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Calmer Days Ahead: Brexpiprazole in Alzheimer's Care

Brexpiprazole for the Treatment of Agitation in Alzheimer Dementia: A Randomized Clinical Trial

Lee D, Slomkowski M, Hefting N, et al. Brexpiprazole for the Treatment of Agitation in Alzheimer Dementia: A Randomized Clinical Trial. *JAMA Neurol*. 2023;80(12):1307-1316. doi:10.1001/jamaneurol.2023.3810

KEY TAKEAWAY: In adults with Alzheimer's dementia, the use of brexpiprazole is safe and improves symptoms of agitation compared to placebo.

STUDY DESIGN: Multi-site, double-blind, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Studies on agitation in dementia indicate atypical antipsychotics have some benefit but often have unfavorable risk profile. The study on effects of brexpiprazole have showed tolerability for 2 mg. This study investigates the effects of 2 mg and 3 mg doses and their effect on agitation.

PATIENTS: Adults with Alzheimer's dementia

INTERVENTION: Brexpiprazole

CONTROL: Placebo

PRIMARY OUTCOME: Agitation improvement

Secondary Outcome: Caregiver burden, safety events, discontinuation

METHODS (BRIEF DESCRIPTION):

- Patients 55–90 years old from seven European sites (Bulgaria, Hungary, Serbia, Slovakia, Spain and Ukraine) as well as the United States and who met criteria for probable Alzheimer's dementia defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association were included in the study.
- Patients were included if they had an onset of agitation at least two weeks prior to screening, Mini-Mental State Examination (MMSE) score of 5–22, head imaging consistent with Alzheimer's disease, requirement for pharmacotherapy based on investigator's judgement after evaluation for reversal factors, and failed trial of redirecting therapy.
- Patients were excluded who had agitation due to non-Alzheimer's related symptoms such as pain or other unstable medical conditions.
- The mean age was similar in both groups (73 years in placebo vs 74 years in treatment group) and most participants were women (51% in placebo vs 59% in treatment group).
- For 12 weeks, the treatment group received 2 mg or 3 mg of oral brexpiprazole daily.
- The comparison group received a placebo.
- Agitation was measured via the Cohen's Mansfield Agitation Inventory (CMAI) with 29 agitated behaviors, with each behavior indices each given a score of 1–7. Total scores range from 29–203, with higher scores indicating worse agitation.
- Caregiver burden was measured using Clinical Global Impression Severity of Illness (CGI-S) and Improvement (CGI-I) scales. Each scale is an observer-rated scale 0–7, with higher scores indicating increasing illness or worsening of disease.
- Safety was measured via reporting of treatment-emergent adverse events (TEAEs).

INTERVENTION (# IN THE GROUP):

- 2 mg: 75
- 3 mg: 153

COMPARISON (# IN THE GROUP): 117

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- Brexpiprazole decreased agitation compared to placebo (least squares mean difference [LSMD] –5.3; 95% CI, –8.8 to –1.9).

Secondary Outcome –

- Brexpiprazole reduced caregiver burden according to the CGI-S scale compared to placebo (mean difference [MD] –0.27; 95% CI, –0.47 to –0.07).
- Brexpiprazole reduced caregiver burden according to the CGI-I scale compared to placebo (MD –0.33; 95% CI, –0.57 to –0.09).
- Brexpiprazole resulted in a higher incidence of TEAE as compared to placebo (41% vs 31%, respectively; no statistical comparison completed).

- Brexpiprazole 2 mg had fewer TEAEs compared to brexpiprazole 3 mg (38% vs 42%, respectively; no statistical comparison completed).
- Discontinuation was higher in the brexpiprazole group compared to placebo (4.3% vs 5.3%, respectively; no statistical comparison completed).
- Discontinuation was higher for brexpiprazole 3 mg compared to brexpiprazole 2 mg (7.2% vs 1.4%, respectively; no statistical comparison completed).

