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LONGEVITY

ABSTRACT & COMMENTARY

## Do Facebook Friends Count — for Health and Longevity?

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**Dr. Feldman reports no financial relationships relevant to this field of study.**

SYNOPSIS: An observational examination of California Facebook users suggested this population has a lower mortality rate than non-Facebook users; the lowest mortality risk is for Facebook users who combine a moderate degree of online social interaction with high offline social activity.

SOURCE: Hobbs W, Burke M, Christakis NA, Fowler JH. Online social integration is associated with reduced mortality risk. *Proc Natl Acad Sci U S A* 2016;113:12980-12984.

Social interactions are important to health and longevity. A 1979 landmark study persuasively documented this association, and several follow-up studies arrived at the same conclusion: People with more friends and more involvement in community tend to live longer.[1,2]

Although the association between social supports and health is clear, the mechanism of action remains unknown. Many researchers believe multiple factors are at work, including social and biological forces. For example, it is thought that the motivation to engage in healthy behaviors benefits from a strong social network. Evidence also suggests that healthy relationships strengthen immune factors.[3,4]

But as we all are aware, the world and our way of socializing and connecting has changed since 1979. As of December 2016, there were more than 1.8 billion active users of the popular social media network Facebook worldwide each month.[5] Increasingly, socialization is virtual, yet we do not know if the online social connections of today provide any of the health benefits documented in studies of offline or real-world

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## Summary Points

- This observational study was designed to determine if there is an association between online social network use and mortality.
- Mortality data were obtained over a two-year period from 4 million Facebook users registered to vote in California and compared with age- and gender-matched non-Facebook user registered voters.
- The mortality rate for Facebook users was found to be about 12% less than the mortality rate for non-Facebook users.
- Hobbs et al further analyzed these data by looking at causes of mortality and Facebook user characteristics.
- The number of accepted online friendships and received photo tags (an indication of offline social activity) both were associated with lower mortality.

settings. The goal in the Hobbs et al study was to determine if the association between social involvement and mortality holds true for online social activity.

Additionally, the investigators decided to further analyze this association by examining mortality from specific disease states and delving deeper into social media use to determine if there was a link or connection to offline use.

The research question for this study was two-fold:
1. Are online social interactions and involvement distinctly associated with decreased mortality?
2. Are health benefits from online social networks actually a reflection of benefits derived from real-world social activity?

Facebook permitted de-identified aggregated data to be collected for this project. Approximately 12 million profiles of California Facebook users met inclusion criteria initially (determined by birth date between 1945 and 1989 and date of Facebook sign up). To homogenize the Facebook and non-Facebook user groups and to control for socioeconomic and educational differences, both the control group (non-Facebook users) and the Facebook user group were then selected from the California Voting Records. This shrunk the original pool of 12 million Facebook users to just more than 4 million users, who then were age- and gender-matched to non-users within the California Voting Records. California Public Health Records were used to determine mortality rates and causes of death from each of these groups.

Social media use among the age- and gender-matched Facebook users was collected over a six-month period. Mortality rates and cause of mortality were collected during a two-year period (2012 and 2013).

Data from the Facebook user population were analyzed further to determine any connection between specific types of Facebook use and mortality. Initiating and accepting friend requests were analyzed separately to determine if either of these measures of online social life was associated with longer life or health. Efforts also were made to determine if specific Facebook social interactions thought to reflect real-world social interactions carried a disproportionate measure of health benefits. The investigators measured the number of accepted photo "tags" (based on previous studies, these identified photos are thought to be a measure of real-world activity)[6] and number of status updates (based on previous studies, updating activity has no known connection to real-world activity).[7]

### SELECTED RESULTS

1. Comparison of Facebook users and non-users present in the California Voting Record: Mortality rate of Facebook users is 88% of non-users.

2. See Table 1 for mortality by causes among Facebook users compared to non-users in the Voter Record.

**Table 1: Mortality Risk Among Facebook vs. Non-Facebook Users**

| Disease | Relative Risk of Death | 95% Confidence Interval |
|---|---|---|
| Infection | 0.72 | 0.63-0.82 |
| Diabetes | 0.62 | 0.56-0.70 |
| Dementia | 0.75 | 0.67-0.83 |
| Ischemic heart disease | 0.81 | 0.76-0.86 |
| Liver disease | 0.65 | 0.59-0.72 |
| Stroke | 0.71 | 0.63-0.80 |

RESULTS IN THE FACEBOOK USER POPULATION

1. Comparison of number of accepted friendships (people asking to be added to an online network) and number of requested friendships (asking to join someone else's online network): Mortality rate for users with the most accepted friendships was about 66% of the rate for those with the least amount of accepted friendships. Mortality rate for users with the most requested friendships was about equal to the rate for those with the least requested friendships — there did not appear to be any association with mortality rate and requests for friendship.

