

GULF WAR ILLNESS

No Updates this Week for Gulf War Illness or Chronic Multisymptom Illness.

CHRONIC FATIGUE SYNDROME

[Feedback on underperformance in patients with Chronic Fatigue Syndrome: The impact on subsequent neuropsychological test performance.](#)

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Appl Neuropsychol Adult. 2018 Oct 31:1-9. doi: 10.1080/23279095.2018.1519509. PMID: 30380922. [Epub ahead of print]

Performance Validity Tests (PVTs) are used to measure the credibility of neuropsychological test results. Until now, however, a minimal amount is known about the effects of feedback upon noncredible results (i.e., underperformance) on subsequent neuropsychological test performance. The purpose of this study was to investigate the effects of feedback on underperformance in Chronic Fatigue Syndrome (CFS) patients. A subset of these patients received feedback on Amsterdam Short-Term Memory (ASTM) failure (i.e., feedback [FB] group). After matching, the final sample consisted of two comparable groups (i.e., FB and No FB; both n = 33). At baseline and follow-up assessment, the patients completed the ASTM and two measurements of information processing speed (Complex Reaction Time [CRT] and Symbol Digit Test [SDT]). Results indicated that the patients in the FB group improved significantly on the CRT, compared to the No FB group. Although not significant, a comparable trend-like effect was observed for the SDT. Independent of the feedback intervention there was a substantial improvement on ASTM performance at re-administration. A limited feedback intervention upon underperformance in CFS patients may result in improvement on information processing speed performance. This implies that such an intervention might be clinically relevant, since it maximizes the potential of examining the patients' actual level of cognitive abilities.

HEADACHE and MIGRAINE

[Sleep Disorders Among People With Migraine: Results From the Chronic Migraine Epidemiology and Outcomes \(CaMEO\) Study.](#)

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Headache. 2018 Nov 1. doi: 10.1111/head.13435. PMID: 30381821. [Epub ahead of print]

OBJECTIVES: We examined the cross-sectional association of sleep apnea and indices of sleep quality with both episodic migraine (EM) and chronic migraine (CM).

BACKGROUND: Sleep apnea and abnormal patterns of sleep, such as insomnia, were associated with migraine onset, severity, and progression in previous research.

METHODS: The Chronic Migraine Epidemiology & Outcomes Study, a longitudinal study, used a series of web-based surveys to assess migraine symptoms, burden, and patterns of health care utilization. Quota sampling was used from September 2012 to November 2013 to generate a representative sample of the US population. Persons who screened positive for sleep apnea on the Berlin Questionnaire are said to be at "high risk" for sleep apnea. Respondents indicated if they believed that they had sleep apnea, if a physician had diagnosed it, and if and how they were treated. Other aspects of sleep quality were assessed using the Medical Outcomes Study (MOS) Sleep Measures.

RESULTS: Of 12,810 eligible respondents with migraine and data on sleep, 11,699 with EM (91.3%) and 1111 with CM (8.7%) provided valid data for this analyses. According to the Berlin Questionnaire, 4739/12,810 (37.0%) were at "high risk" for sleep apnea, particularly persons with CM vs EM (575/1111 [51.8%] vs 4164/11,699 [35.6%]), men vs women (1431/3220 [44.4%] vs 3308/9590 [34.5%]), people with higher body mass index, and older people (all $P < .001$). Among respondents to the MOS Sleep Measures, persons with CM were more likely to report poor sleep quality than those with EM, including sleep disturbance (mean [SD] values: 53.2 [26.9] vs 37.9 [24.3]), snoring (38.0 [33.9] vs 31.0 [32.1]), shortness of breath (34.9 [29.8] vs 15.3 [20.6]), somnolence (44.1 [23.4] vs 32.2 [21.2]), and less likely to report sleep adequacy (34.0 [24.2] vs 39.2 [22.1]).

CONCLUSIONS: Compared with respondents with EM, a larger proportion of those with CM were at "high risk" for sleep apnea and reported poor sleep quality. This reflects an association between CM vs EM and sleep apnea and poor sleep quality; the potential relationships are discussed.

