Betamethasone in Prematurity: Does it Cause Neurodevelopmental Delay?

Neurodevelopmental Outcomes After Late Preterm Antenatal Corticosteroids: The ALPS Follow-Up Study

Gyamfi-Bannerman C, Clifton RG, Tita ATN, et al. Neurodevelopmental Outcomes After Late Preterm Antenatal Corticosteroids: The ALPS Follow-Up Study. *JAMA*. 2024;331(19):1629-1637. doi:10.1001/jama.2024.4303

KEY TAKEAWAY: Betamethasone does not significantly increase the risk of neurodevelopmental delay in children whose mothers received injections due to increased risk of preterm labor.

STUDY DESIGN: Prospective follow-up of multicenter randomized control trial (RCT)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: For pregnant women at risk of delivering a late preterm infant between 34–36 weeks gestation, betamethasone is administered to facilitate lung development per the Antenatal Late Preterm Steroids (ALPS) study. Hypoglycemia is a side effect in these infants, leading to concern for developmental delays. Between 2011–2016, an RCT was conducted to see if there was an increased risk of neurodevelopmental delay in these infants secondary to hypoglycemia.

PATIENTS: Children ≥6 years old

INTERVENTION: 12 mg intramuscular injection (IM) betamethasone

CONTROL: Placebo

PRIMARY OUTCOME: Risk of neurodevelopmental delay

Secondary Outcome: Social responsiveness, child behavior scores, gross motor function

METHODS (BRIEF DESCRIPTION):

- Children ≥6 years old whose mothers participated in the Maternal Fetal Medicine Units Network 2011–2016 were included.
- The prospective follow-up study occurred between 2017–2022 to evaluate if the children who received betamethasone in the previous study demonstrated neurodevelopmental delay vs children who received an equivalent placebo.
- The mean maternal age was 29 years old. The group consisted of non-Hispanic White, Black, Hispanic, Asian, and Native American individuals.
- The children had been born in one of the 17 Maternal-Fetal Medicine Units Network centers of the National Institute of Child Health and Human Development
- Participants with a high risk for preterm delivery between 34–36 weeks gestation received either betamethasone or placebo.
    - One dose of 12 mg betamethasone or two doses if they did not deliver within 24 hours
    - One dose of equivalent placebo or two doses if they did not deliver within 24 hours
- Scales used to assess the primary outcome included Differential Ability Scales-Second Ed (DAS-II), which reported an overall General Conceptual Ability (GCA) and verbal, non-verbal reasoning, and spatial ability cluster scores. The level of delay was measured once by cognitive testing overseen by clinical psychologists
    - The standard deviation (SD)=100; the higher the DAS-II GCA score, the higher the cognitive function.
    - GCA score <85 represents one SD below the mean, representing a possible neurodevelopmental delay.
- Scales used to assess secondary outcomes included the Gross Motor Function Classification System, the Social Responsiveness Scale t-score >65, and the Child Behavior Checklist.
    - Gross Motor Classification greater than Level I represented functional impairment
    - Social Responsiveness Scale: T-score >65 indicated moderate to severe impairment in reciprocal social behavior
    - Child Behavior: Higher t-scores meant more problems

INTERVENTION (# IN THE GROUP): 479

COMPARISON (# IN THE GROUP): 470

FOLLOW-UP PERIOD: Five years

RESULTS:

Primary Outcome –

- There was no difference in the risk of developmental delay in infants whose mothers received IM betamethasone during pregnancy compared to mothers who received placebo (17% vs

19%, respectively; adjusted relative risk [aRR] 0.94; 95% CI, 0.73–1.2).

Secondary Outcome –

- There was no significant difference in gross motor skills, social responsiveness, or child behavior between betamethasone and placebo.

LIMITATIONS:

- This study had a limited sample size.
- Methods of testing for neurodevelopmental delay such as standardized testing do not account for subjective differences in academic performance.
- There was a limited number of neonates born at term to compare to those born preterm.

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Can a Pinch of Blood Save a Pint?

