to a case patient based on age and telephone number area code.

Trained interviewers collected data on type, timing, and frequency of hair dye and risk factors for neuroblastoma (family medical history; medication and vitamin use; and occupational, household, and lifestyle exposures) from the mothers of the case and control patients by telephone. Permanent hair dye was defined as "does not wash out and leaves a line as the hair grows" and temporary hair dye defined as "washes out after one or several shampooings." Only completed phone interviews were used in the final analysis and were obtained for 538 of 741 identified cases (73%) and 504 of 703 matched controls (72%). The incidence of hair dye exposure was 23% (124 of 538) in case patients and 16% (81 of 504) in control patients.[1]

Any hair dye exposure had a statistically significant increase in the risk of neuroblastoma (odds ratio [OR] 1.6; 95% CI, 1.2–2.2). A statistically significant increase in neuroblastoma rates occurred with temporary hair dye use (OR 2.0; 95% CI 1.1–3.7), but not with permanent hair dye use (OR 1.4; 95% CI, 1.0–2.0) or hair dye use during the 1 month before pregnancy (OR 1.4; 95% CI, 0.9–2.2).[1]

A 2002 case-control study also evaluated the risk of childhood brain tumors with mothers who used hair dye 1 month before a positive pregnancy test or throughout pregnancy.[2] Cases were identified from population-based cancer registries of Los Angeles County, 5 counties in the San Francisco Bay area, and 13 counties in the Seattle-Puget Sound area. Cases included children younger than 20 years at diagnosis with benign or malignant primary brain tumor, or cranial nerve/meninges tumor. Controls were matched to cases based on sex, birth year, and region.

The mothers of the case and control children were interviewed in person by a trained interviewer. Only completed interviews were used in the final analysis and were obtained for 540 of 762 identified cases (71%) and 801 of 1,079 matched controls (74%).[2]

The incidence of hair dye exposure was 12% (65 of 540) in case patients and 12% (96 of 801) in control patients. Hair dye use did not cause a statistically significant increase in the risk of childhood brain tumors (OR 0.96; 95% CI, 0.69–1.3). Possible confounding variables of prenatal vitamins, cured meat consumption, rubber nipple or pacifier use, new car exposure, and mother's use of foundation make-up were included in a logistic model/regression analysis, and also showed no differences in the risk of childhood brain tumors.[2]

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In patients with fibromyalgia, is low-dose naltrexone effective in alleviating pain, and does it decrease use of oral opioids?

EVIDENCE-BASED ANSWER

Used alone, low-dose naltrexone modestly reduces pain compared with placebo. No studies have addressed the effect of low-dose naltrexone on oral opioid use in patients with fibromyalgia (SOR: **B**, single small RCT and single nonrandomized pilot study).

A 2013 randomized, double-blind, placebo-controlled crossover study (N=31) compared naltrexone and placebo in patients with fibromyalgia.[1] The patients were all women aged 18 to 65 years who met the 1990 American College of Rheumatology (ACR) diagnostic criteria for fibromyalgia. Patients were excluded if they lived more than 2 hours from the laboratory, had any history or laboratory evidence of inflammatory or rheumatic disease, significant psychiatric distress, depression, or any concurrent opioid use.

After a 2-week period to establish their baseline pain level, patients were randomized to either 4 weeks of placebo or 12 weeks of naltrexone (4.5 mg/d) followed by crossover to the opposite arm without washout. An additional 4 weeks were added as follow-up. Pain self-assessment was recorded daily using the question "Overall, how severe has your pain been today?" on a 0 to 100 scale, with 0 defined as "no pain at all" and 100 as "the worst pain imaginable." The average pain score from the entire 2-week baseline period was compared with the average pain score from the final 3 days before crossover or study termination.[1]

CONTINUED

Naltrexone reduced pain more than placebo (29% vs 18%; *P*=.016). Vivid dreams and headache were the only 2 adverse events reported more frequently with naltrexone than placebo.[1]

A 2009 single-blind, nonrandomized, crossover pilot study (N=10) compared placebo and low-dose naltrexone in patients with moderately severe fibromyalgia.[2] The patients were all women with an average age of 44 years who met the 1990 ACR diagnostic criteria for fibromyalgia. Patients were excluded for current opioid use, concurrent autoimmune or rheumatologic conditions, joint pain or inflammation, rheumatoid factor of more than 20 IU/mL, or erythrocyte sedimentation rate of more than 60 mm/h.

Each patient followed the same schedule: no treatment (baseline) for 2 weeks, placebo for 2 weeks, low-dose naltrexone (4.5 mg/d) for 8 weeks, and then washout for 2 weeks. Symptom severity was recorded daily using a 0 to 100 scale in response to the question, "Overall, how severe have your fibromyalgia symptoms been today?" Multiple secondary outcomes including tolerability and side effects were also recorded. The daily symptom log response rate was 92%.[2]

Naltrexone reduced symptoms compared with baseline by 33% (*P*<.0005), while placebo reduced symptoms compared with baseline by 2.3% (*P*<.003). Naltrexone was not directly compared with placebo. Six patients were considered naltrexone responders (30% reduction in symptoms) and 4 were considered nonresponders. Naltrexone daily tolerability was 96% versus 90% for placebo (significance not reported). Two patients reported vivid dreams with naltrexone and 1 reported nausea and insomnia.[2]

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What are the cognitive risks associated with vitamin B_{12} deficiency in the elderly?

EVIDENCE-BASED ANSWER

Whether serum vitamin B_{12} levels in older adults are associated with cognitive changes is unclear. However, elevated levels of methylmalonic acid, a B_{12} metabolite that reflects low vitamin B_{12} function, are more consistently associated with cognitive decline (SOR: **B**, systematic reviews of longitudinal studies).

A 2013 systematic review, which included 4 longitudinal studies of 1,579 generally healthy elderly individuals, investigated whether an association existed between vitamin B_{12} serum levels and cognitive function as measured by the Mini-Mental State Examination (MMSE) test.[1] The deviation of the MMSE score from the population mean was reported using z-scores and the regression coefficient was calculated to determine the relationship between the MMSE z-scores and vitamin B_{12} levels. In the 3.3 to 9 years that the patients were studied, they completed an annual MMSE and their B_{12} levels were measured.

No statistical association was found between the MMSE z-scores and B_{12} serum levels (β=0.00, 95% CI, –0.00 to 0.01).[1]

A 2012 systematic review of 35 longitudinal studies investigated the association of B_{12} serum markers and cognition in 14,325 patients 47 to 85 years old from 10 countries with a mean follow-up of 5.4 years.[2] Inclusion criteria, such as level of initial cognition (if measured), degree of chronic disease, and amount of folate intake, differed substantially among the studies. Cognitive change was measured with different neuropsychological tests and outcomes were reported as cognitive decline, dementia, or Alzheimer's dementia. Results could not be pooled for meta-analysis. Studies were defined as high quality if 3 reviewers agreed there was a low risk of bias based on the American Dietetic Association Study Quality criteria. Twenty-one of the initial 35 studies were defined as high quality.

Of the 21 high-quality studies, only 3 of 17 that used serum vitamin B_{12} levels as the marker for B_{12} status showed a significant association between low vitamin B_{12} levels and cognitive decline. However, all 4 of the 21 high-quality studies that used methylmalonic acid as the serum marker of low