LIMITATIONS:

- The scales were completed by caregivers and their experiences which may have potential observer bias.
- The study did not include any information about caregivers and their relationship with patients.
- There was a small sample and multiple heterogeneous sites.
- CMAI- minimal clinical improvement in this assessment tool is between -10.6 to-13.5
- CGII and CGIS- minimal clinical improvement in these assessment tools is 1 point
- Drug sponsored/funded study

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Treatment of Rotator Cuff Tears: It's a Lot to Shoulder

Multiple Treatment Comparisons for Large and Massive Rotator Cuff Tears: A Network Meta-Analysis

Maillot C, Martellotto A, Demezon H, Harly E, Le Huec JC. Multiple Treatment Comparisons for Large and Massive Rotator Cuff Tears: A Network Meta-analysis. *Clin J Sport Med*. 2021;31(6):501-508. doi:10.1097/JSM.0000000000000786

KEY TAKEAWAY: Latissimus dorsi transfer may be the most effective for management of large and massive rotator cuff tears (mRCTs). Other conventional treatments including conservative care, partial repair, scaffolds (patch), platelet rich plasma (PRP), reverse total shoulder arthroplasty (RTSA) repair perform similarly with no clear advantage compared to a complete repair.

STUDY DESIGN: Network meta-analysis of 20 non-randomized controlled comparative clinical trials (N=1,233)

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: There is no consensus about the best choice between all the options available, large and mRCT management. This study aimed to determine the comparative effectiveness of current treatment options for the management of large and mRCTs.

PATIENTS: Patients with large and mRCTs

INTERVENTION: Various conventional treatment options

CONTROL: Complete repair

PRIMARY OUTCOME: Shoulder function

METHODS (BRIEF DESCRIPTION):

- The review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.
- A systematic review of English articles using MEDLINE (PubMed), the Cochrane Controlled Trials Register and EMBASE (Ovid) was performed.
- Large and mRCTs were defined as full-thickness tears of at least two rotator cuff tendons or with a diameter width of at least 3 cm to be considered large or 5 cm to be considered massive.
- Various management techniques were included comparing physiotherapy or nonsteroidal anti-inflammatory drugs (NSAID) treatment (conservative), debridement with or without acromioplasty or long biceps tenotomy, complete repair, partial repair, latissimus dorsi transfer, patch, PRP, RTSA.
- These studies reported on functional status of patients with major rotator cuff tears. Improvement in functional scoring was the primary measure of treatment effect.
- Validated scoring systems included the UCLA shoulder score, American Shoulder and Elbow Surgeons (ASES) shoulder outcomes score, Constant-Murley scores (Constant), Japanese Orthopedic Association (JOA) Score, Penn Shoulder Score (PSS), between the preoperative score and the postoperative score at the last follow-up.
- The treatment effect was evaluated by the difference between postoperative and preoperative functional techniques specific score. For each pairwise comparison, the standard mean difference expressed the size of the intervention effect in each study relative to the variability observed in that study.
    - Heterogeneity was tested across interventions.
- The network meta-analysis was based on a Bayesian random effects model, which preserves treatment comparisons within trials.
- Quantitative analyses were performed on an intention-to-treat basis.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Mean 37 months

RESULTS:

Primary Outcome –

- Latissimus dorsi transfer was the most effective treatment for shoulder function (standardized mean difference [SMD] 2.2; 95% CI, 0.28–4.1). This is based on 20 patients across a single study.
- Debridement was the least effective treatment for shoulder function (SMD –2.2; 95% CI, –3.1 to –1.2). This is based on 105 patients across four studies.
- There were no statistically significant differences between conservative treatment, partial repair, patch, PRP, and RTSA.
    - Conservative treatment (SMD –1.1; 95% CI, –2.9 to 0.69)

- Partial repair (SMD –0.44; 95% CI, –1.1 to 0.20)
- Patch (SMD 0.13; 95% CI,G –0.82 to 1.1)
- PRP (SMD 0.01; 95% CI, –0.79 to 0.82)
- RTSA (SMD –0.57; 95% CI, –2.2 to 1.02)

LIMITATIONS:

- Variations in study design, patient populations, surgical techniques, outcome measures, and follow-up period among included studies may have introduced reporting bias.
- Restricting the review to English-language studies may have resulted in selection bias.
- Including both prospective and retrospective studies may have contributed to publication bias.
- Significant heterogeneity across studies limits generalizability and weakens confidence in the findings of this review.

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cfDNA: The New Screening Tool for Maternal Cancer?

