Regulatory Science

45 Off-label prescription of common antidepressants: Examination of evidence available to clinicians

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OBJECTIVES/GOALS: The overarching objective of this study is to inform clinicians, patients, and other stakeholders of the level of evidence and the real-world risk-to-benefit profiles associated with older antidepressant drugs that are frequently used off-label. METHODS/STUDY POPULATION: A PubMed literature review was performed to identify clinical trials conducted in the USA between 2013 and 2023 for trazodone and 2000 and 2023 for escitalopram and citalopram. These studies were examined for robustness, due to sample size, study design, and generalizability. Findings were compared with information provided on UpToDate® LexiDrug™, a primary database used by clinicians to inform prescribing practice. To explore risks associated with off-label use, the FDA adverse event reporting system was probed to identify adverse events reported for each drug; results were systematically categorized by reason for use. To compare the volume of on-label to off-label prescriptions, data will be extracted from electronic health records from University of Southern California-affiliated hospitals. RESULTS/ANTICIPATED RESULTS: Studies conducted on off-label prescriptions of these drugs show primarily small sample sizes, pointing to a limitation in generalizability. For citalopram (N = 77) and trazodone (N = 42), over half of their off-label studies had samples of 50 participants or less. These two drugs also showed low evidence rating for off-label prescription on LexiDrug due to limited power studies. Multiple health agencies recommend against off-label prescriptions for trazodone due to insufficient evidence. There is limited data in the US regarding the volume of off-label prescriptions; however, trazodone's FAERS analysis indicated a large proportion of adverse event reports (1099/7239) come from cases where trazodone was used for insomnia, an off-label indication, compared to depression, the on-label indication (464/7239). DISCUSSION/SIGNIFICANCE OF IMPACT: With 1 in 6 Americans taking antidepressants and 40%–80% of these psychiatric prescriptions being employed off-label, there is a serious and present risk for patients regarding the safety and efficacy of these medications. Awareness must be brought to clinicians to protect patients and encourage evidence-based practice.

Research Management, Operations, and Administration

46 Do we know it when we see it? Moving toward a systematized identification of translational science

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OBJECTIVES/GOALS: We aim to establish a systematic approach to distinguish translational science from translational research. Our goal is to create a simple tool that would enable individuals with different backgrounds and levels of expertise to readily determine whether a study truly features translational science. METHODS/STUDY POPULATION: Participants were recruited from a Clinical and Translational Science Award (CTSA) program hub and randomly divided into 2 groups. One group was asked, with minimal guidance, to categorize whether publications described translational science or translational research. The group met to resolve disagreements and identify key indicators and challenges in determining whether a study involves translational science. They provided input on a set of guiding questions intended to facilitate the identification of translational science. The second group did not participate in discussion or tool development. Both groups reviewed a new set of publications, using the tool to guide their assessments. RESULTS/ANTICIPATED RESULTS: Based on publication assessments, we will assess the percent agreement among reviewers in each group for each publication and across the set. We anticipate that the first group will exhibit higher agreement for its second round of review than its first, owing to the benefit of discussion with colleagues and provision of guiding questions. We anticipate that the tool will also promote higher agreement among the second group in their first round of review. We predict that both groups will exhibit high rates of agreement when reviewing with the support of guiding questions. DISCUSSION/SIGNIFICANCE OF IMPACT: This study will help us understand interpretations of translational science, a term that has sparked debate and disagreement within CTSA hubs. If successful, the guiding questions will provide CTSAs a tool to improve training, proposal responsiveness, and review for translational science projects.

Team Science

47 A CTS approach to golden allies: Merging adoptive cell therapy and nanotechnology in the fight against brain tumors†

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OBJECTIVES/GOALS: Our lab's novel adoptive cellular therapy (ACT) significantly improves survival in brain tumor models. However, there is a lack of biomarkers to assess immunotherapy responses. Our objective is to use gold nanorods to track hematopoietic stem cell migration, a critical arm of ACT, and validate it as a prognostic biomarker. METHODS/STUDY POPULATION: Hematopoietic stem cells (HSCs) were isolated from the bone marrow of 6-week-old C57BL/6J mice and co-cultured with varying gold nanorod (GNR) concentrations and time points. GNR uptake in HSCs was evaluated with inductive coupled plasma mass spectrometry, two-photon luminescence, and tissue histology. After GNR co-culture, HSC viability and differentiation were quantified with flow cytometry and colony forming unit assays. To evaluate the impact of GNRs on HSC reconstitution, mice received myeloablative total body irradiation and intravenously received GNR-labeled HSCs. Computed tomography (CT) contrast of GNRs will be confirmed through microCT. Lastly, mice will intracranially receive KR158b

