GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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Let's Get Hands-On: Manual Therapies for Rotator Cuff Injuries

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Efficacy of Manual Therapy on Shoulder Pain and Function in Patients with Rotator Cuff Injury: A Systematic Review and Meta-Analysis

Liu S, Chen L, Shi Q, et al. Efficacy of manual therapy on shoulder pain and function in patients with rotator cuff injury: A systematic review and meta-analysis. *Biomed Rep*. 2024;20(6):89. Published 2024 Apr 11. doi:10.3892/br.2024.1778

KEY TAKEAWAY: The addition of manual therapy (MT) significantly improves both pain and function in adults with rotator cuff injuries compared to exercise-only therapy or multimodal physiotherapy.

STUDY DESIGN: Meta-analysis of 24 randomized controlled trials (RCTs) (N=1,110)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Conservative treatment for rotator cuff injuries has historically consisted of either prescribed exercise programs or a multi-modal physiotherapy approach including electrotherapy interventions, exercise, and stretching. Manual therapy, or manipulation of joints and tissues by a health care professional such as an osteopathic physician, is another non-invasive treatment option that has not been extensively studied.

PATIENTS: Adults ≥18 years old with rotator cuff injuries

INTERVENTION: Single-session and multi-session manual therapy

CONTROL: Placebo, exercise-only treatment, and multi-modal physiotherapy

PRIMARY OUTCOME: Shoulder pain and function

METHODS (BRIEF DESCRIPTION):

- A comprehensive literature review in both English and Chinese was conducted to identify RCTs that evaluated the efficacy of MT in patients with rotator cuff injuries.
- Studies included those that compared MT with placebo, MT + exercise with exercise alone, and MT-+ multimodal physiotherapy with multimodal physiotherapy alone.
- Primary outcomes were a decrease in various validated pain scores and shoulder/upper extremity functional scores.

INTERVENTION (# IN THE GROUP): 546

COMPARISON (# IN THE GROUP): 564

FOLLOW-UP PERIOD: Varied (1 week to 1 year)

RESULTS:

Primary Outcome –

- A single session of MT showed no significant difference in pain reduction or functional improvement compared to placebo (10 trials; standardized mean difference [SMD] –0.25; 95% CI, –0.51 to 0.01).
- Multiple MT sessions were associated with superior pain relief compared to placebo (10 trials; SMD –0.43; 95% CI, –0.68 to –0.18).
- MT was not associated with an improvement in functional scores compared to placebo (6 trials; SMD 0.20; 95% CI, –0.09 to 0.49).
- MT + exercise therapy resulted in significant improvement in both pain (SMD 0.36; 95% CI, 0.08–0.64) and function (SMD 0.32; 95% CI, 0.11–0.52) over exercise therapy alone.
- MT + multimodal physiotherapy resulted in significant improvement in both pain (mean difference [MD] 1.6; 95% CI, 0.18–3.0) and function (SMD 0.77; 95% CI, 0.43–1.1) over multimodal physiotherapy alone.

LIMITATIONS:

- Only one study had a follow-up greater than one year.
- Studies did not comment on disease progression after manual therapy.
- Confounding factors included therapeutic time window, comorbidities, and degree or type of initial injuries.

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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 Navy Medical Department, the Navy at large, or the Department of Defense.

Clinical Decision Support May Reduce Overtreatment

Reducing Care Overuse in Older Patients Using Professional Norms and Accountability: A Cluster Randomized Controlled Trial

Persell SD, Petito LC, Lee JY, et al. Reducing Care Overuse in Older Patients Using Professional Norms and Accountability: A Cluster Randomized Controlled Trial [published correction appears in Ann Intern Med. 2024 May;177(5):692. doi: 10.7326/L24-0117]. *Ann Intern Med*. 2024;177(3):324-334. doi:10.7326/M23-2183

KEY TAKEAWAY: Clinician decision support (CDS) in the electronic health record (EHR) is a promising intervention to reduce clinician overtreatment.

