial or viral infection in the peripheral tissues involving immune cells, this signal becomes exaggerated and pathological when the vagus nerve itself is infected by neurotropic viruses. However, this appealing hypothesis does not consider the effects of the isolated spike, which is known to lead to reduced levels of acetylcholine and intracerebral inflammation, amongst other things. Semmler et al.[134] found that, five to six months after vaccination, PAVCS

patients had higher levels of antibodies against the AT_1 and MAS receptors than vaccinated individuals without symptoms. The changes in receptor activity and the effect on the protective AT_2R, as well as the temporal course of events, were not investigated, leaving many questions unanswered. Consistent with the hypothesis of immune dysregulation and potential mast cell activation, Purpura et al.[132] identified elevated cytokine and histamine concentrations, particularly IFN-gamma and TNF-alpha, in patients with chronic fatigue syndrome.

In light of these findings, PACVS, including fatigue, should be taken seriously rather than being dismissed as a 'diagnosis of convenience', such as a psychosomatic or autoimmune/immunological disorder.

Within just five months of the start of the vaccination campaign in December 2020, the European authority had received a flood of reports of **cardiovascular side effects**, some of which proved fatal. Of the 525,907 reports received, 212,053 were related to Tozinameran. These included 6,130 cases of hypertension, 5,788 cases of tachycardia, 2,778 cases of thrombosis and 2,240 cases of cardiovascular and sudden death amongst 6,732 fatal adverse reactions. There were also 1,809 cases of arrhythmia, 1,639 cases of pulmonary embolism, 1,003 strokes, 983 cases of blood clotting disorder, 703 cases of myocardial infarction, 562 cases of myo-/pericarditis, 524 cases of acute heart failure and 328 cases of cerebral haemorrhage. There were also 254 cases of cerebral thrombosis/embolism, including 90 cases of sinus vein thrombosis and 221 cases of activated blood coagulation[16]. These cases were consistent with the suspected, pathophysiologically harmful increased activity of Angiotensin II (Ang II) and closely resembled the cardiovascular organ dysfunction associated with SARS-CoV-2 infection[15].

The current case figures (heart diseases: n = 102,514 T; n = 33,086 E; and vascular disorders: n = 65,587 T; n = 19,049 E) showed a further increase to approximately 148–170 % between February 2022[20] and 19 October 2025, which would have been even more pronounced had the numerically significant adverse effects of the ‘reaction group’ – general and local adverse effects (fatalities) – and the ‘investigation group’ (blood pressure, hypertension) been included. The severity of the induced symptoms is characterised by the incidence of fatal side effects (proportion of all deaths: 11.25–14.47% and 3.96–4.59%, respectively; see Table 2).

In the general population, heart-circulatory diseases account for the highest proportion of deaths, with figures ranging from 33.3 to 35.3 per cent per year. In Germany, absolute figures rose steadily from 2019 to 2022, increasing from 331,211 to 358,219[95]. The sharp increase of 17,600 cases in 2022, the second year of the vaccination programme, was particularly dramatic. Similar, though less pronounced, trends were observed for ischaemic heart disease, myocardial infarction and hypertension. In 2023, the figures fell again. The proportion of cardiovascular mortality attributable to the vaccination programme remains unknown.

The strikingly high number of adverse cardiovascular effects and coagulopathies[16, 17, 20], as well as their consequences, can be explained by the synergistic interaction between spike-induced activation of the RAAS, associated spike-mediated effects, reduced nAChR activity and cholinergic dysfunction (see Table 6). The resulting excessive inflammatory and immunological reactions can exacerbate the symptoms, ranging up to cytokine storm or multisystem inflammatory syndrome (MIS). Interestingly, patients with MIS following vaccination frequently (in 97% of cases) suffered from pathological cardiovascular symptoms[135].

