GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of January 6 – 10, 2025

SPOTLIGHT:

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Pharmacotherapy for Alcohol Use Disorder: Does It Work?

Pharmacotherapy for Alcohol Use Disorder: A Systematic Review and Meta-Analysis

McPheeters M, O'Connor EA, Riley S, et al. Pharmacotherapy for Alcohol Use Disorder: A Systematic Review and Meta-Analysis [published correction appears in JAMA. 2024 Oct 2. doi: 10.1001/jama.2024.11331]. *JAMA*. 2023;330(17):1653-1665. doi:10.1001/jama.2023.19761

KEY TAKEAWAY: Naltrexone 50 mg per day and acamprosate significantly reduce alcohol consumption in patients with alcohol use disorder (AUD). However, naltrexone 100 mg per day, injectable naltrexone, and disulfiram, despite holding FDA approval for AUD, do not reduce alcohol consumption.

STUDY DESIGN: Systemic review and meta-analysis of 118 randomized controlled clinical trials (N=20,976)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: AUD affects approximately 10% of the US population and is the 3rd leading preventable cause of death. The treatment of AUD is challenging and often multidisciplinary. It is estimated that <1% of people with AUD receive pharmacotherapy. The FDA has approved three medications for the treatment of AUD, including naltrexone, acamprosate, and disulfiram. This systematic review and meta-analysis aimed to investigate whether these treatments reduced alcohol consumption in patients with AUD.

PATIENTS: Adults with AUD

INTERVENTION: Oral and injectable naltrexone, acamprosate, and disulfiram

CONTROL: Placebo or another medication

PRIMARY OUTCOME: Alcohol consumption

Secondary Outcome: Motor vehicle crashes (MVCs), injuries, quality of life, function, mortality, harms

METHODS (BRIEF DESCRIPTION):

- Eligible studies included adults treated with any of the three FDA-approved (naltrexone, acamprosate, or disulfiram) or any of the six off-label (topiramate, varenicline, baclofen, gabapentin, prazosin, ondansetron) medications for AUD and assessed alcohol consumption as the primary outcome.
- Double-blind randomized clinical trials comparing one of the FDA-approved or off-label medications with a placebo or a different medication were included in the review.
- The intervention medications included:
  - Acamprosate
  - Oral naltrexone 50 mg per day
  - Oral naltrexone 100 mg per day
  - Injectable naltrexone
  - Disulfiram
- The control included either a placebo or a different medication.
- The primary outcome measured alcohol consumption as defined as a return to any drinking, return to heavy drinking, and reduction in drinking days.
  - Heavy drinking was defined as ≥4 drinks per day for women and ≥5 drinks per day for men.
  - Reduction in drinking days was reported statistically as percentages.
- The secondary outcomes measured MVCs, injuries, quality of life, function, mortality, and harm.

INTERVENTION (# IN THE GROUP):

- Naltrexone: 4,604
- Acamprosate: 6,380
- Disulfiram: 622

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Return to any drinking.
  - Acamprosate reduced the risk of return to any drinking compared to placebo (20 studies, n=6,380; relative risk [RR] 0.88; 95% CI, 0.83–0.93; NNT=11).
  - Naltrexone 50 mg per day reduced the risk of return to any drinking compared to placebo (16 studies, n=2,347; RR 0.93; 95% CI, 0.87–0.93; NNT=18).
  - Naltrexone 100 mg per day did not reduce the risk of return to any drinking compared to placebo (3 studies, n=946; RR 0.97; 95% CI, 0.91–1.0).

- Injectable naltrexone did not reduce the risk of return to any drinking compared to placebo (2 studies, n=939; RR 0.96; 95% CI, 0.90–1.0).
- Disulfiram did not reduce the risk of return to any drinking compared to placebo (3 studies, n=622; RR 1.03; 95% CI, 0.90–1.2).