STUDY DESIGN: Multi-site, parallel-group, single-blind, controlled, cluster randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The American Geriatric Society Choosing Wisely guidelines recommend that elderly patients should not have prostate-specific antigen (PSA) screening, urine testing for nonspecific reasons, or titration of hemoglobin A1C (HbA1c) to goal <7.0%. Clinician adherence to these changing guidelines is challenging. Traditional approaches to curtailing over-testing and overtreatment have focused on clinician education, but behavioral strategies for eliciting change may improve outcomes. This study investigated if CDS is effective in facilitating behavioral changes in primary care clinicians.

PATIENTS: Primary care clinicians

INTERVENTION: CDS + education

CONTROL: Clinician education

PRIMARY OUTCOME: Urine testing for nonspecific reasons, PSA screening, and diabetes overtreatment
Secondary Outcome: Rate of prostate biopsy, prostate magnetic resonance imaging (MRI), new prostate cancer diagnosis, overall use of urinalyses, overall use of urine cultures, emergency department (ED) visits or hospitalization with hypoglycemia diagnosis

METHODS (BRIEF DESCRIPTION):

- Physicians, physician assistants, advanced practice nurses, and nurse practitioners who belonged to a primary care practice affiliated with a specific regional health network were included in the study.
- Clinicians who piloted the program or who joined after the intervention began were excluded from the study.
- Participants in the intervention group received CDS pop-up EHR alerts discouraging orders counter to Choosing Wisely tenets; if they signed the orders, a follow-up prompt appeared asking clinicians to document their clinical rationale.
- Physicians were emailed a link to an interactive module that utilized cases and multiple-choice questions to educate clinicians on Choosing Wisely tenets. Participation was measured through Research Electronic Data Capture (REDCap).
- The following were measured as the primary outcomes:
  - The rate of PSA testing in men without prostate cancer was calculated by dividing the number of men who received PSA testing by the total number of eligible men.
    - Eligibility criteria included individuals ≥76 years old with no history of prostate cancer, no androgenic medication use, and attendance at an appointment with a clinician in the year before the study began.
  - The rate of urine testing for non-specific reasons was calculated by dividing the number of women who received urine testing but lacked a diagnostic code indicating a relevant urinary sign, symptom, or indication by the total number of eligible women.
    - Eligibility criteria included individuals ≥65 years old, attendance at an appointment with a participating clinician, and having had a urinalysis or urine culture done within two days before the appointment to two days after. If the same person was eligible multiple times, only the first visit was included.
- The rate of diabetes over treatment was calculated by dividing the number of patients who had a HbA1c <7.0 % and who were taking either insulin, sulfonylurea, or meglitinide by the number of eligible patients.

    - Eligibility criteria included individuals ≥75 years old and attendance at an appointment with a clinician in the year before the study began.
- The following was measured as the secondary outcomes:
    - The rate of prostate biopsy, prostate MRI, and new prostate cancer diagnosis was determined based on diagnostic codes at either 12 or 18 months after the intervention.
    - Overall use of urinalyses and overall use of urine cultures were assessed within one day before a clinic appointment to two days afterward.
        - Eligibility criteria included women ≥65 years old, and attendance with a clinician in the 90 days before the intervention. If the same person was eligible multiple times, only the first visit was included.
    - ED visits or hospitalization with hypoglycemia diagnosis included individuals with a diabetes diagnosis, HbA1c <7.0%, and taking an oral hypoglycemic medication or insulin.
- Outcomes were assessed 12 months prior to intervention and 18 months after the intervention.

INTERVENTION (# IN THE GROUP): 184

COMPARISON (# IN THE GROUP): 187

FOLLOW-UP PERIOD: 18 months

RESULTS:

Primary Outcome –

- CDS + education decreased PSA screening compared to clinician education alone (adjusted differences in differences [aDID] –8.7; 95% CI, –10 to –7.1).
- CDS + education decreased urine testing for nonspecific reasons compared to clinician education alone (aDID –5.5; 95% CI, –7.0 to –3.6).
- CDS + education decreased diabetes overtreatment compared to clinician education alone (aDID –1.4; 95% CI, –2.8 to –0.03).