2. Results related to Facebook user offline (real-world) activity: Mortality rate was lowest (about 70% of average) for those with the greatest number of "tagged" photographs and the fewest status updates. In earlier studies, tagged photos were thought to represent offline activity, while status updates were less predictive and perhaps negatively associated with offline activity.[6,7] Mortality rates for specific disorders among Facebook users with the highest number of accepted friends is displayed in Table 2. Hobbs et al noted the greatest decrease in mortality risk occurred in socially linked disorders. The risk of most cancers was unchanged.

## ■ COMMENTARY

This large-scale, observational study was designed to determine if online socialization via Facebook was associated with any of the health benefits provided by offline or real-world socialization, including a reduced mortality risk.

Hobbs et al were very clear about the limitations of this study. They noted that despite attempts to control for socioeconomic differences between the Facebook user and non-user groups, it was likely that these differences not only existed but also influenced the results, given that socioeconomic factors are known to affect longevity. Hobbs et al also noted that this study did not imply or establish causality. That may come later, but

**Table 2: Mortality Risk Among Facebook Users with Highest Number of Accepted Friends**

| | Relative Risk | 95% Confidence Interval |
|---|---|---|
| Cardiovascular disease | 0.91 | 0.87-0.96 |
| Drug overdose | 0.78 | 0.70-0.87 |
| Suicide | 0.73 | 0.66-0.80 |

for now, caution is advised to distinguish causality from correlation.

Also of note is that while the number of subjects was impressively large, the time period to study longevity was too short. Two years simply is not long enough to study mortality rates conclusively. Following these groups over a lifetime will give much more valuable and meaningful information and a chance to see if the numbers and trend persist after two years. Additionally, it should be mentioned that there are other social media outlets in addition to Facebook. Although we know the control group was non-Facebook users, we do not know any other information about their social media use. Any conclusions drawn about social media use from this study must account for this narrow perspective.

Hobbs et al noted more valuable information was found from the in-depth look at Facebook users. Initially, they hypothesized that a larger friend network in general would be associated with lower mortality. They were surprised to learn that while more accepted friend requests was associated with reduced mortality rates, requests for friends had no such association.

It is difficult to know what to make of this finding. Hobbs et al interpreted this information to mean that seeking support from others may not be as significant in lowering health risk as accepting support. While this may be accurate, other valid explanations may emerge as we better understand what friend requests and acceptance represents in an online world.

Working with findings from another study, Hobbs et al used receiving photo tags as a measure of offline activity. Although it seems that a linear relationship exists here, with more received photo tags corresponding with a decreased mortality rate, the conclusion is not as convincing. Although receiving photo tags may represent an offline life, it is not as clear that the converse is true; that is, there is no evidence that fewer received photo tags mean less offline socialization. It may be that photos are sent more often within specific social groups determined by factors such as age, socioeconomic status, possession of a smartphone, and interest in taking photos.

This study is innovative in approach and produced suggestive findings, but the clinical usefulness is not readily apparent. Certainly, there is no evidence that urging patients to send more photos or accept more friend requests will improve longevity. But there are some valuable takeaways. If we look at this study as a pioneering approach to identify health implications of Facebook use, possibilities for future clinical application arise. There have been many negative studies regarding online activity and health. These findings give us hope that specific use of online social media may bestow health benefits.[8,9]

For now, a clinician is on solid ground recommending use of social media in moderation to enhance rather than replace offline or real-world social involvement. Although results imply that accepting friends as opposed to reaching out online is more valuable for health, there seems to be little harm (and perhaps even greater rewards) in both accepting and requesting friendships in the real world. Finally, this study serves as a reminder of the importance of taking a fresh look at established findings as our society and norms change and develop over time. ■


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## MULTIPLE SCLEROSIS

ABSTRACT & COMMENTARY

# High-dose Biotin Shows Promise for Arresting Progressive Multiple Sclerosis Disability


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**Dr. Decker reports no financial relationships relevant to this field of study.**


SYNOPSIS: In this double-blind, placebo-controlled study, patients with primary or secondary progressive multiple sclerosis were randomized to receive 100 mg of pharmaceutical-grade biotin or placebo thrice daily for 12 months. The primary endpoint of an improvement in the Expanded Disability Status Scale or a decrease in timed 25-foot walk time was achieved in 12.6% of the biotin-treated patients compared to no one in the placebo group ($P = 0.005$).

SOURCE: Tourbah A, Lebrun-Frenay C, Edan G, et al. MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: A randomised, double-blind, placebo-controlled study. *Mult Scler* 2016;22:1719-1731.