Small-Volume Blood Collection Tubes to Reduce Transfusions in Intensive Care: The STRATUS Randomized Clinical Trial

Siegal DM, Belley-Côté EP, Lee SF, et al. Small-Volume Blood Collection Tubes to Reduce Transfusions in Intensive Care: The STRATUS Randomized Clinical Trial. *JAMA*. 2023;330(19):1872-1881. doi:10.1001/jama.2023.20820

KEY TAKEAWAY: Small-volume blood collection tubes do not reduce the average number of red blood cell (RBC) transfusions for patients in the intensive care unit (ICU) compared to standard-volume blood collection tubes

STUDY DESIGN: Multi-site, cross-over, open-label, randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Individuals who stay in the ICU often require multiple lab draws, which cumulatively may drop them below the threshold for an RBC transfusion. Currently, the industry standard is "large volume" tubes (4–6mL) to ensure laboratory evaluation is successful. No large studies have evaluated both sufficiency for lab analysis and impact on transfusion risk. This study sought to determine whether lower-volume collection tubes reduce the number of blood transfusions in ICU patients.

PATIENTS: Adults admitted to ICU >48 hours

INTERVENTION: Small-volume blood collection tubes

CONTROL: Standard-volume blood collection tubes

PRIMARY OUTCOME: Number of RBC transfusions

Secondary Outcome: RBC units transfused per person, insufficient specimens, ICU mortality, hospital mortality, hospitalization duration, ICU duration, change in hemoglobin (Hb) during ICU admission

METHODS (BRIEF DESCRIPTION):

- 25 ICUs with ≥14 beds and capacity for mechanical ventilation in Canada were transitioned in random order from large to small volume (2–3 mL) collection tubes, over two years, excluding six months due to COVID.
    - Two sites transitioned to small volume tubes every six weeks as dictated by a computer randomization.
- Patients selected were adult medical-surgical critically ill patients admitted for >48 hours.
- The chosen intervention was a soft draw tube for laboratory analysis that collects 2–3 mL of blood.
- The control was a standard volume BD Vacutainer® tube which gathers 4–6 mL of blood from the patient.
- The primary outcome measured the number of RBC units transfused during the ICU stay per patient.
- The following secondary outcomes were measured:
    - Patients receiving ≥1 unit of RBCs in the ICU: Adjusted to decrease Hb by 1 g/dL for each RBC unit received.
    - The number of samples reported as insufficient volume using laboratory systems information.
    - Change in Hb during ICU stay (not adjusted for transfusion)
    - Length of ICU and hospital stay
    - Mortality in ICU and hospital
- Analysis for comparison was completed using a general Poisson mixed model.

INTERVENTION (# IN THE GROUP): 10,261

COMPARISON (# IN THE GROUP): 10,940

FOLLOW-UP PERIOD: Duration of hospitalization (death, discharge, or 30 days)

RESULTS:

Primary Outcome –

- There was no significant difference in the number of RBC units transfused for small-volume tubes compared to standard-volume tubes (mean difference [MD] –0.07; 95% CI, –0.19 to 0.03).

Secondary Outcome –

- There was no statistically significant difference in RBC units transfused per person, insufficient volume samples, ICU mortality, hospital mortality, length of hospitalization, length of ICU stay, or change in Hb during ICU stay for small-volume tubes compared to standard-volume tubes

LIMITATIONS:

- There was no standard threshold for transfusion across all sites.
- There was no singular volume dictated as small vs large; rather, they were presented as a range of values.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the Air Force at large, or the Department of Defense.

Does Vitamin C Actually Improve Iron Absorption?

Effect of Dietary Factors and Time of Day on Iron Absorption From Oral Iron Supplements in Iron Deficient Women

von Siebenthal HK, Moretti D, Zimmermann MB, Stoffel NU. Effect of dietary factors and time of day on iron absorption from oral iron supplements in iron deficient women. *Am J Hematol*. 2023;98(9):1356-1363. doi:10.1002/ajh.26987

KEY TAKEAWAY: Supplemental iron taken in the morning with ascorbic acid-rich foods, without coffee or breakfast, improves absorption.

STUDY DESIGN: Randomized, open-label, cross-over trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Oral iron supplementation is the first-line treatment for iron-deficient women and is recommended to be taken in the morning with ascorbic acid. However, these studies only assessed the effects of dietary inhibitors/enhancers on iron absorption from low doses of iron found in foods and/or iron forticants added to foods. Similarly, it remains unclear what dose of ascorbic acid is effective. This study compared iron absorption between doses taken in the morning vs in the afternoon.