- Return to heavy drinking:
  - Acamprosate did not reduce the risk of heavy alcohol consumption compared to placebo (7 studies, n=2,496; RR 0.99; 95% CI, 0.94–1.1).
  - Naltrexone 50 mg per day reduced the risk of heavy alcohol consumption compared to placebo (23 studies, n=3,170; RR 0.81; 95% CI, 0.72–0.90; NNT=11).
  - Naltrexone 100 mg per day did not reduce the risk of heavy alcohol consumption compared to placebo (2 studies, n=858; RR 0.93; 95% CI, 0.84–1.0).
  - Injectable naltrexone did not reduce the risk of heavy alcohol consumption compared to placebo (2 studies, n=615; RR 1.0; 95% CI, 0.82–1.2).
  - Disulfiram had insufficient evidence to report statistical results for this outcome.
- Reduction in drinking days
  - Acamprosate reduced drinking days compared to placebo (14 studies, n=4,916; weighted mean difference [WMD] –8.3; 95% CI, –12 to –4.4).
  - Naltrexone 50 mg per day reduced drinking days compared to placebo (15 studies, n=1,992; WMD –5.1; 95% CI, –7.2 to –3.0).
  - Naltrexone 100 mg per day did not reduce drinking days compared to placebo (3 studies, n=1,023; WMD –2.3; 95% CI, –5.6 to 0.99).
  - Injectable naltrexone did not reduce drinking days compared to placebo (2 studies, n=467; WMD –5.0; 95% CI, –9.5 to 0.49).
  - Disulfiram had insufficient evidence to report statistical results for this outcome.

Secondary Outcome –

- There was insufficient evidence to report results for MVCs, injuries, quality of life, function, mortality, and harms in the included studies.

LIMITATIONS:

- Some of the studies included participants with diagnoses of both AUD and depression and some included participants without both AUD and depression. Thus, there was a possibility that depression could be a confounding factor.
- There was insufficient evidence to report statistical results for several outcomes included in the analysis.
- Studies may have selectively reported outcomes.
- Due to small sample sizes and small number of events, evidence was insufficient to report adverse events.

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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.

CNS-Active Medications: De-Prescribing Initiatives and Reducing the Incidence of Falls in Older Adults

Reducing Central Nervous System-Active Medications to Prevent Falls and Injuries Among Older Adults: A Cluster Randomized Clinical Trial

Phelan EA, Williamson BD, Balderson BH, et al. Reducing Central Nervous System-Active Medications to Prevent Falls and Injuries Among Older Adults: A Cluster Randomized Clinical Trial. *JAMA Netw Open*. 2024;7(7):e2424234. Published 2024 Jul 1. doi:10.1001/jamanetworkopen.2024.24234

KEY TAKEAWAY: Educational interventions and clinician support to discontinue or reduce the dose of central nervous system (CNS)-active medications for older adults do not reduce the incidence of medically treated falls.

STUDY DESIGN: Cluster randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: According to the American Geriatric Society Beers criteria, CNS-active medications have long been attributed to an increased risk of falls in older patients. This study aimed to assess the effect of patient education and clinician decision support when prescribing CNS-active medications on the incidence of falls in older adults.

PATIENTS: Adults ≥60 years old

INTERVENTION: Patient education and clinician decision support to de-prescribe

CONTROL: Usual care

PRIMARY OUTCOME: Medically-treated falls

Secondary Outcome: Medication discontinuation, sustained medication discontinuation, dose reduction

METHODS (BRIEF DESCRIPTION):