Progressive multiple sclerosis (MS) is a diagnosis that no one wants to hear, as it progresses more rapidly than that of a relapse-remitting course. A diagnosis of primary or secondary progressive MS is made retrospectively based on patient history, and relapse-remitting MS (RRMS) transitions to secondary progressive multiple sclerosis (SPMS) in approximately 80% of patients with RRMS.[1] Primary progressive multiple sclerosis (PPMS) occurs in approximately 10% of MS patients.[2] Treatment options for the disease in the progressive state are limited, as therapies that are effective for RRMS have limited to no efficacy.[3] Given these statistics and information, it is not surprising that patient populations also seek integrative medicine providers for additional support.

Sedel et al found success in a small pilot study (n = 23) investigating biotin as a therapy for patients with non-active progressive MS. They found that more than 90% of patients had some degree of clinical improvement

## Summary Points

- Patients with primary or secondary progressive multiple sclerosis received 100 mg of pharmaceutical-grade biotin (vitamin B7) or placebo dosed three times daily for one year.
- The primary endpoint was an improvement in the Expanded Disability Status Scale or a 20% decrease in timed 25-foot walk time, as assessed at nine and 12 months.
- The authors found that 12.6% of patients randomized to receive biotin achieved the primary endpoint vs. none of those treated with placebo.
- Clinician- and patient-assessed impressions of change also were significantly better in the biotin group ($P < 0.001$ and $P = 0.009$, respectively).

with high doses of biotin ranging from 100 mg to 300 mg (as compared to typical adult daily intake of 30 mcg/day to 100 mcg/day).[4] This larger, randomized, double-blind, placebo-controlled study assessed the effect of biotin dosed at 100 mg three times daily vs. placebo (randomized 2:1, intervention:placebo) in patients diagnosed with SPMS and PPMS.

The 154 patients (103 randomized to intervention and 51 to placebo) enrolled in this study ranged from 18-75 years of age (meeting the revised McDonald and Lublin criteria for PPMS or SPMS) and also had evidence of spastic paraparesis. For eligibility, patients were required to have an Expanded Disability Status Scale (EDSS) evaluation showing disease progression during the previous two years. Patients with clinical or radiological evidence of inflammatory activity within the past year were excluded. Concomitant medications, such as immune modulators and immunosuppressive drugs, were allowed if they were introduced a sufficient period before the study. If necessary, intravenous methylprednisolone without oral taper was allowed for relapse. Physical therapy (PT) was allowed during the study, with the exception of intensive inpatient PT programs.

The primary endpoint evaluated to determine efficacy of therapy was MS-related disability: either an improvement in the EDSS by ≥ 1 point (≥ 0.5 for initial scores of 6-7) or a 20% decrease in timed 25-foot walk time as evaluated at nine and 12 months. Secondary endpoints of mean change in EDSS from start to month 12, clinician and patient-assessed impression of change, and various additional markers of disease state also were assessed. An extended intervention period in which both groups received biotin at the dosage of 100 mg three times daily was included to further evaluate the treatment efficacy. Patients and investigators remained blinded to the initial intervention during the extension period.

Thirteen patients (12.6%; 95% confidence interval [CI], 6.9-20.6%) of the group treated with biotin had a reduction in their EDSS score or a 20% decrease in their 25-foot walk time at nine months, reconfirmed at month 12, compared to no one in the placebo group (95% CI, 0.06-0.19; $P = 0.005$). At a three-month evaluation point, 10 of these 13 patients were observed to have reduced EDSS scores while five had improved walk times, with two improving in both categories. Secondary endpoints of clinician and patient-assessed global impression of change were significantly better in the biotin group ($P < 0.001$ and $P = 0.009$, respectively). At months nine and 12, EDSS scores were observed to progress in 13.6% of the placebo group and 4.2% of the biotin group ($P = 0.07$).

Additional analysis showed the endpoint of reduced disability was achieved more frequently in patients not taking fampridine (a potassium channel blocker medication commonly used in patients with MS) than patients who were taking fampridine (12 vs. one patient), and in those who had a baseline EDSS of 4.5-5.5 than those with baseline EDSS of 6-7 (6 of 28 vs. 7 of 75). At month 24, in the extended evaluation when both groups were given biotin, 14 (15.4%) patients of the biotin-biotin group and five (11.9%) patients in the placebo-biotin group had reduced MS-related disability by the same parameters. Additionally, two patients in the intervention group who were not observed to have improvements at 12 months were better at month 24. With the patients who were on biotin for both 12-month periods, the mean EDSS scores were relatively stable over 24 months (0.04 ± 0.62).