PATIENTS: Healthy adult women with iron deficiency

INTERVENTION: Iron + ascorbic acid, coffee, breakfast, or water in the afternoon

CONTROL: Iron taken + water in the morning

PRIMARY OUTCOME: Fractional iron absorption (FIA) and total iron absorption (TIA) for each condition

Secondary Outcome: Iron status, hepcidin, inflammatory markers

METHODS (BRIEF DESCRIPTION):

- Women 18–45 years old, iron deficient but not anemic, with a BMI 19–27, weight <70 kg, otherwise healthy, not pregnant or lactating, nonsmokers were included in the study.
- Patients were randomized to a condition sequence, with non-masked assignments. Sequences were generated so that each isotope was used only once in each block and the reference condition was given on 1st day of one block and the afternoon condition on 3rd day of the other block.
- Iron was administered on days one, three, five, 22, 24, and 26 between 7–9 AM after an overnight fast and on days five or 26 between 4–6 PM after a four-hour fast.
  - The afternoon dose was taken four hours after consumption of a standardized lunch of vegetarian lasagna.
  - All morning doses were taken after an overnight fast.
- Iron was labeled with 57FeFum, 54FeFum, or 58FeFum.
- Labeled iron was consumed together with the iron supplement with a glass of water under the following six conditions:
  - With water only (reference) in the morning
  - With 80 mg ascorbic acid (AA) in the morning
  - With 500 mg AA in the morning
  - With coffee in the morning
  - With breakfast including coffee and orange juice containing about 90 mg AA
  - With water only in the afternoon
- After the dose was taken, patients were not allowed to eat/drink for three hours except 500 mL of water.
- Blood was drawn for hemoglobin (Hgb), iron studies, CRP, hepcidin, and alpha-1-acid glycoprotein (AGP) on days one, 22, and 43. Amounts of tracers were collected on days 22 and 43. Fractional iron absorption was calculated based on the isotope.
- Primary outcomes were FIA and TIA for each condition.
  - FIA was calculated based on erythrocyte incorporation of multiple isotopic labels.
  - TIA was calculated based on FIA and total iron consumed per condition.
- Secondary outcomes measured:
  - Iron status vis serum ferritin, Hb, sTfR, serum iron, TIBC, and TS
  - Hepcidin
  - Inflammation markers (CRP)
  - FIA and TIA were reported as median values (IQR).

INTERVENTION (# IN THE GROUP): 34

COMPARISON (# IN THE GROUP): The same 34 patients

FOLLOW-UP PERIOD: 43 days

RESULTS:

Primary Outcome –

- Iron + 80 mg ascorbic acid resulted in higher FIA compared to iron + water in the morning (27% vs 21%; *p*<.001).
- Iron + 500 mg ascorbic acid resulted in higher FIA compared to iron + water in the morning (31% vs 21%; *p*<.001).
- There was no difference in FIA between 80 mg ascorbic acid and 500 mg ascorbic acid (*p*=.226).
- Iron + coffee resulted in lower FIA compared to iron + water in the morning (9.5% vs 21%; *p*=.001).
- Iron + breakfast resulted in lower FIA compared to iron + water in the morning (6.9% vs 21%; *p*<.001).
- Iron + breakfast in the morning resulted in lower FIA compared to iron + coffee in the morning (*p*=.008).
- There was no difference in FIA for iron + water in the afternoon compared to iron + water in the morning (13% vs 21%; no p-value provided).
- The TIA for each condition is as follows:
  - Iron + ascorbic acid 500 mg (31 mg; IQR, 26–51)
  - Iron + ascorbic acid 80 mg (28 mg; IQR, 20–34)
  - Iron + water in the afternoon (13 mg; IQR, 10–22)
  - Iron + coffee (9.8 mg; IQR, 6.3–17)
  - Iron + breakfast (7.2 mg; IQR, 4.3–14)
  - Iron + water in the morning (20 mg; IQR, 13–26)

Secondary Outcome –

- Morning iron supplementation improves some measures of iron status compared to the afternoon.
  - Serum ferritin (19 µg/mL vs 28 µg/mL; *p*<.001)
  - Serum iron (15 µg/mL vs 11 µg/mL; *p*=.001)
  - TS (27 µg/mL vs 19 µg/mL; *p*<.001)
  - There was no significant difference in Hb, sTfR, or TIBC.
- Serum hepcidin was higher in the afternoon than morning (1.7 nmol/L vs 0.75 nmol/L; *p*<.001).
- There was no difference in CRP inflammatory markers.