Prenatal cfDNA Sequencing and Incidental Detection of Maternal Cancer

Turriff AE, Annunziata CM, Malayeri AA, et al. Prenatal cfDNA Sequencing and Incidental Detection of Maternal Cancer. *N Engl J Med*. 2024;391(22):2123-2132. doi:10.1056/NEJMoa2401029

KEY TAKEAWAY: Routine obstetrical cell-free DNA (cfDNA) sequencing that is either non-reportable or unusual could become a screening tool for detecting maternal cancer in asymptomatic pregnant and post-partum patients.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 4 (downgraded due to small sample size and lack of comparison group)

BRIEF BACKGROUND INFORMATION: The use of cfDNA sequencing is the standard for aneuploidy screening worldwide. It is routine for pregnant patients. On occasion, there are unexpected or non-reportable results. This has led to increased incidence of detection of maternal cancer. This is a concern in primary care because of the lack of current guidelines for management of abnormal or non-reportable screening results. This study aimed to determine the presence of maternal cancer in patients who had abnormal routine cfDNA sequencing in pregnancy.

PATIENTS: Women who received abnormal or non-reportable results in routine prenatal cfDNA sequencing

INTERVENTION: Cancer screening protocol

CONTROL: None

PRIMARY OUTCOME: Presence of cancer

METHODS (BRIEF DESCRIPTION):

- Patients who had abnormal or non-reportable routine obstetrics cfDNA sequencing in pregnancy were informed by the sequencing lab or their provider of the option to participate in the IDENTIFY study.
- Participants who were ≥18 years old, currently pregnant or within two years post-partum, who had their sequencing completed at one of 12 sequencing laboratories across North America were included in the study.
- Patients were excluded if their sequencing results had insufficient fetal fraction.
- If qualified, patients received the study-determined cancer screening protocol.
- The primary outcome was measured using the cancer screening protocol which included rapid full body magnetic resonance imaging (MRI), laboratory tests including (complete blood count with differential, comprehensive metabolic panel with liver and renal function tests, vitamin B12 level test), tumor markers (CA 125, CA 15-3, CA 27.29, CA 19-9, carcinoembryonic antigen [CEA]), fecal occult blood test, family and medical history, cervical cancer screening (Pap test) if due, consultation with genetic counselor and medical oncologist, and placental biopsies at the time of delivery, if available.
- Investigators performed an exploratory analysis of the 50-kb sequencing traces to stratify patterns. These patterns were then associated with the incidence of cancer.
- To analyze the primary outcome, each portion of the cancer screening protocol was evaluated with sensitivity, specificity, area under the receiver-operating characteristic (AUC ROC) curve, positive predictive value (PPV), and negative predictive value (NPV).
- AUC, a metric that represents the area under the ROC curve, has values ranging from 0–1, with scores of 0.90–1.00 indicating excellent discrimination and 0.50 indicating no discrimination (equivalent to random guessing).

INTERVENTION (# IN THE GROUP): 107

COMPARISON (# IN THE GROUP): The same 107 patients

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Cancer was detected in 49% of the cohort.
- Whole body MRI was highly effective at detecting malignancy (AUC ROC 93; 95% CI, 88–98).
  - Sensitivity: 98%
  - Specificity: 89%
  - PPV: 90%
  - NPV: 98%

- Serum tumor markers had fair detection of malignancy (AUC ROC 71; 95% CI, 62–80).
  - Sensitivity: 68%
  - Specificity: 74%
  - PPV: 71%
  - NPV: 71%
- Specific tumor markers (CEA, CA 15-3, CA 19-9) had poor detection of malignancy (AUC ROC 69; 95% CI, 61–77).
  - Sensitivity: 48%
  - Specificity: 91%
  - PPV: 83%
  - NPV: 65%
- Fecal occult blood had fair detection of malignancy (AUC ROC 74; 95% CI, 56–93).
  - Sensitivity: 50%
  - Specificity: 99%
  - PPV: 80%
  - NPV: 95%

LIMITATIONS:

- This study had a small sample size, so the findings may not apply to the general population.
- There is no percentage for the total amount of cfDNA testing done that resulted in abnormal or non-reportable result, making it difficult to determine if the number of cancer cases being detected is like what is expected in the general population.
- There is no control group to compare to, so the findings are not generalizable to detection rates expected in a population.
- The cost of the screening tests might not be feasible for many patients outside of the study. This makes it difficult to apply the cancer screening protocol to the general population.
- No initial hypothesis was stated for the study.