During the placebo-controlled study, 12 (11.7%) patients from the intervention group and nine (17.6%) patients from the placebo group withdrew from the study. Of these, six in the treatment group withdrew because of adverse events (suicide, mucocutaneous rash, asthenia, muscle spasms, abdominal pain, and libido disorder), while seven from the placebo group withdrew because of adverse events (overdose, dry mouth, intracranial hemorrhage, mental disorder, extrasystoles, muscle spasticity, and pregnancy). Five patients (4.9%) in the biotin group and four patients (7.8%) in the placebo group experienced MS relapse during the placebo-controlled study.

### ■ COMMENTARY

Given that progressive MS patients typically do not

experience a reduction in EDSS scores, the current findings are noteworthy for this population.[5] Since potentially effective medication options are minimal and the information from this study has rapidly populated patient support networks for individuals with MS, providers should be aware of the study. Overall safety was considered comparable to the placebo population. Although adverse events such as a mucocutaneous rash often suggest a reaction to intake of a new substance, subsequent patch testing was negative for biotin.

One issue of clinical importance that was observed with the biotin intervention was laboratory findings suggesting hyperthyroidism in six patients during the placebo-controlled phase and five patients during the extension phase. This apparent hyperthyroidism (low thyroid-stimulating hormone and high triiodothyronine or thyroxine) was determined to be due to biotin interference with standard thyroid laboratory tests, as a biotinylated antibody is used for this testing.[6] Only one patient of the six with apparent hyperthyroidism was found to have Graves' disease (iodine-induced hyperthyroidism) as confirmed by histology.

The proposed mechanism by which these observed effects of biotin may affect progressive MS are not via alteration of the inflammatory aspect of this disease. Rather, it has been suggested that the biotin-dependent carboxylases, which are involved in production of key intermediaries of the Krebs cycle, are supported by increased biotin, meeting increased energy demands of unmyelinated axons, which may be up to 5,000 times higher than those that are myelinated.[7,8] Mitochondrial injury associated with inflammation also may reduce energy availability.[9] Three of these biotin-dependent carboxylases are expressed in astrocytes and neurons and play a central role in neuronal energy production. The combination of a potential energy deficit and increased need is proposed to lead to a virtual hypoxia. Biotin, which is completely orally absorbed and transported across the blood-brain barrier in a saturable system,[10] can be provided to the central nervous system with oral supplementation.

The effects of both lower and higher dosages of biotin were assessed in the pilot study (dosages ranging from 100 mg to 600 mg). Although symptom improvements were seen with dosages of 300 mg daily compared to 100 mg, no further benefit was appreciable at the higher dosage of 600 mg.[4] In this study, mild transient diarrhea was noted with biotin supplementation. Although the high-dose biotin formulation used in this study, known as MD1003 or Cerenday, currently is in Phase III trials that are scheduled to complete in September 2019, higher-dose biotin supplements are available from numerous nutraceutical companies at doses of 8 mg to 10 mg per capsule, and from some as a powder or 100 mg capsule.

The lack of an intention-to-treat analysis, which makes a thorough assessment of these findings incomplete, is noteworthy about the Tourbah et al study. The considerable number of dropouts from both groups (11.7% from the intervention group and 17.6% from the placebo group) may affect the significance of the current findings. However, since a high percentage also dropped out of the placebo group, the results may not change dramatically; however, it should have been included for completeness.

A reasonable strategy given the possible benefit and minimal negative implications other than cost would be to initiate biotin at the dosage of 100 mg three times daily for individuals with MS of either a primary or secondary progressive course. An initial evaluation at three months would be prudent, as many of the individuals in the current reported study did experience reduced EDSS scores or improved walk times by this point in the study. However, if improvement has not yet been seen, there still is potential for such, as some individuals did not have measurable disease-course improvements until 24 months. Thus, if the cost of therapy was not prohibitive, patients could choose to continue if desired. Additionally, medications and disease EDSS score at the time of intervention also should be considered, as those on the medication fampridine and with an EDSS score of 6-7 were less likely to experience improvements. ■

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# Intravenous Nutrient Therapies — Worth the Cost?

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Intravenous nutrient therapies (IVNT) are gaining in popularity, with IVNT clinics popping up in many cities throughout the United States.[1] The IV nutrient clinics are marketing IVNT to maintain overall wellness, enhance weight loss, boost immune function, increase athletic performance, cure hangovers, and treat particular conditions.[1,2] IVNTs have been popular treatments in integrative healthcare clinics for decades as treatments for numerous health conditions.[2,3] It is difficult to estimate the number of IVNT clinics and providers in the United States; however, a study investigating the use of IV vitamin C (component of many IVNT formulas) in 2006 and 2008 found that the manufacturers' yearly sales were 750,000 and 855,000 vials, respectively.[3] And, these were thought to be underestimates. Unfortunately, the increase in the use of IVNT in both healthy individuals and those with health conditions has not translated into increased published research studies investigating the efficacy and safety of IVNT.