HEADACHE and MIGRAINE (Continued)

[Health care Resource Utilization and Migraine Disability Along the Migraine Continuum Among Patients Treated for Migraine.](#)

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Headache. **2018 Oct 30**. doi: 10.1111/head.13421. PMID: 30375650. [Epub ahead of print]

OBJECTIVE: To examine the disability, health care resource utilization, and direct annual costs among patients with migraine, categorized according to the number of headache days experienced in the past month.

BACKGROUND: Migraine exists on a continuum of different attack frequencies and associated levels of disability. People with migraine have increased health care utilization and incur substantially more direct costs than those without the disease. While the broad implications of migraine are evident, there is a need to comprehensively describe the impact of headache frequency on the burden of illness.

DESIGN/METHODS: Data from a cross-sectional, self-administered, Internet-based survey of respondents recruited from the US National Health and Wellness Survey panel were assessed. Adults who had self-reported migraine diagnosis or migraine symptoms in the past 3 months were grouped by their frequency of headache days in the past month: low-frequency episodic migraine (LFEM, <4 days), moderate-frequency episodic migraine (MFEM, 4-9 days), high-frequency episodic migraine (HFEM, 10-14 days), and chronic migraine (CM, ≥15 days). Headache-related disability was determined from the Headache Impact Test (HIT-6) scores, and health care resource utilization was assessed by the number of ER visits, hospitalizations, and visits to health care practitioners (HCPs) in the past 12 months. The estimated annual direct costs were calculated from the number of each type of visit and all-cause cost data from the 2014 Medical Expenditure Panel Survey.

RESULTS: A total of 1347 patients (LFEM, n = 813; MFEM, n = 301; HFEM, n = 105; CM, n = 128) were included. Patient groups differed significantly by comorbidity index, education and income level, alcohol consumption, and insurance type. Overall, patients with LFEM had the least disability and lowest health care utilization and direct costs. Patients with CM scored 3.7 points (adjusted mean score [95% confidence interval, CI] 68.2 [67.3, 69.0] points) higher on HIT-6 compared with those in the LFEM group (64.5 points [64.1, 64.8]), while those with HFEM and MFEM scored 2.4 (66.8 points [65.9, 67.8]) and 2.3 (66.7 points [66.2, 67.3]) points higher, respectively (all, P < .001). The CM and MFEM groups reported significantly more HCP visits ([mean ± standard error] CM: 7.03 ± 0.83; MFEM: 5.34 ± 0.42; vs LFEM: 3.48 ± 0.18; both, P < .001) and migraine-related hospitalizations (CM: 0.06 ± 0.03; MFEM: 0.05 ± 0.02; vs LFEM: 0.02 ± 0.01; both, P < .05) than the LFEM group. There were significant differences in the total direct costs between the CM and MFEM groups compared with the LFEM group (CM: \$3155 ± \$609; MFEM: \$2721 ± \$342; vs LFEM: \$1560 ± \$118; both, P < .001), with differences largely driven by costs of HCP visits.

CONCLUSIONS: In patients with migraine, as the number of headache days increased, so did the burden of disease (disability, health care utilization, and direct costs). Elucidating the burden associated with EM and CM has implications for guiding treatment decisions and management of patients with migraine.

HEADACHE and MIGRAINE (Continued)

[Implications for the migraine SNP rs1835740 in a Swedish cluster headache population.](#)

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J Headache Pain. **2018 Nov 1**;19(1):100. doi: 10.1186/s10194-018-0937-0. PMID: 30382894.

BACKGROUND: Cluster headache is a severe headache disorder with unknown aetiology. The pathophysiology and symptoms present certain common features with migraine. Specifically, activation of the trigeminal vascular system seems to be involved in both disorders, which is hypothesized to result in neurogenic inflammation and vasodilation of the cerebral vessels. In addition, genetic factors have been implicated in both migraine and cluster headache.

OBJECTIVE: In order to determine whether or not migraine and cluster headache share genetic risk factors, we screened two genetic variants known to increase the risk of migraine in Sweden in a Swedish cluster headache case-control study population.

METHODS: In all, 541 patients and 581 control subjects were genotyped for rs1835740 in close proximity to MTDH (metadherin) and rs2651899 in the PRDM16 (PR/SET domain 16) gene, using TaqMan® real-time PCR and pyrosequencing. In addition, we analyzed MTDH gene expression in a subset of the material, using reverse transcription real-time PCR to determine relative mRNA levels in primary fibroblast cell lines from patients and controls.