LIMITATIONS:

- Only 34 subjects completed the study. All participants were relatively young, with low to normal BMI and weight, making the study results limited in the scope of application, as these subjects do not represent a broader patient population often seen in family medicine.
- No statistical analysis was performed comparing each condition for TIA.
- The study did not include anemic patients, or the effect of iron supplementation on anemia, which is often the patient population receiving iron supplementation.
- Effects of enhancers and inhibitors may be overestimated, as subjects fasted overnight and again for three hours after supplementation.
- Breakfast contained multiple things that could enhance or inhibit absorption individually, but this was not tested separately.

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A Different Juice in the Joint: Nonsteroidal Anti-Inflammatory vs Corticosteroid Injections

Nonsteroidal Anti-Inflammatory Drug Injections vs Steroid Injections in the Management of Upper and Lower Extremity Orthopedic Conditions: A Systematic Review with Meta-Analysis

Rhim HC, Ruiz J, Taseh A, et al. Nonsteroidal Anti-Inflammatory Drug Injections versus Steroid Injections in the Management of Upper and Lower Extremity Orthopedic Conditions: A Systematic Review with Meta-Analysis. *J Clin Med*. 2024;13(4):1132. Published 2024 Feb 17. doi:10.3390/jcm13041132

KEY TAKEAWAY: Intraarticular non-steroidal anti-inflammatories (NSAID) injections produce similar pain relief compared to corticosteroid injections for shoulder impingement and knee osteoarthritis (OA).

STUDY DESIGN: Systematic review and meta-analysis of 22 randomized controlled trials (RCTs), five retrospective comparative studies, and one quasi-experimental study (N=2,113)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to small sample size, high risk of bias and heterogeneity of included studies)

BRIEF BACKGROUND INFORMATION: Corticosteroid injections and oral NSAIDs are both the main therapeutic options for treating musculoskeletal conditions, but both have the potential for significant risks and side effects. NSAID injections are a promising therapeutic option that may minimize systemic side effects while providing significant pain relief and functional improvement. However, the efficacy of NSAID injections in comparison to corticosteroids is not well established.

PATIENTS: Adults with knee OA or shoulder impingement syndrome

INTERVENTION: NSAID injection

CONTROL: Corticosteroid injection

PRIMARY OUTCOME: Pain at one month and three months

METHODS (BRIEF DESCRIPTION):

- Meta-analysis of patients with shoulder impingement syndrome included five RCTs (n=490).
  - Injections were subacromial.
  - The NSAID used in all studies was ketorolac (30–60 mg), while the specific corticosteroids used and doses varied significantly by study (40–80 mg triamcinolone, 6–7 mg betamethasone, 40 mg methylprednisolone).
- Meta-analysis of patients with knee osteoarthritis included three RCTs (n=178).
  - NSAIDs used were either 30 mg of ketorolac + 25 mg of sodium hyaluronate, 30 mg of ketorolac, or 20 mg of tenoxicam, while corticosteroid injections again varied significantly in dose (20–40 mg of triamcinolone or 80 mg of triamcinolone + 25 mg sodium hyaluronate).
- Pain was measured via the visual analog scale (VAS) at one month (both shoulder impingement and knee OA) and three months after treatment (knee OA only).
  - VAS is a scale from 0–10 that measures a patient's pain intensity using facial expressions, where 10 is the highest level of pain.
- Weighted mean difference (WMD) between NSAID and corticosteroid injections was used to measure the effect on pain based on the VAS
- Heterogeneity was assessed with Q and I^2 statistics.

INTERVENTION (# IN THE GROUP):

- Shoulder impingement: 228
- Knee osteoarthritis: 89

COMPARISON (# IN THE GROUP):

- Shoulder impingement: 262
- Knee osteoarthritis: 89

FOLLOW-UP PERIOD:

- Shoulder impingement: One month
- Knee osteoarthritis: One month and three months

RESULTS:

Primary Outcome –

- There was no significant difference in pain after one month between subacromial NSAID and steroid injections in patients with shoulder impingement (weighted mean difference [WMD] −0.24; 95% CI, −1.2 to 0.75; I^2=95%).
- There was no significant difference in pain at one month between intraarticular NSAID and steroid injections in patients with knee OA (WMD 0.75; 95% CI, −0.41 to 1.9; I^2=90%).