Secondary Outcome –

- CDS + education decreased the rate of urinalysis use in women ≥65 years old compared to clinician education alone (aDID –1.0, 95% CI, –2.0 to –0.2).
- There was no difference in the rate of prostate biopsy, prostate MRI, new prostate cancer diagnosis, overall use of urine cultures, ED visits, or hospitalization with hypoglycemia diagnosis in the CDS + education group compared to clinician education alone.

LIMITATIONS:

- CDS may have decreased the rates of urinalyses being ordered without appropriate documentation of indications in the EHR which could be a confounder to determining the effect of the intervention on testing rates.
- Evaluation of PSA testing rates did not account for whether the patients being tested had indications for testing separate from screening (such as signs and symptoms of prostate cancer).
- The BEAGLE trial only evaluated the efficacy of the CDS tool in one EHR system.
- The COVID-19 pandemic occurred between the pre-intervention and post-intervention periods.
- The secondary outcomes likely did not have time to fully manifest in the limited 18-month duration of the post-intervention period.

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Didn't See This Coming: Fenofibrate as Treatment for Early Diabetic Retinopathy

Effect of Fenofibrate on Progression of Diabetic Retinopathy

Preiss D, Logue J, Sammons E, et al. Effect of Fenofibrate on Progression of Diabetic Retinopathy. *NEJM Evid*. 2024;3(8):EVIDoa2400179. doi:10.1056/EVIDoa2400179

KEY TAKEAWAY: Fenofibrate reduces the progression of diabetic retinopathy or maculopathy compared to placebo in participants with early retinal changes.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Diabetic retinopathy is a common complication of diabetes. However, treatment for advanced disease is expensive and sometimes ineffective. This study aimed to investigate if fenofibrate could be a cost-effective treatment option for early treatment of diabetic retinopathy.

PATIENTS: Adults with non-referable diabetic retinopathy or maculopathy

INTERVENTION: Fenofibrate

CONTROL: Placebo

PRIMARY OUTCOME: Composite of developing referable diabetic retinopathy or maculopathy

Secondary Outcome: Time to any progression of diabetic retinopathy or maculopathy, development of referable maculopathy, muscular edema, change in visual function, quality of life, visual acuity

METHODS (BRIEF DESCRIPTION):

- Adults >18 years old (mean 61 years) with diabetes mellitus (DM) and non-referable diabetic retinopathy or maculopathy on a screening retinal examination within the last three years and an estimated glomerular filtration rate (eGFR) ≥40 were included in the study.
- Participants were randomized 1:1 to receive 145 mg fenofibrate or placebo
- The dosing frequency of fenofibrate was determined by the renal function of the participant.
  - Individuals with GFR >60 received fenofibrate 145 mg daily.
  - Individuals with GFR 30–59 received fenofibrate 145 mg on alternate days.
- Participants continued routine retinal screening and were contacted every six months for four years.
- The primary outcome was the composite measure of time to development of referable diabetic retinopathy or maculopathy or treatment for diabetic retinopathy or maculopathy.
- Referable diabetic retinopathy or maculopathy was defined as:
  - Moderately severe or severe non-proliferative diabetic retinopathy
  - Proliferative diabetic retinopathy
  - Blot hemorrhage or exudate near the foveal center
- The secondary outcomes measured the time to any progression of diabetic retinopathy or maculopathy, development of referable maculopathy, muscular edema, change in visual function, quality of life, and visual acuity.
  - The time to any progression of diabetic retinopathy or maculopathy was determined by digital retinal images.
  - Development of macular edema was identified on slit lamp examination or optical coherence tomography.
  - Any change in visual function was determined by the Visual Function Questionnaire-25 data.
  - Quality of life was determined based on EQ-5DL-5L questionnaire data.
  - Visual acuity methodology was not provided.