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To Test or Not to Test (Yet): Assessing STI Screening Frequency in PrEP Users

Can We Screen Less Frequently for STI Among PrEP Users? Assessing the Effect of Biannual STL Screening on Timing of Diagnosis and Transmission Risk in the AMPrEP Study

Jongen VW, Zimmermann HML, Goedhart M, et al. Can we screen less frequently for STI among PrEP users? Assessing the effect of biannual STI screening on timing of diagnosis and transmission risk in the AMPrEP Study. *Sex Transm Infect*. 2023;99(3):149-155. doi:10.1136/sextrans-2022-055439

KEY TAKEAWAY: Reducing sexually transmitted infection (STI) screening frequency among pre-exposure prophylaxis (PrEP) users results in delayed diagnosis, potentially increasing transmission.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The optimal screening frequency for STIs for PrEP users is not widely agreed upon, and STI screening is costly. Because this population is at high risk of STIs, and these are usually asymptomatic, regular screening is key. This study aimed to assess whether screening could be spaced to save costs while avoiding an increase in undiagnosed STIs.

PATIENTS: Men who have sex with men (MSM) and transgender adults in Amsterdam on PrEP

INTERVENTION: Quarterly STI screening

CONTROL: Biannual STI screening

PRIMARY OUTCOME: Time to diagnosis of STIs

Secondary Outcome: Risk factors for asymptomatic STIs

METHODS (BRIEF DESCRIPTION):

- Human immunodeficiency virus (HIV) negative adults who self-reported as MSM or transgender and reported condomless anal sex with casual partners, bacterial STI diagnosis, or sex with a known HIV positive partner with a detectable or unknown viral load in the last six months were included.
- All participants were tested every three months for chlamydia and gonorrhea with urine, rectal and pharyngeal samples, and for syphilis with blood samples.
- Participants who developed symptoms of an STI or were informed of exposure to an STI by a partner were offered immediate testing and treatment, and were not included in the number of total asymptomatic STI diagnoses.
- To determine the number of asymptomatic STIs that would have been delayed in diagnosis by decreasing screening frequency, the number of STIs diagnosed at biannually scheduled visits (months 6, 12, 18 etc.) were pooled and subtracted from the total asymptomatic STIs diagnosed at all visits.
- The total number of potentially delayed STI diagnoses and incidence rate ratios of asymptomatic STI diagnosis were calculated.
- The primary outcomes measured the proportion of total asymptomatic diagnosed at quarterly intervals in comparison to overall number of asymptomatic STI diagnoses
- Secondary outcomes included multivariate analysis for determination of risk factors for development of asymptomatic STIs including age, condomless anal sex with known and unknown partners, and participation in chemsex.
    - Chemsex was defined as the use of gamma-hydroxybutyrate/gamma-butyrolactone, mephedrone, or crystallized methamphetamine around the time of sex.

INTERVENTION (# IN THE GROUP): 366

COMPARISON (# IN THE GROUP): The same 366 patients

FOLLOW-UP PERIOD: 54 months

RESULTS:

Primary Outcome –

- Quarterly visits diagnosed 483 of the 932 asymptomatic bacterial STIs (52%) compared to biannual visits (no statistical analysis completed).
- 193 of 366 participants (53%) could have transmitted these asymptomatic STIs during the delay until biannual screening (no statistical analysis available).

Secondary Outcome –

- Older age decreased risk of asymptomatic STI diagnosis (incidence rate ratio [IRR] 0.86 per 10-year increase in age; 95% CI, 0.80–0.92).
- Condomless sex with known and unknown and unknown partners increased the risk of asymptomatic STI diagnosis:

    - Known: (IRR 1.4; 95% CI, 0.80–0.92)
    - Unknown: (IRR 1.9; 95% CI, 1.5–2.3)
- Chemsex increased the risk of asymptomatic STI diagnosis (IRR 1.5; 95% CI, 1.3–1.8).

LIMITATIONS:

- The population studied were early adopters of PrEP who were mostly White and highly educated and may not be representative of the current population on PrEP.
- Participants may have changed their sexual behaviors due to the screening and testing.
- Some infections may have cleared without treatment, and some would likely have resulted in symptoms leading to patients seeking treatment resulting in an overestimation of missed infections.