Conclusions

1. The safety profile of spike-inducing Covid-19 vaccines is characterised primarily by the class-specific spike core competencies and the long-lasting systemic presence of spike proteins. Since the start of the mass vaccination campaigns, the unknown extent of spike antigen production in the vaccinated individual's body and the unknown consequences of vaccine optimisation (the use of modified mRNA and the proline substitution for the purpose of spike antigen optimisation) have signalled uncertainty not only regarding the vaccine's efficacy, but also regarding the potential risk of side effects. It is undeniable that spike-based Covid-19 vaccines can cause a wide range of side effects, some of which are serious, and affect almost all organ systems. These far exceed all other conventional vaccines in terms of numbers and diversity.

2. This is caused by the effects of spikes, which can interfere with the body's ability to maintain homeostasis.

    - Non-neutralised, systemically active vaccine spikes primarily activate RAAS functions by downregulating the protective ACE2 spike receptor enzyme, resulting in an increase in Ang II that is harmful to the body.

    - The impairment or loss of cholinergic physiological counterbalancing functions, caused by nAChR-inhibition, exacerbates RAAS activation. Inhibition of nAChRs is triggered by neurotoxin-like spike protein structures. With the exception of sequence aa 375–390, these spike structures are not located within the antigenic receptor-binding domain (RBD) region. This means that they are likely to escape neutralisation by antibodies. Consequently, they remain fully effective. This harmful synergism is facilitaded by the local combined presence of effectors from both systems.

In principle, this results in a disruption of systemic homeostasis. In concrete terms, it depends on the organ-specific expression of counteracting regulators, on opposing regulatory effects, dose-dependent effects and time-dependent effects within the regulatory systems, as well as on comorbidities, age, gender, drug interactions and genetic predispositions. Several factors, including elevated angiotensin II levels, the inhibition of nAChR/CAP and the TLR4 activation, promote inflammatory and immunological processes, as well as harmful reactions involving the cardiovascular, coagulation, nervous and musculoskeletal systems etc.

The symptoms caused by spike glycoproteins, including long-lasting conditions such as Long Covid and Post-Vaccine Syndrome, must be taken seriously and should neither be ignored nor dismissed as psychosomatic.

3. Therapeutic intervention should be aimed at restoring and stabilising homeostasis. There are two basic options for achieving this:

    - Angiotensin receptor blockers (ARBs) have been used to treat cardiovascular diseases since 1995 and are the preferred choice for inhibiting RAAS activation, particularly for counteracting the effects of the main effector, Angiotensin II (Ang II).

      Reasons: ARBs block the effects of Ang II at the AT_1 receptor. They do not affect the action of Ang II on the AT_2 receptor. The AT_2 receptor mediates protective, pathogenetically beneficial effects such as vasodilation, reduced sympathetic activity, reduced ROS production and reduced levels of inflammatory cytokines. Consequently, the effects of the AT_2 receptor support the blockade of the AT_1 receptor both in the periphery and in the CNS.

In cases where vasoconstrictive symptoms predominate, vasodilators such as calcium channel blockers or anti-catecholamines may be used in addition or as an alternative.

- The n-cholinergic nervous system, which exerts a counter-regulatory effect and has been rendered inactive by vaccine spikes, requires reactivation.

  Options for cholinergic activation and the restoration of the cholinergic anti-inflammatory pathway (CAP) include acetylcholine analogues, acetylcholinesterase inhibitors (e.g. donepezil and rivastigmine), and vagus nerve stimulation.

In cases of severe symptoms, a combination of therapeutic measures is a viable option.

Other alternatives (e.g. AT_2R agonists, Ang 1-7 analogues; spike blockers, enhanced spike degradation, prevention of ACE2 downregulation) are under discussion.

Limitations

The analysis is limited by the following factors:

- a lack of detailed individual ADR-information
- non-validated reporting and documentation systems
- an absence of a suitable comparison population
- an unrecorded and unknown number of people vaccinated during the same period.

Due to the extensive nature of the data set, only a very limited number of examples could be included in this analysis.

Relevant scientific publications, predominantly from recent years, were consulted to interpret the findings. Given the overwhelming burden of symptoms suffered by those affected, the therapeutic approach urgently requires validation through specifically designed, randomised controlled trials.

Conflicts of Interest Statement

The author has no conflicts of interest to declare

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