The indications for IVNT use are numerous and somewhat vague.[1-4] Historically, IVNT has been purported to be used to treat upper respiratory infections and fatigue.[2,4] Currently, IVNT is purported to treat or adjunctively treat fibromyalgia syndrome (FMS), fatigue, cancer, depression, asthma, migraines, cardiovascular disease, allergies, narcotic withdrawal, and hyperthyroidism.[1-5] With the exception of magnesium sulfate and calcium as monotherapy, few studies support the use of IVNT.[2,6,7]

One of the most well-known IVNTs is vitamin C, which was made famous by Linus Pauling. Ewan Cameron reported high-dose IV vitamin C improved survival times in cancer patients in 1976.[8] IVNTs contain a wide assortment of vitamins and minerals other than vitamin C.[1,2,9] Currently, the most popular IVNT probably is the "Myers' cocktail," which contains 2-5 mL magnesium chloride hexahydrate (20%), 1-3 mL calcium gluconate (10%), 1 mL vitamin B12 (hydroxocobalamin; 1,000 mcg/mL), 1 mL vitamin B6 (pyridoxine hydrochloride (100 mg/mL), vitamin B5 (dexpanthenol 250 mg/mL), 1 mL of vitamin B complex 100 (B complex), and 4-20 mL of vitamin C (222 mg/mL).[2]

## Summary Points

- The actual use of IV nutrient therapies (IVNT) currently is unknown.
- There are numerous IVNT formulations containing various nutrients that have not been adequately researched for safety and/or efficacy.
- IVNT has surprisingly high costs both financially and because of potential health risks.

According to one of the most well-cited articles on IVNT, the use of the Myers' cocktail can be traced back to John Myers, who pioneered the use of IV vitamins and minerals for the treatment of various conditions.[2] After Myers died in 1984, a number of his patients began seeking infusions from Alan Gaby.[2] Gaby reports that he did not know the exact formula that Myers used and had to design the modified Myers' formula as described previously.[2] IVNT providers use various formulations in different clinics as demonstrated on the IVNT clinic websites, such as RestoreIV.com and Remedyroom.com.

### CLINICAL RESEARCH

Much of the knowledge that supports the use of IVNT other than the use of IV magnesium and calcium is anecdotal and from individual case studies.[1-5] IV magnesium sulfate has been studied as a treatment for asthma and has demonstrated benefit in adults and children.[6] IV magnesium also has been investigated as a treatment for headaches and migraines and has demonstrated mixed results.[7]

Currently, the efficacy of high-dose IV vitamin C as a cancer treatment is unclear and being investigated.[10-12] A 2015 systematic review concluded that there is no high-quality evidence to suggest that vitamin C, whether oral or IV, enhances antitumor effects of chemotherapy or reduces its toxicity.[11] ClinicalTrials.gov has numerous registered research studies investigating the use of

IV vitamin C as a cancer treatment that have been completed but have yet to publish findings.[12] Currently, the National Institutes of Health considers IV vitamin C to be experimental and recommends that it be used only in the context of a clinical trial.[10]

In a 2009 randomized, placebo-controlled trial investigating the effects of IVNT in FMS patients, the authors found no difference between the placebo and the IVNT groups.[5] The placebo group received lactated Ringer's solution intravenously, while the IVNT group received a Myers' cocktail once a week for eight weeks, with both groups demonstrating improvement in FMS symptoms.[5] The authors found a strong placebo effect within this study, which is consistent with other studies demonstrating a greater placebo effect for IV infusions in health clinics over oral administration.[1,5]

## CONTRAINDICATIONS/SIDE EFFECTS

According to Padayatty et al, it is difficult to determine the actual numbers of adverse events with IV vitamin C, as use and adverse events are underreported.[3]

Known contraindications to IV vitamin C are pre-existing renal insufficiency or failure and glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, as these individuals are predisposed to vitamin C toxicity. There have been cases of individuals with G-6-PD deficiency who have experienced acute hemolysis due to high-dose IV vitamin C.[13] Acute oxalate nephropathy and renal failure also have been reported after high-dose IV vitamin C.[14-16]