RESULTS: We found a trend for association between rs1835740, which is reported to affect MTDH mRNA levels, and cluster headache in our Swedish case-control material ($p = 0.043$, $X^2 = 4.102$). This association was stronger in a subgroup of patients suffering from both cluster headache and migraine ($p = 0.031$, $X^2 = 6.964$). We could further confirm that rs1835740 has an effect on the transcriptional activity of MTDH. In this Swedish cluster headache cohort we did not find an association with the rs2651899 variant.

CONCLUSIONS: We conclude that rs1835740 is a potential risk factor for cluster headache in Sweden. Our data indicates that rs1835740 and MTDH might be involved in neurovascular headaches in general whilst rs2651899 is specifically related to migraine.

[The migraine eye: distinct rod-driven retinal pathways' response to dim light challenges the visual cortex hyperexcitability theory.](#)

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Pain. **2018 Oct 29**. doi: 10.1097/j.pain.0000000000001434. PMID: 30376534. [Epub ahead of print]

Migraine-type photophobia, most commonly described as exacerbation of headache by light, affects nearly 90% of the patients. It is the most bothersome symptoms accompanying an attack. Using subjective psychophysical assessments, we showed that migraine patients are more sensitive to all colors of light during ictal than during interictal phase and that control subjects do not experience pain when exposed to different colors of light. Based on these findings, we suggested that color preference is unique to migraineurs (as it was not found in control subjects) rather than migraine phase (as it was found in both phases). To identify the origin of this photophobia in migraineurs, we compared the electrical waveforms that were generated in the retina and visual cortex of 46 interictal migraineurs to those generated in 42 healthy controls using color-based electroretinography and visual evoked potential paradigms. Unexpectedly, it was the amplitude of the retinal rod-driven b-wave, which was consistently larger (by 14-19% in the light-adapted and 18-34% in the dark-adapted flash ERG) in the migraineurs than in the controls, rather than the retinal cone-driven a-wave or the visual evoked potentials that differ most strikingly between the two groups. Mechanistically, these findings suggest that the inherent hypersensitivity to light among migraine patients may originate in the retinal rods rather than retinal cones or the visual cortex. Clinically, the findings may explain why migraineurs complain that the light is too bright even when it is dim to the extent that non-migraineurs feel as if they live in a cave.

HEADACHE and MIGRAINE (Continued)

[Headache at the Time of First Symptom Manifestation of Multiple Sclerosis: A Prospective, Longitudinal Study.](#)

[Gebhardt M](#)¹, [Kropp P](#)², [Hoffmann F](#)¹, [Zettl UK](#)³.

Eur Neurol. 2018 Oct 26;80(3-4):115-120. doi: 10.1159/000494092. PMID: 30368493. [Epub ahead of print]

AIMS: Headaches have not been considered a typical symptom of multiple sclerosis (MS), although since 2000, almost every study showed high prevalence. We screened 50 MS patients at the time of first occurrence of neurological symptoms and found the highest prevalence of headache in MS that was ever recorded (78%). Postmortem histological analyses of MS patients' brains revealed lymphoid follicle-like structures in the cerebral meninges and a pathophysiological link between headache, and high inflammatory activity especially in the initial phase of MS could be suspected. The aim of this study was to get insights into the persistence of headache in the further progress of the disease.

METHODS: In a prospective, multicenter study, 50 MS patients at the time of first symptom manifestation were screened for the presence of headache within the last 4 weeks and again 6 months later with help of the Rostock Headache Questionnaire (Rokoko) as well as using the evaluation of case history and clinical-neurological investigation.

RESULTS: We found a decrease of headache prevalence after 6 months from 78 to 61% ($p = 0.01$). We could also show a decrease of headache frequency, measured by days with headache in the last 4 weeks (9.5 vs. 5.9, $p = 0.001$). Migraine or probable migraine was the most frequent headache. In both investigations, the most frequent headache was recurrent pain with pulsating and throbbing character that lasted between 4 and 72 h.