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Double Shot, Same Kick: COVID and Flu Safety

Safety of Simultaneous vs Sequential mRNA COVID-19 and Inactivated Influenza Vaccines: A Randomized Clinical Trial

Walter EB, Schlaudecker EP, Talaat KR, et al. Safety of Simultaneous vs Sequential mRNA COVID-19 and Inactivated Influenza Vaccines: A Randomized Clinical Trial. *JAMA Netw Open*. 2024;7(11):e2443166. Published 2024 Nov 4. doi:10.1001/jamanetworkopen.2024.43166

KEY TAKEAWAY: Simultaneous COVID-19 and influenza vaccination results in similar rates of moderate or greater reactogenicity compared to receiving the sequential administration a few days apart.

STUDY DESIGN: Randomized placebo-controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to underpowered study)

BRIEF BACKGROUND INFORMATION: COVID-19 and influenza vaccines are often recommended to be administered in proximity. Participants have concerns regarding receiving too many vaccines simultaneously, including overall efficacy and increase in adverse events. Few studies exist comparing the safety and efficacy of simultaneous or sequential administration of vaccines for COVID-19 and influenza. This study aimed to assess the safety of simultaneous and sequential administration of COVID-19 and influenza vaccines.

PATIENTS: Nonpregnant participants who were eligible to receive COVID-19 and influenza vaccines

INTERVENTION: Coadministration or simultaneous administration

CONTROL: Sequential administration

PRIMARY OUTCOME: Composite reactogenicity
Secondary Outcome: Adverse events (AE), serious adverse events (SAE), serious adverse events of special interest (AESIs), health-related quality of life (HRQOL)

METHODS (BRIEF DESCRIPTION):

- Nonpregnant participants ≥5 years old receiving a primary two-dose mRNA COVID-19 vaccine series or nonpregnant participants ≥12 years old receiving a booster mRNA COVID-19 vaccine were included in the study.
- Participants were randomized to receive either:
  - Coadministration or simultaneous administration of intramuscular (IM) mRNA COVID-19 vaccine and either influenza standard (participants <65, 0.5mL) or high (participants >65, 0.7mL) dose quadrivalent or placebo vaccine at first visit
  - Sequential administration of IM mRNA COVID-19 vaccine and either standard (participants <65, 0.5mL) or high (participants >65, 0.7mL) dose quadrivalent or placebo vaccine at a second visit 8–15 days later
- Immunoglobulin G (IgG) levels were measured to evaluate baseline COVID-19 immunity.
- The primary outcome measured the composite reactogenicity, defined as moderate, severe or potentially life-threatening symptoms of fever, chills, myalgia, and/or arthralgia.
- The following were measured as the secondary outcomes:
  - AEs were measured as the percentage of participants with solicited and unsolicited AEs within seven days after visit one.
  - AESIs and SAEs were measured as the percentage of participants with AESIs and SAEs on days 1–121 after vaccination visits.
  - HRQOL was assessed among participants ≥12 years old on the first day and for seven days using the following scales:
    - The EuroQol 5-Dimension 5-Level Visual Analogue Scale (EQ-VAS) measures health status. Scores range from −0.109 to 1, with higher scores indicating a better self-reported quality of life.
    - The EuroQol 5-Dimension 5-Level Index (EG-5D-5L) assesses activities of daily living, mobility, self-care, usual activities, pain, anxiety, and/or depression. Scores range from 0–100, with higher scores indicating better self-reported quality of life.

INTERVENTION (# IN THE GROUP): 169

COMPARISON (# IN THE GROUP): 166

FOLLOW-UP PERIOD: Within seven days after each visit for AEs and 121 days for SAEs after the two visits

RESULTS:

Primary Outcome –

- Simultaneous administration did not significantly affect reactogenicity compared to sequential administration (26% vs 31%, respectively; site-adjusted difference −5.6 percentage points [pp]; 95% CI, −15 to 4.0).

Secondary Outcome –

- There was no significant difference in AEs, SAEs, AESIs, and HRQOL between simultaneous and sequential administration of COVID-19 and influenza vaccines.

LIMITATIONS:

- The study was underpowered to meet the noninferiority objective.
- The limited sample size may not assess less common adverse events.
- The study was not generalizable to pregnant patients, children, or older adults due to their lack of representation in the study sample.
- The trial did not evaluate the most recent (monovalent) COVID-19 vaccine that is currently available and being used.

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