- Outcome analyses were based on 2,367 adult patients with a mean age of 71 years old from Washington State from 18 primary care clinics.
- Included patients were community-dwelling adults ≥60 years old, prescribed at least one medication from any of five targeted medication classes (opioids, sedative-hypnotics, skeletal muscle relaxants, tricyclic antidepressants, and first-generation antihistamines).
- Patients not on one of the target medication classes or outside of the clinics evaluated were excluded from the study.
- Patients were blinded and randomized to one of the following treatment groups:
  - Education was modeled after the Developing Pharmacist-Led Research to Educate and Sensitize Community Residents to the Inappropriate Prescriptions Burden in the Elderly (D-PRESCRIBE).
  - Education was administered by sending a brief version of the evidence-based pharmaceutical opinions (EBPO) to clinicians via the electronic health record (EHR) staff messaging system with a hyperlink to the full-length EBPO on the study website.
- Records were ascertained from electronic utilization files of the health plan encounters. Data was collected for at minimum three consecutive months and at six, nine, and 12-month intervals.
- Randomization was at the clinic level to avoid cross-clinician contamination.
- Health plan disenrollment and death were the only reasons for the loss of follow-up.
- Outcomes were measured by the time (in days) of the first incidence of medically treated falls.
- Secondary outcomes were measured by records reporting rates of medication discontinuation, continuation of medication discontinuation, and overall reported dose reduction of any and each target medication class.

INTERVENTION (# IN THE GROUP): 1,106

COMPARISON (# IN THE GROUP): 1,261

FOLLOW-UP PERIOD: One year

RESULTS:

Primary Outcome –

- Providing patient education and clinician decision support related to CNS-active medications did not significantly reduce the incidence of medically treated falls compared to usual treatment (estimated hazard ratio [HR] 1.1; 95% CI, 0.94–1.3).

Secondary Outcome –

- Providing patient education and clinician decision support increased discontinuation, sustained discontinuation, and dose reduction for tricyclic antidepressants compared to usual treatment (adjusted relative risk [RR] 0.19; 95% CI, 1.3–2.5).

- Providing patient education and clinician decision support did not affect discontinuation, sustained discontinuation, and dose reduction for opioids, sedative-hypnotics, skeletal muscle relaxants, or first-generation antihistamines compared to usual treatment.

LIMITATIONS:

- The study was limited to the geographical region of Washington state and to only community-dwelling people from participating clinics, limiting generalizability.
- There was a small representation of minorities in the participants.
- Participants were primarily non-frail older adults.
- Non-prescription anti-histamine use and non-medically treated falls were unknown.
- This trial was conducted during the COVID-19 pandemic, which had increased demands on healthcare professionals and the healthcare system.

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Virtually Indistinguishable: The Role of Online Group Therapy

Online Group Therapies for Anxiety, Obsessive-Compulsive, and Trauma-Related Disorders: A Systematic Review

Laurito LD, Dos Santos-Ribeiro S, Moreira-de-Oliveira ME, et al. Online group therapies for anxiety, obsessive-compulsive, and trauma-related disorders: a systematic review. *Front Hum Neurosci*. 2024;17:1286865. Published 2024 Jan 11. doi:10.3389/fnhum.2023.1286865

KEY TAKEAWAY: Online group therapy may be effective in the treatment of social anxiety disorders (SAD) and post-traumatic stress disorders (PTSD).

STUDY DESIGN: Systematic review of two open-label trials and eight randomized control trials (N=749)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to the quality of included studies and lack of a pooled data analysis)

BRIEF BACKGROUND INFORMATION: Certain psychiatric disorders such as anxiety disorder, obsessive-compulsive and related disorders, and trauma-related disorders (AOTDs) can have an isolating effect on the patient. Group therapy has been a mainstay of treatment for many of these disorders and, with the advancement of technology and acceptance of individual online psychotherapies, may be successfully facilitated in an online format. This systematic review aimed to evaluate the effect of online group psychotherapy on symptoms of AOTDs.

PATIENTS: Adults diagnosed with AOTDs

INTERVENTION: Online group treatment

CONTROL: No control

PRIMARY OUTCOME: Changes in symptoms

METHODS (BRIEF DESCRIPTION):

- Study selections were conducted via an electronic search in PUBMED, PsycINFO, Web of Science, and the ClinicalTrials.gov registry to include those that met inclusion criteria.
- Patients ≥18 years old who received a formal diagnosis of an AOTD were included in the review.
- Online group treatments included internet-based therapy (IBT) (4 studies), video teleconference (VTC) (5 studies), and IBT + VTC (1 study), all of which involved an interaction among participants in the presence of or facilitation by a therapist.
- Active participation by group members was required.
- The primary outcome was an improvement in symptom severity in patients with AOTDs after initiation of online group therapy.
- A variety of symptom measures were used that utilized internet-based therapy, video teleconferencing, or a combination of both.
- Symptom severity was assessed at baseline and after intervention.