CONCLUSION: Headaches should be taken seriously as an important symptom in early MS. The decrease of headache 6 months after first symptom manifestation of MS could be a result of the immunomodulatory therapy. Young patients in whom migraine-like headaches occur should obligatory undergo an MRI of the head, and in the case of abnormal findings differential diagnosis should be initiated. This could reduce latency until final diagnosis of MS and enable early treatment.

CHRONIC PAIN

[Prevalence of comorbid chronic pain and mental health conditions in Canadian Armed Forces active personnel: analysis of a cross-sectional survey.](#)

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CMAJ Open. 2018 Nov 2;6(4):E528-E536. doi: 10.9778/cmajo.20180093. PMID: 30389752. Print 2018 Oct-Dec.

BACKGROUND: Chronic pain conditions and mental disorders have high prevalence rates in military populations. However, few investigations have examined the comorbidity between chronic pain conditions and specific mental disorders among Canadian active military personnel.

METHODS: We conducted a secondary analysis of data from the 2013 Canadian Forces Mental Health Survey (CFMHS) concerning the population of regular members. Diagnostic interviews assessed the presence of mental disorders, and participants self-reported chronic pain conditions (i.e., arthritis, back problems, musculoskeletal conditions, migraines) and indicators of pain severity. We used multiple logistic regressions to assess associations between chronic pain conditions and mental disorders. We used cross-tabulations to assess the prevalence of pain severity indicators in comorbid relationships compared with the chronic pain condition alone. We used moderation analyses to examine the interactions between pain condition by pain severity, and pain condition by activity limitation, respectively, on mental disorders.

RESULTS: The CFMHS included data from 6696 regular members and had a response rate of 79.8%. About one-quarter ($n = 1761$) of military personnel reported having chronic pain. In the fully adjusted model, all assessed pain conditions were significantly associated with posttraumatic stress disorder (PTSD) (odds ratio [OR] range 1.86-2.55), and several pain conditions were associated with major depressive episode, generalized anxiety disorder and panic disorder. Back problems were significantly associated with all mental disorders apart from alcohol use disorders (OR range 1.40-2.17). Cross-tabulations showed higher prevalence estimates of endorsement for pain severity indicators among pain conditions and comorbid mental disorders, compared with pain conditions alone. Formal moderation analyses showed a significant relationship between migraine and activity limitation on PTSD.

INTERPRETATION: Chronic pain conditions are prevalent and co-occur with mental disorders among Canadian regular force members. Greater understanding of these chronic pain conditions and mental disorders and their impact on people's abilities to adapt to both military and civilian life is needed.

CHRONIC PAIN (Continued)

[The neural basis of induced phantom limb pain relief.](#)

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Ann Neurol. **2018 Nov 1**. doi: 10.1002/ana.25371. PMID: 30383312. [Epub ahead of print]

OBJECTIVE: Phantom limb pain (PLP) is notoriously difficult to treat, partly due to an incomplete understanding of PLP-related disease mechanisms. Non-invasive brain stimulation (NIBS) is used to modulate plasticity in various neuropathological diseases, including chronic pain. While NIBS can alleviate neuropathic pain (including PLP), both disease and treatment mechanisms remain tenuous. Insight into the mechanisms underlying both PLP and NIBS-induced PLP relief is needed for future implementation of such treatment and generalisation to related conditions.

METHODS: We used a within-participants, double-blind, and sham-controlled design to alleviate PLP via task-concurrent NIBS over the primary sensorimotor missing hand cortex (S1/M1). To specifically influence missing hand signal processing, amputees performed phantom hand movements during anodal transcranial direct current stimulation. Brain activity was monitored using neuroimaging during and after NIBS. PLP ratings were obtained throughout the week after stimulation.

RESULTS: A single session of intervention NIBS significantly relieved PLP, with effects lasting at least one week. PLP relief associated with reduced activity in the S1/M1 missing hand cortex after stimulation. Critically, PLP relief and reduced S1/M1 activity correlated with preceding activity changes during stimulation in the mid- and posterior insula and secondary somatosensory cortex (S2).