- There was no significant difference in pain at three months between intraarticular NSAID and steroid injections in patients with knee OA (WMD −0.089; 95% CI, −0.35 to 0.1; I^2=0%).

LIMITATIONS:

- A limited number of studies and total number of patients were included in the meta-analyses of shoulder impingement syndrome and knee osteoarthritis.
- There was significant statistical and clinical heterogeneity between studies in terms of specific NSAID and corticosteroid drugs and doses used.
- Many included studies were at moderate or high risk of bias (predominantly bias in the selection of reported outcomes).

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What are the Effects of Altitude Training on Athletes?

Effect of Altitude Training on the Aerobic Capacity of Athletes: A Systematic Review and Meta-Analysis

Chen B, Wu Z, Huang X, Li Z, Wu Q, Chen Z. Effect of altitude training on the aerobic capacity of athletes: A systematic review and meta-analysis. *Heliyon*. 2023;9(9):e20188. Published 2023 Sep 16. doi:10.1016/j.heliyon.2023.e20188

KEY TAKEAWAY: High-altitude training in aerobic athletes can improve maximum oxygen uptake and hemoglobin levels when compared to athletes who trained at low altitudes.

STUDY DESIGN: Systematic review and meta-analysis of 17 quantitative controlled studies (N=235)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: Altitude training in aerobic athletes has been studied. However, the results are varied, and different types of altitude training have yet to be compared. The altitude at which the training is performed, the duration, and the training mode: high-altitude living and low-altitude training (Hi-Lo) or high-altitude living and high-altitude training (Hi-Hi), are factors under consideration that have yet to be shown superior when compared to one another. An awareness of these findings could inform the guidance given to athletes seeking input from their primary care providers.

PATIENTS: Aerobic athletes

INTERVENTION: High altitude training

CONTROL: Low altitude training or before training

PRIMARY OUTCOME: Maximum oxygen uptake and hemoglobin level

Secondary Outcome: Duration, altitude, mode of training

METHODS (BRIEF DESCRIPTION):

- Studies of athletes involved in aerobic sports, regardless of nationality, ethnicity, and disease, who trained at high altitude or sea level, and had their maximum oxygen uptake (VO_2 max) and hemoglobin (Hb) level measured were included.
- In some studies, athletes' VO_2 max and Hb levels were compared before and after altitude training, while other studies compared VO_2 max and Hb levels of athletes who trained at sea level compared to high altitude.
- Altitude levels of the studies ranged from 1,816 to 3,000 meters.
- The duration of altitude training in the studies ranged from 2–6 weeks.
- VO_2 max and Hb levels were assessed as the primary outcomes of the study.
  - Athletes' VO_2 max and Hb levels were compared for different training modes.
- VO_2 max improvement was measured for the duration (3 weeks and <3 weeks), altitude (≥2,500 meters and <2,500 meters), and mode of training (Hi-Hi and Hi-Lo) as the secondary outcomes of the study.
- The effect size was measured using standardized mean difference.
- Heterogeneity among the studies was measured by I^2 value.

INTERVENTION (# IN THE GROUP): 160

COMPARISON (# IN THE GROUP): 158

FOLLOW-UP PERIOD: Varied (2 weeks to 6 weeks)

RESULTS:

Primary Outcome –

- Altitude training resulted in higher VO_2 max compared to training at sea level or before training (12 studies, n=184; standardized mean difference [SMD] 0.67; 95% CI, 0.35–1.0; I^2=30%).
- Altitude training resulted in higher Hb levels compared to training at sea level or before training (6 studies, n=61; SMD 0.50; 95% CI, 0.11–0.90; I^2=0%).

Secondary Outcome –

- Compared to training at sea level or before training, VO_2 max improved at:
  - <3 weeks of altitude training (3 studies, n=46; SMD 0.81; 95% CI, 0.2–1.4)
  - Three weeks of altitude training (5 studies, n=83; SMD 0.80; 95% CI, 0.3–1.3)
  - <2,500 meters altitude training (6 studies, n=78; SMD 0.70; 95% CI, 0.2–1.2)
  - ≥2500 meters altitude training (6 studies, n=106; SMD 0.68; 95% CI, 0.2–1.2)
  - Hi-Lo training mode (8 studies, n=127; SMD 0.79; 95% CI, 0.3–1.3)