INTERVENTION (# IN THE GROUP): 576

COMPARISON (# IN THE GROUP): 575

FOLLOW-UP PERIOD: Median four years

RESULTS:

Primary Outcome –

- Fenofibrate reduced the composite progression of developing referable diabetic retinopathy or maculopathy compared to placebo (hazard ratio [HR] 0.73; 95% CI, 0.58–0.91).

Secondary Outcome –

- Fenofibrate reduced the following compared to placebo:
  - Any retinopathy or maculopathy progression (HR 0.74; 95% CI, 0.61–0.90)

    - Progression to referable maculopathy (HR 0.66; 95% CI, 0.52–0.85)
    - Macular edema (HR 0.5; 95% CI, 0.30–0.84)
- Fenofibrate did not affect visual function, quality of life, or visual acuity compared to placebo.

LIMITATIONS:

- The intervention was not consistent in all participants as patients with impaired kidney function took fenofibrate on alternate days vs daily.
- Adherence to trial treatment was self-reported.
- Participants were predominantly White males which may limit generalizability to other races and gender.

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Is Stress Ulcer Prophylaxis Safe with Ventilation?

Stress Ulcer Prophylaxis During Invasive Mechanical Ventilation

Cook D, Deane A, Lauzier F, et al. Stress Ulcer Prophylaxis during Invasive Mechanical Ventilation. *N Engl J Med*. 2024;391(1):9-20. doi:10.1056/NEJMoa2404245

KEY TAKEAWAY: Pantoprazole may help significantly reduce the risk of upper gastrointestinal (GI) bleeding in mechanically ventilated patients but has no significant effect on mortality.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Critically ill patients in the intensive care unit (ICU) often receive acid suppression therapy since they are at increased risk of upper GI bleeding through stress-induced ulcers. The most common form of acid suppression therapy given is proton-pump inhibitors (PPIs). However, a recent blinded trial showed pantoprazole, compared to a placebo, lowered the risk of upper GI bleeding but increased the risk of death in patients with severe illness. A network meta-analysis showed that PPIs could not be ruled out as a risk for *Clostridioides difficile (*C. difficile) infections or healthcare-associated pneumonia.

PATIENTS: Adults with invasive mechanical ventilation

INTERVENTION: Pantoprazole 40 mg

CONTROL: 0.9% sodium chloride

PRIMARY OUTCOME: Severe upper GI bleed, 90-day all-cause mortality

Secondary Outcome: Ventilator-associated pneumonia, C. difficile infection, death in ICU or hospital

METHODS (BRIEF DESCRIPTION):

- This blinded trial was conducted at 68 hospitals in Canada, England, United States, Australia, Brazil, Kuwait, Pakistan, and Saudi Arabia.
- It included patients ≥18 years old undergoing invasive mechanical ventilation in the ICU that was expected to continue after the day of randomization.
- Patients were excluded if they had received more than one daily dose equivalent of acid suppression in the ICU, if patients had invasive ventilation initiated at least 72 hours before randomizations, or if acid suppression therapy was indicated or contraindicated.
- Patients were assigned a 1:1 ratio of pantoprazole (40 mg in 0.9% sodium chloride) or placebo (0.9% sodium chloride).
- Pantoprazole and the placebo were administered by bedside staff in a blinded manner for 90 days or until discontinuation of the ventilation.
- Placebo or pantoprazole was resumed if invasive ventilation was restarted during a patient's index ICU admission.
- GI bleeding was defined as any bleeding that required a single blood transfusion, vasopressor treatment, diagnostic endoscopy, computed tomography angiography (CTA), surgery, death, disability, or prolonged hospitalization.
- The primary safety outcome was death from any cause at 90 days.

INTERVENTION (# IN THE GROUP): 2,417

COMPARISON (# IN THE GROUP): 2,404

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- Pantoprazole reduced upper GI bleeding compared to the placebo group (hazard ratio [HR] 0.30; 95% CI, 0.19–0.47).
- There was no difference in 90-day mortality between the pantoprazole group and the placebo group (HR 0.94; 95% CI, 0.85–1.0).