INTERVENTION (# IN THE GROUP): 434

COMPARISON (# IN THE GROUP): 315

FOLLOW-UP PERIOD: Variable (6–14 weeks)

RESULTS:

Primary Outcome –

- IBT resulted in a greater reduction of symptoms in clinician-assisted IBT compared to a self-guided or waitlist intervention (4 studies, n=337; p<.001).
- VTC resulted in no difference in symptoms compared to in-person sessions (5 studies, n=306; p>.05).
- IBT + VTC resulted in an overall mean reduction in symptoms (1 study, n=5; no p-value reported).

LIMITATIONS:

- Two authors published six of the included papers. In addition, the restrictive selection criteria may limit the scalability of the intervention.
- A significant portion of the selected studies had no female representation in the sample. Notably, these were studies examining online interventions for PTSD.
- Due to a lack of homogeneity in research terms, there may have been studies that met selection criteria but were filtered out in the preliminary stages of selection.
- No studies were found directly addressing online group therapy in panic disorders, specific phobias, or obsessive-compulsive disorders, but were instead included as comorbidities in the selected studies.
- Differences in the implementation of VTC and IBT between studies may affect the accuracy of outcome interpretation.

- The lack of a pooled analysis of data from all studies is another limitation, resulting in a downgrade to STEP 2.

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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.

After Restrictive Abortion Policies: Climbing Infant Mortality in Texas

Infant Deaths After Texas' 2021 Ban on Abortion in Early Pregnancy

Gemmill A, Margerison CE, Stuart EA, Bell SO. Infant Deaths After Texas' 2021 Ban on Abortion in Early Pregnancy. *JAMA Pediatr*. 2024;178(8):784-791. doi:10.1001/jamapediatrics.2024.0885

KEY TAKEAWAY: The enactment of Senate Bill 8 (SB8) in the state of Texas in 2021, which greatly restricted the availability of abortions, was associated with increases in infant and neonatal deaths in the following year compared to other US states.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: In September of 2021, the state of Texas enacted SB8 which banned abortions after detectable embryonic cardiac activity, the most restrictive law in the country. Prior to the Dobbs decision removing federal protections for abortion access, infant mortality was generally decreasing. It has been hypothesized that abortion restrictions passed since then would increase infant mortality. This study examines the association between SB8 and subsequent infant mortality.

PATIENTS: Infant and neonates

INTERVENTION: After SB8 in Texas

CONTROL: Before SB8, 28 other US states, synthetic control "Texas"

PRIMARY OUTCOME: Infant and neonatal mortality
Secondary Outcome: Infant mortality broken down by cause of death

METHODS (BRIEF DESCRIPTION):

- The study population comprised infant deaths during the study period, based on publicly available death certificate data from the Centers for Disease Control and Protection (CDC) Provisional Multiple Cause of Death database for Texas plus 28 comparison states for infants (age <1 year) and 19 comparison states for neonates (age <28 days).
- The intervention was compromised of 10 months during which SB8 was in effect, beginning seven months after passage of the bill (based on the assumption that infants delivering then would have been the earliest group to have been in their first trimester when the bill was implemented).
- Investigators compared the number of infant deaths and infant mortality rate in Texas during the exposure period to infant deaths in Texas prior to the exposure period, in other US states excluding Texas, and an augmented synthetic control Texas (ASCT).
    - They created the ASCT by extrapolating infant death and mortality rates during the period prior to the enactment of SB8.
    - They also used states with similar pre-exposure infant deaths and mortality rates as well as similar covariates (advanced maternal age, maternal education level, and Medicaid enrollment) to create the ASCT.
- Investigators compared the number and percent change of infant deaths in the exposure period vs the pre-exposure period.
- They used a comparison of the observed vs the predicted number of infant deaths and mortality rates.
- Investigators also compared the percent changes in infant deaths attributed to specific causes during the exposure period vs the pre-exposure period, as well as in Texas vs other US states excluding Texas.