INTERPRETATION: The observed correlation between PLP relief and decreased S1/M1 activity confirms our previous findings linking PLP with increased S1/M1 activity. Our results further highlight the driving role of the mid-and posterior insula, as well as S2, in modulating PLP. Lastly, our novel PLP intervention using task-concurrent NIBS opens new avenues for developing treatment for PLP and related pain conditions.

[Army and Navy ECHO Pain Telementoring Improves Clinician Opioid Prescribing for Military Patients: an Observational Cohort Study.](#)

[Katzman JG](#)¹, [Qualls CR](#)², [Satterfield WA](#)^{3,4}, [Kistin M](#)⁵, [Hofmann K](#)⁶, [Greenberg N](#)⁷, [Swift R](#)⁵, [Comerci GD Jr](#)⁸, [Fowler R](#)⁹, [Arora S](#)⁵.

J Gen Intern Med. **2018 Oct 31**. doi: 10.1007/s11606-018-4710-5. PMID: 30382471. [Epub ahead of print]

BACKGROUND: Opioid overdose deaths occur in civilian and military populations and are the leading cause of accidental death in the USA.

OBJECTIVE: To determine whether ECHO Pain telementoring regarding best practices in pain management and safe opioid prescribing yielded significant declines in opioid prescribing.

DESIGN: A 4-year observational cohort study at military medical treatment facilities worldwide.

PARTICIPANTS: Patients included 54.6% females and 46.4% males whose primary care clinicians (PCCs) opted to participate in ECHO Pain; the comparison group included 39.9% females and 60.1% males whose PCCs opted not to participate in ECHO Pain.

INTERVENTION: PCCs attended 2-h weekly Chronic Pain and Opioid Management TeleECHO Clinic (ECHO Pain), which included pain and addiction didactics, case-based learning, and evidence-based recommendations. ECHO Pain sessions were offered 46 weeks per year. Attendance ranged from 1 to 3 sessions (47.7%), 4-19 (32.1%, or > 20 (20.2%).

MAIN MEASURES: This study assessed whether clinician participation in Army and Navy Chronic Pain and Opioid Management TeleECHO Clinic (ECHO Pain) resulted in decreased prescription rates of opioid analgesics and co-prescribing of opioids and benzodiazepines. Measures included opioid prescriptions, morphine milligram equivalents (MME), and days of opioid and benzodiazepine co-prescribing per patient per year.

KEY RESULTS: PCCs participating in ECHO Pain had greater percent declines than the comparison group in (a) annual opioid prescriptions per patient (-23% vs. -9%, $P < 0.001$), (b) average MME prescribed per patient/year (-28% vs. -7%, $p < .02$), (c) days of co-prescribed opioid and benzodiazepine per opioid user per year (-53% vs. -1%, $p < .001$), and (d) the number of opioid users (-20.2% vs. -8%, $p < .001$). Propensity scoring transformation-adjusted results were consistent with the opioid prescribing and MME results.

CONCLUSIONS: Patients treated by PCCs who opted to participate in ECHO Pain had greater declines in opioid-related prescriptions than patients whose PCCs opted not to participate.

CHRONIC PAIN (Continued)

[Clinical Strategies for the Treatment and Management of Patients Prescribed Long-term Opioid Therapy.](#)

[Wyse JJ](#)^{1,2}, [Ganzini L](#)^{1,3}, [Dobscha SK](#)^{1,3}, [Krebs EE](#)^{4, 5}, [Zamudio J](#)¹, [Morasco BJ](#)^{1,3}.

Pain Med. **2018 Nov 2**. doi: 10.1093/pm/pny211. PMID: 30388259. [Epub ahead of print]

Objectives: Across diverse health care systems, growing recognition of the harms associated with long-term opioid therapy (LTOT) for chronic pain has catalyzed substantial changes to policy and practice designed to promote safer prescribing and patient care. Although clear goals have been defined, how clinics and providers should most effectively implement these changes has been less well defined, and facilities and providers have had substantial flexibility to innovate.

Methods: Qualitative interviews were conducted with 24 Department of Veterans Affairs (VA) clinicians across the United States who prescribe LTOT for chronic pain. Interviews probed the practices and initiatives providers utilized to meet opioid safety requirements and address common challenges in caring for patients prescribed LTOT.