Secondary Outcome –

- There were no significant differences in ventilator-associated pneumonia, C. difficile infection, death in the ICU, and death in the hospital.

LIMITATIONS:

- There was no data regarding microbiome modification as a mechanism for infection risk.
- No patient-reported disability outcomes were taken into consideration.
- The Clinical Pulmonary Infection Score (CPIS) was used to define pneumonia, given the attributable mortality.

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Is Vaginal Estrogen Therapy Safe for Women with a History of Breast Cancer?

Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study

Cold S, Cold F, Jensen MB, Cronin-Fenton D, Christiansen P, Ejlertsen B. Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study. *J Natl Cancer Inst*. 2022;114(10):1347-1354. doi:10.1093/jnci/djac112

KEY TAKEAWAY: The use of vaginal estrogen therapy (VET) or menopausal hormone therapy (MHT) shows no increased risk of breast cancer recurrence in patients who have had early-stage estrogen-positive breast cancer. However, the use of VET and aromatase inhibitors does show an increased risk of breast cancer recurrence.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Currently, few studies exist to inform the risk of using estrogen therapy following breast cancer diagnosis. Potential benefits must be balanced against harms that are not well known. Prior studies have been limited by low sample size or have shown conflicting evidence regarding the risk.

PATIENTS: Postmenopausal women diagnosed with non-metastatic breast cancer

INTERVENTION: Vaginal estrogen therapy or menopausal hormonal therapy

CONTROL: No hormonal therapy

PRIMARY OUTCOME: Recurrence of breast cancer

Secondary Outcome: Mortality

METHODS (BRIEF DESCRIPTION):

- Postmenopausal Danish women 35–95 years old diagnosed with invasive early-stage nonmetastatic estrogen-positive breast cancer from 1997–2004 and did not receive chemotherapy were included.
- Women who took hormonal therapy prior to breast cancer diagnosis were excluded.
- The cohort was grouped into four main categories;
  - Received no adjuvant endocrine therapy
  - Received tamoxifen
  - Received aromatase inhibitor
  - Received a sequence of tamoxifen and aromatase Inhibitor
- The intervention group filled two prescriptions of VET or MHT during the study period.
  - The use of VET and MHT varied in time length along with dose and frequency.
  - Users were classified in a dichotomous variable based on whether they filled two prescriptions or not, regardless of strength, frequency, and length of prescription.
- The comparison group was women who did not use hormonal therapy.
- Mortality and recurrence were obtained by looking at the Danish Breast Cancer Group (DBCG) registry.

INTERVENTION (# IN THE GROUP):

- VET: 1,957
- MHT or both MHT ± VET: 133

COMPARISON (# IN THE GROUP): 6,371

FOLLOW-UP PERIOD:

- Recurrence: Median 9.8 years
- Mortality: Median 15 years

RESULTS:

Primary Outcome –

- VET use was not associated with the risk of breast cancer recurrence compared to never-users (hazard ratio [HR] 1.1; 95% CI, 0.89–1.3).
- The use of VET while on aromatase inhibitor was associated with an increased risk of breast cancer recurrence compared to never-users (HR 1.4; 95% CI, 1.0–1.9).
- MHT use was not associated with the risk of breast cancer recurrence compared to never-users (HR 1.1; 95% CI, 0.62–1.8).

Secondary Outcome –

- Neither VET use nor MHT use was associated with the risk of mortality compared to non-hormonal users. The adjusted hazard ratios for overall survival compared to never-users are:
  - Users of VET (adjusted HR for overall survival [OS] 0.78; 95% CI, 0.71–0.87)
  - Users of MHT (adjusted HR for OS 0.94; 95% CI, 0.70–1.3)

LIMITATIONS:

- Inherent to the study design; this was not a randomized control study.