INTERVENTION (# IN THE GROUP): 1,913 infant deaths and 1,233 neonatal deaths in Texas during the study period between March and December 2022

COMPARISON (# IN THE GROUP):

- 1,697 predicted infant deaths and 1,088 predicted neonatal deaths in Texas between March and December of 2022
- 1,985 infant deaths and 1,295 neonatal deaths in Texas in 2021
- 18,261 infant deaths and 11,661 neonatal deaths in the US excluding Texas

FOLLOW-UP PERIOD: No follow-up period was reported outside of the study timeline

RESULTS:

Primary Outcome –

- After SB8 there was a greater increase in annual infant deaths in Texas compared to other US states

(13% vs 1.8% change; no statistical analysis completed).
- After SB8 there was a greater increase in the infant mortality rate in Texas compared to other US states (8.3% vs 2.2% change; no statistical analysis completed).
- After SB8, there was no difference in observed infant deaths in Texas compared to predicted deaths (217 excess deaths; 95% CI, –122 to 554).
- After SB8, there was a greater increase in annual neonatal deaths in Texas compared to other US states (10% vs 1.6% change; no statistical analysis completed).
- After SB8, there was a greater increase in the neonatal mortality rate in Texas compared to other US states (5.8% vs 2.0% change; no statistical analysis completed).
- After SB8, there was no difference in observed neonatal deaths in Texas compared to predicted deaths (145 excess deaths; 95% CI, –161 to 450).

Secondary Outcome –

- After SB8 there was a greater increase in infant mortality by cause in Texas compared to other US states (no statistical analysis completed).
  - Congenital abnormalities (23% vs –2.9%)
  - Maternal complications of pregnancy (18% vs 7.8%)
  - Unintentional injuries (21% vs 1.1%)
  - Sudden infant death syndrome (11% vs 3.3%)
  - Necrotizing enterocolitis of newborns (73% vs 6.4%)
  - Atelectasis (24% vs 16%)
  - No difference between preterm birth or placental complications

LIMITATIONS:

- There was a lack of statistical evaluation for several outcomes.
- The lack of birth month and gestational age data led to an estimate of SB8's "exposure period" rather than having inclusion criteria that patients were conceived at the time of or after implementation of SB8.
- The small sample size of data available likely contributes to the wide confidence intervals.
- States with <10 infant deaths were not included, limiting the ability to examine the effects of race and ethnicity.
- The covariates used in the development of the synthetic control were limited to advanced maternal age, maternal education level, and Medicaid enrollment.
- Fetal deaths were not studied.

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THC for Tourette's: Taming the Tics

Tetrahydrocannabinol and Cannabidiol in Tourette Syndrome

Mosley PE, Webb L, Suraev A, et al. Tetrahydrocannabinol and Cannabidiol in Tourette Syndrome. *NEJM Evid.* 2023;2(9):EVIDoa2300012. doi:10.1056/EVIDoa2300012

KEY TAKEAWAY: Tetrahydrocannabinol (THC) and cannabidiol (CBD) may reduce motor tics in severe Tourette syndrome.

STUDY DESIGN: Double-blind, randomized, crossover trial

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

BRIEF BACKGROUND INFORMATION: Tourette syndrome is a disorder characterized by uncontrolled motor and vocal tics. Inadequate response to current therapies has given medical marijuana an increasing interest as an alternative therapy for the reduction of tics.