- Hi-Hi training mode (3 studies, n=47; SMD 0.52; 95% CI, 0.02–1.0)

LIMITATIONS:

- Small sample sizes were used in each study.
- Seven studies were repeated designs that had the same participants in the intervention and control. Therefore, the total number of patients in the study is fewer than the number of patients who received the intervention plus the number of patients who received the control.
- Efforts of athletes, coaching styles, weather, and history of injury of athletes, among other variables, are difficult to account for, and their impacts on the outcomes are unknown.
- More research is needed as other individual studies have shown conflicting results when it comes to identifying which altitude training regime is most effective for increasing aerobic capacity.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

Can Initial Serum Urate Predict the Rate of Future Gout Flares?

Serum Urate and Recurrent Gout

McCormick N, Yokose C, Challener GJ, Joshi AD, Tanikella S, Choi HK. Serum Urate and Recurrent Gout. *JAMA*. 2024;331(5):417-424. doi:10.1001/jama.2023.26640

KEY TAKEAWAY: Patients with a baseline serum urate level of ≥6 mg/dl are at an increased risk of developing recurrent gout flares.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Gout, which affects approximately 12 million adults in the United States, is characterized by persistent hyperuricemia and monosodium urate crystals in the joints. Symptoms include joint pain, redness, warmth, and swelling. The urate saturation point is approximately 6.8 mg/dL. Given the number of people with a history of gout, this study investigated the correlation between serum urate levels and gout recurrence.

PATIENTS: Adults with gout

INTERVENTION: Serum urate ≥6 mg/dL

CONTROL: Serum urate <6 mg/dL

PRIMARY OUTCOME: Recurrent gout flares

METHODS (BRIEF DESCRIPTION):

- The UK Biobank, a cohort of over 500,000 adults 40–69 years old, recruited by the UK National Health Service between 2006–2010 served as the source population.
- The study included all UK Biobank participants with a history of gout at baseline, defined as having a gout diagnosis in primary care data before enrollment.
- Demographic characteristics:
  - Mean age of 60 years old
  - 86% men and 99% White
  - Mean serum urate 6.9 mg/dL
- Inclusion criteria:
  - At least one primary care and prescription medicine for gout
  - Baseline serum urate measurement
- Serum urate levels were categorized as <6.0 mg/dL, 6.0–6.9 mg/dL, 7.0–7.9 mg/dL, 8.0–8.9 mg/dL, 9.0–9.9 mg/dL, and ≥10 mg/dL, with a level of <6.0 mg/dL serving as the reference group.
- A gout flare within 30 days of a previous flare encounter was considered part of the same episode.
- Recurrent flare-ups were defined as hospitalizations with gout as the primary discharge diagnosis, diagnosis of a new acute gout episode in primary care records, or diagnosis of gout in primary care records and a same-day prescription for gout or a pertinent procedure.
- Rate ratios were adjusted for age, sex, and race.

INTERVENTION (# IN THE GROUP): 2,556

COMPARISON (# IN THE GROUP): 1,057

FOLLOW-UP PERIOD: 10 years

RESULTS:

Primary Outcome –

- As serum urate levels increased recurrent gout flares also increased compared to serum urate levels <6 mg/dL:
  - 6.0–6.9 mg/dL (adjusted rate ratio [aRR] 3.4; 95% CI, 2.6–4.4)
  - 7.0–7.9 mg/dL (aRR 6.9; 95% CI, 5.4–8.8)
  - 8.0–8.9 mg/dL (aRR 8.7; 95% CI, 6.7–11)
  - 9.0–9.9 mg/dL (aRR 11; 95% CI, 8.0–15)
  - ≥10 mg/dL (aRR 11; 95% CI, 7.7–17)

LIMITATIONS:

- Limited generalizability due to lack of non-White males included and source population UK biobank participants have better socioeconomic status than the general UK population.

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Can Music Improve the Well-Being of Patients with Dementia?

Music Therapy Increases Social and Emotional Well-Being in Persons with Dementia: A Randomized Clinical Crossover Trial Comparing Singing to Verbal Discussion

Reschke-Hernández AE, Gfeller K, Oleson J, Tranel D. Music Therapy Increases Social and Emotional Well-Being in Persons With Dementia: A Randomized Clinical Crossover Trial Comparing Singing to Verbal Discussion. *J Music Ther.* 2023;60(3):314-342. doi:10.1093/jmt/thad015

KEY TAKEAWAY: Singing-based music therapy significantly improves feelings, pleasure, and social engagement among care facility residents with Alzheimer's disease and related dementias (ADRD) compared to an analogous non-music condition.