Results: Innovative strategies in the design and organization of clinical practice (urine drug testing, informed consent, limiting transfer requests, specialty patient panel) and resources utilized (engaged pharmacists, non-opioid pain treatments, intra-organizational collaborations) are described.

Conclusions: We conclude with recommendations designed to improve opioid prescribing practices, both within the VA and in other settings.

[The association between multiple sclerosis and pain medications.](#)

[Burkill S](#)^{1,2}, [Montgomery S](#)^{2,3,4}, [Kockum J](#)^{5,6}, [Piehl F](#)^{5,6}, [Strid P](#)^{5,6}, [Hillert J](#)⁵, [Alfredsson L](#)^{7,8}, [Olsson T](#)^{5,6}, [Bahmanyar S](#)^{1,2}.

Pain. **2018 Oct 29**. doi: 10.1097/j.pain.0000000000001429. PMID: 30376533. [Epub ahead of print]

Multiple sclerosis (MS) patients are at greater risk of pain than people without the disease, however the occurrence and characteristics of pain among these patients are incompletely described. We aimed to assess characteristics of pain amongst MS patients using MS patients who were recruited to participate in three studies in Sweden (n=3,877), and were matched with individuals without MS (n=4,548) by sex, year of birth, and region of residence. The Prescribed Drugs Register identified prescribed pain medication, overall and restricted to those given four or more prescriptions in one year to assess chronic pain. Anatomical therapeutic chemical codes classified whether pain was neuropathic, musculoskeletal, or migraine. Cox proportional hazard models were used to estimate associations. Our findings showed MS patients were at increased risk of pain treatment, with a hazard ratio (HR) of 2.52 (95% confidence interval 2.38-2.66). The largest magnitude HR was for neuropathic pain (5.73, 5.07-6.47) for which 34.2% (n=1,326) of the MS and 7.15% (n=325) of the non-MS cohort were prescribed a treatment. The HR for chronic pain treatment was 3.55 (3.27-3.84), indicating an increased effect size relative to any pain treatment. Chronic neuropathic pain showed the largest HR at 7.43 (6.21-8.89). Neuropathic pain was shown to be the primary mechanism leading to increased risk of pain in MS patients.

OTHER RESEARCH OF INTEREST

[Feasibility of Addressing Environmental Exposure Questions Using Department of Defense Biorepositories.](#) Proceedings of a Workshop—in Brief (2018)

National Academies of Sciences, Engineering, and Medicine. **2018**. *Feasibility of Addressing Environmental Exposure Questions Using Department of Defense Biorepositories: Proceedings of a Workshop—in Brief*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/25287>.

Contributors: National Academies of Sciences, Engineering, and Medicine; Division on Earth and Life Studies; Committee on the Feasibility of Addressing DoD's Environmental Exposure Questions with Biorepositories; Elizabeth Boyle, Rapporteur.

The past decade has seen advancements in methods for measuring environmental exposures in biological specimens, such as blood or tissue. Chemicals can now be measured more accurately and with smaller volumes of specimens.

Biorepositories that store many biospecimens are maintained by the Department of Defense (DoD) for medical purposes.

To help determine the feasibility of using these biorepositories to conduct research on environmental and occupational exposures experienced by servicemembers, the National Academies of Sciences, Engineering, and Medicine convened a two-day workshop in June 2018. This publication briefly summarizes the presentations and discussions from the workshop.

OTHER RESEARCH OF INTEREST (Continued)

The vermiform appendix impacts the risk of developing Parkinson's disease.

[Killinger BA](#)¹, [Madaj Z](#)¹, [Sikora JW](#)², [Rey N](#)^{1,3}, [Haas AJ](#)¹, [Vepa Y](#)¹, [Lindqvist D](#)^{4,5}, [Chen H](#)⁶, [Thomas PM](#)², [Brundin P](#)¹, [Brundin L](#)¹, [Labrie V](#)^{7,8}.

Sci Transl Med. 2018 Oct 31;10(465). pii: eaar5280. doi: 10.1126/scitranslmed.aar5280. PMID: 30381408.