- While there was not an increased risk seen, users of VET or MHT may differ from non-users in that, as described in the article, nonusers of VET and MHT were older, had larger tumors, and were more likely to have lymph node metastasis.

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More Harm than Good? The Risk of Erythrocytosis in Gender Affirming Hormone Therapy

Erythrocytosis in Gender-Affirming Care with Testosterone

Porat AT, Ellwood M, Rodina M, Dianat S. Erythrocytosis in Gender-Affirming Care With Testosterone. *Ann Fam Med*. 2023;21(5):403-407. doi:10.1370/afm.3018

KEY TAKEAWAY: Erythrocytosis along with associated thromboembolic events are rare in individuals undergoing therapy for gender-affirming hormone therapy (GAHT) therefore, monitoring of hemoglobin (hgb) and hematocrit (hct) every three months may be unnecessary.

STUDY DESIGN: Descriptive fixed cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: It is well-known that testosterone therapy is associated with an increased risk of erythrocytosis. However, most of the data available is related to cisgender men with hypogonadism. This study aimed to identify the prevalence of erythrocytosis in transgender and nonbinary individuals who used testosterone therapy for the sake of gender affirmation and assessed whether or not affected individuals were at increased risk for thrombotic events, particularly after factoring in additional risk factors like smoking, obesity, and obesity-related illnesses.

PATIENTS: Adult using testosterone therapy for GAHT

INTERVENTION: Testosterone cypionate injections or testosterone gel

CONTROL: Not applicable

PRIMARY OUTCOME: Erythrocytosis incidence

METHODS (BRIEF DESCRIPTION):

- Individuals ≥16 years old who received care at Virginia League for Planned Parenthood (and its affiliations) from 1/1/2017–12/31/2019 who were prescribed testosterone for GAHT and did not miss therapy for more than one month were included in the study.
  - Median age 21 years old (ranged from 16–60 years)
  - 61% were White, 12% African American, 1.8% Asian, 0.01% Native Hawaiian or Other Pacific Islander, and 24% preferred not to answer.
- At baseline, 10 individuals' hct and hgb were within range for "men" (albeit elevated for women), so they were also included in the study.
- Weekly testosterone cypionate injections (40–120 mg) or testosterone gel were assessed as the intervention of the study.
- Due to the study design, there was no comparator as all participants received the study intervention.
- The primary outcome assessed erythrocytosis incidence amongst study participants.
- Measurements were checked every three months and erythrocytosis severity was based on the following hct levels:
  - Mild Hct 50–51.9%
  - Moderate hct 52–53.9%
  - Severe >54% (requires treatment).

INTERVENTION (# IN THE GROUP):

- Testosterone cypionate: 279
- Testosterone gel: 3

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: 20 months

RESULTS:

Primary Outcome –

- 13% of individuals on testosterone for GAHT developed mild erythrocytosis at 20 months.
- 1.0% of individuals on testosterone for GAHT developed moderate erythrocytosis at 20 months.
- 0.6% of individuals on testosterone for GAHT developed severe erythrocytosis at 20 months.
- Of those who developed erythrocytosis at 20 months, risk factors such as smoking, obesity, and obstructive sleep apnea (OSA) were identified. Five of them smoked and the mean BMI was 33. None had a diagnosis of OSA

LIMITATIONS:

- There was a high loss to follow up after 20 months.
- The study lacked documentation on the type of testosterone injection used (intramuscular vs subcutaneous) to see if there was a difference in the incidence of erythrocytosis based on the type.
- Participants were not in a closed health system, so the study was unclear if patients with erythrocytosis were diagnosed or treated for a thromboembolic event at an outside facility.

- Smoking status was difficult to assess in the overall population compared to those who developed erythrocytosis in the study.
- There was no control or comparison group. Limited evidence on this population was reported at baseline, so it is unclear if the incidence of erythrocytosis found in this study is significant compared to similar individuals who are not receiving hormone therapy or to those who use a different form of testosterone therapy.

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