STUDY DESIGN: Randomized clinical crossover trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: Music-based interventions have shown promise in improving pleasure and social engagement in individuals with ADRD. This study compared the effects of a singing-based music therapy intervention with a non-music verbal discussion activity on emotional states, social engagement, and overall well-being in ADRD patients. By contrasting the musical engagement of music therapy with the cognitive demands of verbal discussions, the study aimed to investigate which approach more effectively enhances psychosocial outcomes for people with ADRD.

PATIENTS: Elderly adults with ADRD

INTERVENTION: Singing-based music therapy

CONTROL: Verbal discussion

PRIMARY OUTCOME: Changes in feeling, pleasure, and social engagement

METHODS (BRIEF DESCRIPTION):

- Participants in the study were residents of care facilities in Iowa, 65–97 years old, diagnosed with ADRD.
- Singing-based music therapy consisted of live, participant-preferred songs that were performed with acoustic guitar accompaniment, focusing on thematic topics such as travel, nature, hobbies, love, and friendship.
- Verbal discussions consisted of facilitated discussions on the same thematic topics led by interventionists, utilizing conversation starters and trivia to engage participants.
- Each session lasted 25 minutes three times per week.
- Each intervention phase lasted two weeks followed by a two-week washout at crossover.
- Changes in feelings, pleasure, and social engagement were measured for the primary outcome using the following:
  - Feelings were measured using the Dementia Mood Picture Test (DMPT). Scores range from 0–12, with higher scores indicating a more positive mood.
  - Pleasure was measured using the Observed Emotion Rating Scale (OERS). Scores range from 0–2, with higher scores indicating more time spent in a specific mood.
  - Social engagement was measured using the Menorah Park Engagement Scale (MPES). Scores range from 0–2, with higher scores indicating more time spent at a specified level of engagement.
- All scales were converted to a percent of maximum possible scores and presented as percent mean change.

INTERVENTION (# IN THE GROUP): 32

COMPARISON (# IN THE GROUP): The same 32 participants

FOLLOW-UP PERIOD: Eight weeks

RESULTS:

Primary Outcome –

- Singing-based music therapy significantly improved feelings compared to verbal discussion (mean change 8.5%; 95% CI, 4.2–13).
- Singing-based music therapy resulted in significantly greater pleasure compared to verbal discussion (mean change 28%; 95% CI, 35–50).
- Singing-based music therapy significantly improved social engagement compared to verbal discussion (mean change 73%; 95% CI, 64–92).

LIMITATIONS:

- The reliance on self-report measures (DMPT) for assessing feelings assumes participants' ability to accurately reflect on and report their emotional states, which may not be feasible for all individuals, particularly those with cognitive impairments.
- Despite efforts to minimize bias through training and quality assurance strategies, both data takers and interventionists may have influenced outcomes due to differences in skill levels, observational rigor, or unintentional preference for a specific treatment condition.
- The intervention design focused on a protocol-based music therapy approach grounded in the Clinical Practice Model for Persons with Dementia, which may not fully capture the variability and complexity of more holistic or individualized music therapy practices.
- The short duration of the intervention and washout period between sessions may have constrained the depth and duration of observed effects, potentially underestimating the long-term impacts of the interventions.
- The lack of representation from marginalized or underrepresented groups in the study sample highlights a significant gap in the generalizability of findings and cultural sensitivity in aging research and music therapy literature.

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Double Defense: Dual Antiplatelet Therapy Over Aspirin in Acute Stroke

Clopidogrel Plus Aspirin vs Aspirin Alone in Patients with Acute Mild to Moderate Stroke: The ATAMIS Randomized Clinical Trial

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KEY TAKEAWAY: Dual antiplatelet therapy (DAPT), aspirin + clopidogrel is superior to aspirin alone for the prevention of early neurological deterioration after moderate acute ischemic stroke.