In the FMS study, one out of 34 participants who received the Myers' cocktail IV reported an adverse event, with increased feelings of depression, insomnia, and dyspepsia, and had increases in blood pressure.[5] A 2016 non-randomized, controlled study compared the effect of IV vitamin C to another IVNT formulation containing different combinations of zinc, glutathione, alpha-linoleic acid, and B vitamins on blood pressure levels during and at the end of IV treatment. The researchers found that high-dose IV vitamin C (30 g) reduced both systolic and diastolic blood pressure by 6-7 mmHg, while IVNT containing B12 increased both systolic and diastolic blood pressure by 13 mmHg and 11.5 mmHg, respectively.[9]

There is also a case report of a patient who was using high-dose oral vitamin C and amygdalin (B-17), which resulted in cyanide poisoning; one of the breakdown products of amygdalin is cyanide.[17]

Gaby recommends that elderly patients may have a lower tolerance to the Myers' infusion and may require lower doses of the nutrients.[2] Patients with cardiac disease and those taking medications that deplete potassium should be screened for hypokalemia before receiving a Myer's infusion because of the risk of cardiac arrhythmias. There have been reports of anaphylaxis to thiamine that often occur after multiple separate administrations of thiamine. According to Gaby, from 1965-1985, nine deaths worldwide were attributed to IV, intramuscular, or subcutaneous administration of thiamine.[2] The more common side effects to the Myers' infusion are a burning sensation at the injection site and phlebitis caused by the hypertonicity of the infusion. These side effects can be decreased by diluting the nutrients and repositioning the needle at the injection site. Hypotension also can occur and appears to be due to administering the infusion too quickly, which can lead to lightheadedness and syncope. Infection is also a risk, particularly in individuals with underlying illnesses who may be at higher risk.

## LOGISTICS

Most insurance companies do not cover the cost of IVNT, so the cost can be prohibitive. IVNT infusions at RemedyRoom.com in New Orleans cost anywhere from $149 to $249 and RestoreIV.com in Philadelphia start at $99 and go up to $149. The administration of the IV nutrients is the biggest cost, as it can take hours to infuse some IVNT infusions. The IVNT clinics also advertise "add ons," including other nutrients (glutathione, coenzyme Q10, selenium, alpha-lipoic acid, zinc, fatty acids) and even UV light treatment of blood.

## CONCLUSION

IVNT is used widely, and physicians should be aware that both healthy individuals and those with health conditions may seek IVNT treatments. Physicians should be aware of potential interactions of IVNT with both conventional treatments and integrative treatments. The safety profile of IVNT is not well-established and efficacy remains questionable, as the placebo effect may be the reason individuals feel better after IVNT. The cost is quite high for these treatments without insurance coverage, and risks to IVNT range from mild to severe. IVNT is seriously lacking in research on safety and efficacy, so physicians should educate patients about potential risks. ■

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ABSTRACT & COMMENTARY

# Stroke Risk from Use of Cannabis, Tobacco, and Alcohol

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**Dr. Fahey reports no financial relationships relevant to this field of study.**

SYNOPSIS: No associations between cannabis use in young adulthood and strokes later in life were found in multivariable models. An almost doubled risk of ischemic stroke was observed in those with cannabis use > 50 times; this risk was attenuated when adjusted for tobacco usage. Smoking ≥ 20 cigarettes per day was clearly associated both with strokes before 45 years of age and with strokes throughout the follow-up.

SOURCE: Falkstedt D, Wolff V, Allebeck P, et al. Cannabis, tobacco, alcohol use, and the risk of early stroke. A population-based cohort study of 45,000 Swedish men. *Stroke* 2017;48:265-270. doi: 10.1161/STROKEAHA.116.015565.

Stroke is a prominent global public health problem and its increasing incidence in young adults is alarming. It is the third leading cause of death in developed countries.[1] The total number of people having a stroke every year has increased because of the improvement of acute stroke care, and more people are living with the devastating after effects.[1] Increasing evidence has shown that diet and lifestyle changes can decrease the modifiable risk factors of stroke by more than 90%.[1]

## Summary Points

- This study found no evident association between cannabis use and stroke, including stroke before 45 years of age.
- Tobacco smoking showed a clear, dose-response shaped association with stroke across multivariable models.