The pathogenesis of Parkinson's disease (PD) involves the accumulation of aggregated α -synuclein, which has been suggested to begin in the gastrointestinal tract. Here, we determined the capacity of the appendix to modify PD risk and influence pathogenesis. In two independent epidemiological datasets, involving more than 1.6 million individuals and over 91 million person-years, we observed that removal of the appendix decades before PD onset was associated with a lower risk for PD, particularly for individuals living in rural areas, and delayed the age of PD onset. We also found that the healthy human appendix contained intraneuronal α -synuclein aggregates and an abundance of PD pathology-associated α -synuclein truncation products that are known to accumulate in Lewy bodies, the pathological hallmark of PD. Lysates of human appendix tissue induced the rapid cleavage and oligomerization of full-length recombinant α -synuclein. Together, we propose that the normal human appendix contains pathogenic forms of α -synuclein that affect the risk of developing PD.

Safety, Tolerability, and Feasibility of Young Plasma Infusion in the Plasma for Alzheimer Symptom Amelioration Study: A Randomized Clinical Trial.

[Sha SJ](#)¹, [Deutsch GK](#)¹, [Tian L](#)², [Richardson K](#)³, [Coburn M](#)⁴, [Gaudio JL](#)¹, [Marcal T](#)⁵, [Solomon E](#)⁶, [Boumis A](#)¹, [Bet A](#)⁴, [Mennes M](#)⁷, [van Oort E](#)⁷, [Beckmann CF](#)⁷, [Braithwaite SF](#)⁸, [Jackson S](#)⁸, [Nikolic K](#)⁸, [Stephens D](#)⁸, [Kerchner GA](#)¹, [Wyss-Coray T](#)¹.

JAMA Neurol. 2018 Oct 29. doi: 10.1001/jamaneurol.2018.3288. PMID: 30383097. [Epub ahead of print]

Importance: Young mouse plasma restores memory in aged mice, but, to our knowledge, the effects are unknown in patients with Alzheimer disease (AD).

Objective: To assess the safety, tolerability, and feasibility of infusions of young fresh frozen plasma (yFFP) from donors age 18 to 30 years in patients with AD.

Design, Setting, and Participants: The Plasma for Alzheimer Symptom Amelioration (PLASMA) study randomized 9 patients under a double-blind crossover protocol to receive 4 once-weekly infusions of either 1 unit (approximately 250 mL) of yFFP from male donors or 250 mL of saline, followed by a 6-week washout and crossover to 4 once-weekly infusions of an alternate treatment. Patients and informants were masked to treatment and subjective measurements. After an open-label amendment, 9 patients received 4 weekly yFFP infusions only and their subjective measurements were unmasked. Patients were enrolled solely at Stanford University, a tertiary academic medical center, from September 2014 to December 2016, when enrollment reached its target. Eighteen consecutive patients with probable mild to moderate

Interventions: One unit of yFFP from male donors/placebo infused once weekly for 4 weeks.

Main Outcome and Measures: The primary outcomes were the safety, tolerability, and feasibility of 4 weekly yFFP infusions. Safety end point analyses included all patients who received the study drug/placebo.

Results: There was no difference in the age (mean [SD], 74.17 [7.96] years), sex (12 women [67%]), or baseline Mini-Mental State Examination score (mean [SD], 19.39 [3.24]) between the crossover (n = 9) and open-label groups (n = 9). There were no related serious adverse events. One patient discontinued participation because of urticaria and another because of an unrelated stroke. There was no statistically significant difference between the plasma (17 [94.4%]) and placebo (9 [100.0%]) cohorts for other adverse events, which were mild to moderate in severity. The most common adverse events in the plasma group included hypertension (3 [16.7%]), dizziness (2 [11.1%]), sinus bradycardia (3 [16.7%]), headache (3 [16.7%]), and sinus tachycardia (3 [16.7%]). The mean visit adherence (n = 18) was 86% (interquartile range, 87%-100%) and adherence, accounting for a reduction in the total visit requirement due to early patient discontinuation, was 96% (interquartile range, 89%-100%).

Conclusions and Relevance: The yFFP treatment was safe, well tolerated, and feasible. The study's limitations were the small sample size, short duration, and change in study design. The results warrant further exploration in larger, double-blinded placebo-controlled clinical trials.

Trial Registration: ClinicalTrials.gov Identifier: [NCT02256306](#).