STUDY DESIGN: Open-label randomized clinical trial with a blinded endpoint

LEVEL OF EVIDENCE: STEP 3 (downgraded due to open-label design and short follow-up)

BRIEF BACKGROUND INFORMATION: The benefit of dual antiplatelet therapy for the prevention of recurrent stroke has been demonstrated in minor ischemic stroke and transient ischemic attack (TIA) by previous studies. Guidelines currently recommend aspirin monotherapy for patients with mild to moderate acute stroke who are not given reperfusion therapy. This clinical trial investigated the benefit of dual antiplatelet therapy in patients with mild to moderate ischemic stroke for the prevention of early neurological deterioration.

PATIENTS: Adult patients with ischemic stroke

INTERVENTION: Aspirin + clopidogrel

CONTROL: Aspirin monotherapy

PRIMARY OUTCOME: Early neurologic deterioration at seven days

Secondary Outcome: Bleeding events, recurrent stroke

METHODS (BRIEF DESCRIPTION):

- The ATAMIS randomized clinical trial compared aspirin and aspirin + clopidogrel in 2,763 patients with acute ischemic stroke over 90 days.
- Patients from 66 sites in China for the trial were identified.
- Individuals with acute stroke identified by computed tomography or magnetic resonance imaging (MRI) with the onset of symptoms <48 hours, baseline National Institutes of Health Stroke Scale (NIHSS) score of 4–10, and >18 years old were included in the study.
- Patients eligible for and having received thrombectomy or thrombolytics, history of intracerebral hemorrhage, allergy to aspirin or clopidogrel, gastrointestinal or urinary tract bleeding in the last three months, and indication for anticoagulation (atrial fibrillation) were excluded from the study.
- Patients were randomized in a 1:1 ratio into each group using a computer-generated random sequence.
    - The clopidogrel + aspirin group received a 300 mg clopidogrel loading dose, then clopidogrel 75 mg daily + aspirin 100 mg daily from day one to day 14. From day 15 to day 90, they either continued daily aspirin or daily clopidogrel.
    - The aspirin group received 100 mg to 300 mg from day one to day 14, followed by aspirin 100 mg from day 15 to day 90.
- Patients had an average age of 66 years in both groups, the average BMI was 24 in both groups, and hypertension was the most common comorbid condition (62%).
- After seven days, the patients were evaluated using NIHSS. Scores range from 0–42, with higher scores indicating more severe neurological deficits. Scores were measured by a certified neurologist who was blinded to the subject's group.
    - An increase in NIHSS score of ≥2 points was defined as early neurological deterioration.
- Secondary outcomes included change in NIHSS at 14 days compared with baseline, risk of new stroke within 90 days, and functional improvement at 90 days measured by modified Rankin Score. Scores range from 0–6, with higher scores indicating a greater degree of disability.

INTERVENTION (# IN THE GROUP): 1,502

COMPARISON (# IN THE GROUP): 1,413

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- The aspirin + clopidogrel group had a reduced rate of early neurological decline at seven days compared to aspirin alone (relative risk [RR] 0.71; 95% CI, 0.53–0.96; NNT=53).
- Prespecified subgroup analyses of the primary outcome showed no differences by age, gender, medical history, NIHSS score at randomization, or stroke characteristics.
- However, the treatment effect was significantly greater in the subgroup with time from symptom onset to treatment initiation <24 hours vs ≥24 hours (risk difference [RD] –3.6; 95% CI, –6.0 to –1.1 vs RD 0.6; 95% CI, –1.4 to 2.7, respectively; *p*=.01 for interaction).

Secondary Outcome –

- There was no significant difference between the two groups for risk of new ischemic or hemorrhagic stroke within 90 days, functional outcome (modified Rankin Scale) improvement at 90 days, or change in NIHSS from baseline at 14 days.
- Safety outcomes between the two groups were not significantly different, including mucocutaneous hemorrhage, organ hemorrhage, intracranial hemorrhage, symptomatic intracranial hemorrhage, and any bleeding events.

LIMITATIONS:

- The study was open-label, which may have affected whether the groups were treated equally, but this potential source of bias was mitigated by the primary endpoint of the NIHSS score being assessed by blinded neurologists.
- Treatment allocation was also unblinded, which may have introduced bias in randomization.
- Neurologic deterioration in the first seven days is a largely disease-oriented outcome; though previously associated with poor longer-term outcomes, it was not in this study.
- The study population included only individuals from China and may not be generalizable to other ethnicities.
- A greater frequency of NIHSS scores may have given a more accurate reflection of neurological decline, as it was measured only once at seven days.

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