PATIENTS: Adults with severe Tourette syndrome

INTERVENTION: THC + CBD oil

CONTROL: Placebo

PRIMARY OUTCOME: Severity of tics

METHODS (BRIEF DESCRIPTION):

- 14 male and eight female participants 18–70 years old were recruited from various movement disorder clinics in South East Queensland.
  - All individuals were diagnosed with either moderate to severe tics.
- Exclusion criteria included those currently on anti-psychotic medication, neurological or psychiatric commodities, active suicidality, and pregnancy.
  - Those currently using cannabis were excluded if they failed to stop one month prior to the study.
- Participants were randomized to receive six weeks of THC + CBD solution up to a maximum dose of 20 mg of each daily, or placebo.
- Following a four-week washout, the crossover was performed and intervention and placebo groups were switched for an additional six weeks.
- The primary outcome was assessed using the Yale Global Tic Severity Scale (YGTSS), a questionnaire with scores ranging from 0–50. Higher scores correlate with elevated intensity, frequency, number, and complexity of tics.

INTERVENTION (# IN THE GROUP): 22

COMPARISON (# IN THE GROUP): 22

FOLLOW-UP PERIOD: 16 weeks

RESULTS:

Primary Outcome –

- THC + CBD oil reduced tic severity more than placebo at six weeks (8.9 vs 2.5, respectively; *P*=.01).

LIMITATIONS:

- Only 19 participants remained after the washout period. Of those 19 participants, it is unsure who was cannabis naive.
- Three participants were unable to reach the maximum indicated dose due to adverse effects of drowsiness and cognition impairment. Of these participants, two participants took 3 mL of the target 4 mL daily dose.

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Every Step You Take: Role of Rivaroxaban in Intermittent Claudication

Rivaroxaban for Patients with Intermittent Claudication
Ramacciotti E, Volpiani GG, Britto KF, et al. Rivaroxaban for Patients with Intermittent Claudication. *NEJM Evid*. 2024;3(9):EVIDoa2400021. doi:10.1056/EVIDoa2400021

KEY TAKEAWAY: Rivaroxaban + aspirin significantly improved total walking distance in patients with peripheral arterial disease (PAD) and symptomatic intermittent claudication compared to aspirin alone.
STUDY DESIGN: Randomized controlled trial
LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: There is a lack of evidence for effective medical treatments for both PAD and intermittent claudication. Previous trials demonstrated the efficacy of rivaroxaban + aspirin in decreasing major cardiovascular and limb adverse events in patients with PAD. This study evaluates whether rivaroxaban + aspirin can improve the total walking distance in patients with PAD and intermittent claudication.

PATIENTS: Adults with symptomatic PAD and intermittent claudication
INTERVENTION: Rivaroxaban + aspirin
CONTROL: Aspirin only
PRIMARY OUTCOME: Six-minute walking distance
Secondary Outcome: Total walking distance without claudication

METHODS (BRIEF DESCRIPTION):

- Patients studied were adults >18 years old with symptomatic PAD, ankle-brachial index (ABI) of <0.85, and total walking distance of <500 m before claudication symptoms.
- Patients were excluded if they had intermittent claudication symptoms, recent stroke, and active cancer.
- Patients were randomized to receive rivaroxaban 2.5 mg twice a day + aspirin 100 mg daily vs aspirin 100 mg daily.
- Patients were supervised using a six-minute walking test and treadmill walking test with patient-reported occurrence of claudication symptoms.

INTERVENTION (# IN THE GROUP): 46
COMPARISON (# IN THE GROUP): 42

FOLLOW-UP PERIOD: 24 weeks

RESULTS:
Primary Outcome –

- Rivaroxaban + aspirin improved the six-minute walk test compared to aspirin alone (absolute difference [AD] 68; 95% CI, 19–116).

Secondary Outcome –

- Rivaroxaban + aspirin improved total walking distance compared to aspirin alone (AD 79; 95% CI, 7–150).

LIMITATIONS:

- The small sample size (n=88) led to imbalances in baseline patient characteristics.
- There was a high exclusion rate, which limited external generalizability.
- The results lacked generalizability to patients taking cilostazol.
- The outcome focuses on walking distances, which may not fully capture the impact of the treatment on patients' quality of life.

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