These modifiable risk factors (tobacco, alcohol, poor diet, sedentary lifestyle, hypertension) appear in late adolescence, allowing for early intervention and prevention opportunities.[2] Falkstedt et al found a noteworthy connection between cannabis and tobacco use in a recent study. A small number of cases of stroke occurred among men who mainly smoked cannabis and who reported occasional tobacco or alcohol use. Despite reports linking cannabis to cerebrovascular effects that could lead to stroke, there is a lack of epidemiological evidence to support these claims.[3] Most of the strokes occurred in chronic cannabis users who also mixed it with tobacco or smoked tobacco after smoking cannabis.[3] Most of the current information available on the association of cannabis and stroke comes from clinical reports and retrospective studies. The association of stroke and cannabis use has been examined in

| Table 1: Pooled Results for Adjusted HR for Cannabis, Tobacco, and Alcohol Consumption | | |
|---|---|---|
| **Stroke < 45 y of Age** | **Hazard ratio** | **95% CI** |
| Cannabis > 50 times | 0.93 | 0.34-2.57 |
| Smoking tobacco > 20 cigarettes per day | 5.04 | 2.80-9.06 |
| Alcohol > 25 drinks per week | 1.56 | 0.60-4.03 |

the literature, but separating the risk of stroke from cannabis as opposed to tobacco, alcohol, cocaine, and amphetamines has been difficult.[4]

With the increasing legalization of cannabis around the world and the large number of individuals estimated to be using the drug, about 180 million annual users,[5] it is imperative to encourage more longitudinal and prospective studies on cannabis users. In this population-based cohort, Falkstedt et al examined a survey of 49,321 Swedish men who had enlisted in military service between 18 and 20 years of age, along with a two-day medical and psychological screening. These men also completed two questionnaires examining social and behavioral aspects of substance use.

The authors recorded the quantities of exposure to cannabis, alcohol, and tobacco. A thorough baseline was established by recording baseline health data on these men: height, weight, blood pressure, body mass (calculated), cardiorespiratory fitness levels, current medical diagnosis, educational level (estimated), parental history of CVD, and socioeconomic status during childhood. Stroke incidences for these individuals between the ages of 29 to 59 were followed from 1971 to 2009 using the National Hospital Discharge Register.

The Cox proportional-hazards regression was used to examine cannabis use in young adulthood as a possible risk factor for all strokes until 59 years of age. Hemorrhagic strokes associated with cannabis use and strokes occurring before 45 years of age were examined without dividing them into stroke type because of the low numbers. Ischemic strokes were examined separately. After crude models were computed, three models were estimated: 1) body mass index, cardiorespiratory fitness, migraine, diabetes mellitus, and early parental CVD; 2) socioeconomic status in young adulthood; and 3) tobacco and alcohol use. Analysis was performed by SAS version 9.4 for Windows.

Within the cohort follow-up period until 59 years of age, there were 1,037 first-time strokes (48% ischemic, 23% hemorrhagic), and before 45 years of age, there were 192 first-time strokes (40% ischemic, 27% hemorrhagic). Interestingly, cannabis use had no association with stroke before 45 years of age found in multivariable models: cannabis use > 50 times (hazard ratios [HR], 0.93; 95% confidence interval [CI], 0.34-2.57). Alcohol and tobacco use showed clear dose-response associations with stroke before 45 years of age. (*See Table 1.*) There was no significant association between cannabis use in young adulthood and overall incidence of stroke until 59 years of age (HR, 0.95; 95% CI, 0.59-1.53). Clear, dose-response association was demonstrated between cigarettes smoked and stroke (HR, 5.04; 95% CI, 2.80-9.06), and with strokes throughout the follow-up (HR, 2.15; 95% CI, 1.61-2.88). A link between alcohol use and stroke was suggested by crude models (HR, 1.56; 95% CI, 0.60-4.03) and adjusting for alcohol and tobacco use (HR, 1.39; 95% CI, 0.91-2.13), none of the cannabis groups showed an increased hazard of stroke.

## ■ COMMENTARY

According to the Global Burden of Disease 2010 study, worldwide age-standardized stroke mortality has decreased over the last two decades; however, deaths and disability from stroke are increasing.[1,6] This means the number of individuals who survive stroke and live with disability is increasing.[2] Cigarette smoking showed a clear dose-response relationship with increased stroke risk, while the authors found no clear association between cannabis and stroke risk. They were unable to confirm previous research[4,8] on the increased risk of stroke with cannabis consumption. Few cases of stroke were reported in this study among heavy users of cannabis who only used tobacco and alcohol sparingly. In addition, the authors had difficulty controlling for confounding variables, such as separating tobacco and alcohol users from those who used only cannabis.

This speaks more of the importance, as emphasized by the World Health Organization, on the growing use of cannabis around the world[4] and the co-use of cannabis and tobacco. Hemachandra et al performed a cross-sectional study, based on self-reported data, and did not differentiate the amount of tobacco smoked.[9] Westover et al found an increased risk of ischemic stroke with cannabis use and an even bigger risk with tobacco.[10] Research has shown that more than 90% of the disabilities caused by strokes are attributable to modifiable risk factors: smoking tobacco, alcohol consumption, unhealthy diet, sedentary lifestyle, and hypertension.[6] These modifiable risk factors may be present as early as late adolescence and clearly represent a public health problem.[1]

The scope of global stroke epidemiology is shifting.[1] Increasing clinical,[11] retrospective, and case studies have linked smoking cannabis to stroke, especially in people younger than 45 years of age.[5] Marijuana is the most

commonly used illegal drug in the world.[6] Interestingly, most cannabis users consider smoking marijuana to be relatively harmless to their health. They also routinely mix cannabis with tobacco and smoke them together[7] or smoke a cigarette after smoking cannabis.[8] This complicates the research on cannabis and stroke. It is a well-known fact that smoking tobacco has been linked to stroke. The relationship between cannabis and stroke is multifaceted and includes many confounding variables, such as smoking tobacco and consuming other drugs, including alcohol, while smoking cannabis.[9] Heavy alcohol consumption has been shown to increase the relative risk of stroke, while low or moderate consumption has been shown to be protective.[12] Many studies have shown the effect of cannabis on the cardiovascular system and the risk of cerebrovascular complications.[13]

Despite the research linking cannabis with stroke, it has been difficult to separate cannabis from these confounding[14] factors, and very little epidemiological data have been produced in support of it.[3,17] The case reports that link cannabis to acute strokes[11] and ischemic strokes[16] have shown a clear indication that more research is needed in this area.[11] More research is needed on the mixing of cannabis with tobacco and smoking them together, too.[18] In the future, more epidemiological evidence, in the form of prospective studies examining the link between cannabis and stroke, is needed to establish a clear risk of stroke in cannabis smokers.[19] More evidence is needed to prove cannabis independently affects stroke.[10,16]

Recommendations include increasing longitudinal epidemiological prospective studies on all groups of cannabis smokers[17] because of the growing popularity of cannabis inhalation. These studies should include both those who use other drugs, such as tobacco, and those not using other drugs. Primary prevention remains the key to stroke prevention, and one should focus on the modifiable risk factors mentioned earlier.[4] Future research should be centered on primary prevention and continue to explore possible risk factors,[20] as well as on the increasing number of strokes in young adults[21] associated with the increased consumption, legalization, and decriminalization of cannabis.[5]

Until proven otherwise, all patients should be warned about possible dangers of marijuana use in combination with tobacco and other drugs causing an increased risk for stroke. ■



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## CME INSTRUCTIONS

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## CME QUESTIONS

1. **Findings from the Facebook study regarding social media use show:**
   a. suggestive evidence that use of Facebook to reflect or promote offline socialization may enhance longevity.
   b. conclusive evidence that Facebook use for socialization offers limited health benefits compared to real-world interactions.
   c. socialization enhances longevity online and offline in most age groups with the exception of online use of Facebook in those 65 years of age or older.
   d. there is little evidence that online social media enhances longevity except in those who accept the most friend requests and post tagged photos.

2. **In some patients with primary or secondary progressive multiple sclerosis (MS), biotin (100 mg three times daily) was observed to:**
   a. reduce MS-related disability as measured by an improved score on the Expanded Disability Status Scale (EDSS) or a 20% decrease in 25-foot walk time.
   b. improve EDSS score; however no improvements in 25-foot walk time were seen.
   c. improve 25-foot walk time by 20%; however no improvements in EDSS score were seen.
   d. not affect MS-related disability as measured by EDSS score or 25-foot walk time.

3. **Which of the following is *false* regarding high-dose IV vitamin C?**
   a. High dose IV vitamin C is an efficacious and safe treatment in cancer patients.
   b. Glucose-6-phosphate dehydrogenase deficiency is a contraindication to receiving IV vitamin C.
   c. Renal disease is a contradiction to receiving IV vitamin C.
   d. Linus Pauling is a noble prize recipient.

4. **Which of the following is true regarding IVNT?**
   a. IVNT is a safe and efficacious treatment for fibromyalgia syndrome.
   b. The benefit that is reported from IVNT in fibromyalgia patients may be due to the placebo effect.
   c. IVNT is inexpensive and covered by insurance.
   d. There are no reported allergies to thiamine, an ingredient in some IVNT formulations.

5. **What association links cannabis use to strokes?**
   a. Smoking cannabis out of a pipe
   b. Eating cannabis in your food
   c. Chronic smoking of cannabis mixed with tobacco in a joint
   d. Smoking hashish made from cannabis

## CME OBJECTIVES

**Upon completion of this educational activity, participants should be able to:**

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
- describe and critique the objectives, methods, results, and conclusions of useful, current, peer-reviewed, clinical studies in alternative medicine as published in the scientific literature.

## [IN FUTURE ISSUES]

Omega-3 fatty acids and dietary retinopathy

Beetroot juice and endurance

Tai chi for osteoarthritis

Chiropractic for migraine