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glioma and GNR-labeled HSC bio-distribution will be measured after ACT and correlated with survival outcomes. RESULTS/ANTICIPATED RESULTS: We have demonstrated that GNRs are readily taken up by HSCs within 30 minutes, and retained within intracellular compartments, via TPL. Incubation of GNRs with HSCs did not significantly alter cell viability or differentiation, supporting the GNR's favorable biosafety profile. Colony-forming unit assays revealed that GNR incubation did not significantly disrupt the total number of colonies formed and qualitatively, colonies did not demonstrate significant lineage differences. GNR-labeled HSCs demonstrated significant reconstitution after myeloablative total body irradiation in mice. We expect that GNR-labeled HSCs will distribute to the glioma microenvironment and draining lymph nodes, positively correlating with long-term survival after ACT. DISCUSSION/SIGNIFICANCE OF IMPACT: GNRs harbored high biosafety and feasibility for tracking HSC migration after ACT. We seek to translate this theranostic tool into the current first-in-human clinical trials at our institution for patients diagnosed with neuroblastoma and diffuse intrinsic pontine glioma to improve immunotherapies against brain malignancies.

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Perinatal opioid exposure compromises placental structure and alters immune function at the maternal–fetal interface†

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OBJECTIVES/GOALS: Opioid use disorder (OUD) in pregnancy and its implications on the maternal-fetal interface has been relatively understudied. Here, we aimed to uncover the impact of maternal OUD on placental structure, function, and inflammatory responses and further stratified our findings by maternal hepatitis C (HCV) infection. METHODS/STUDY POPULATION: To address this knowledge gap, we collected placental tissue from healthy pregnancies (control) and those with opioid use disorder with and without maternal HCV infection. First, placental development was assessed by gross and histological examination of the placenta. Immune cells were then isolated from decidua (maternal) and chorionic villous (fetal) placental tissues, and the frequency and phenotype of immune subsets were determined by flow cytometry. Markers of inflammation, placental perfusion, growth factors, tissue remodeling, and vascularization were measured in placental tissue homogenate by multiplex Luminex assay. Finally, gene expression alterations in placental architecture were assessed by Visium spatial transcriptomics, integrating transcriptomic data with spatial information. RESULTS/ANTICIPATED RESULTS: Our results indicate that maternal OUD impairs placental perfusion/development and is accompanied by increased markers of inflammation in the decidua (IL-1Ra, IL-2, IL-18, IP-10, MIP-1β, and TNFα) and villous (IL-6 and IL-8). Furthermore, markers of angiogenesis and placental development are altered in the decidua, including increased EGF and IL-6Ra, but decreased FLT-1, FLT-4, and bFGF. The abundance of placental immune cells is varied with OUD/HCV, including decreased frequencies of decidual macrophages and NK cells, critical for blood supply to the fetus, and increased abundance of infiltrating maternal macrophages in fetal chorionic villous. Finally, spatial transcriptomics revealed aberrant infiltration of activated immune cells and modified processes associated with inflammation and angiogenesis. DISCUSSION/SIGNIFICANCE OF IMPACT: Altogether, these findings suggest a profound impact of maternal OUD with and without maternal HCV infection on the structure, function, and immune landscape of the maternal–fetal interface that can alter fetal development and maturation.

Biostatistics, Epidemiology, and Research Design

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Burden of trauma in incident Parkinson's disease patients

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OBJECTIVES/GOALS: We investigated the risk of trauma in the form of fractures and traumatic brain injuries (TBIs) among Medicare beneficiaries with incident Parkinson's disease (PD) age ≥67 compared to population-based controls. Secondarily, we examined the risk of death following a fracture in PD cases compared to controls. METHODS/STUDY POPULATION: We identified incident PD cases (N = 94,317) within a population-based sample of 2017 Medicare beneficiaries. Controls (N = 471,585) were matched 5:1 on month and year. We obtained claims data from 2017 to 2019 to follow cases and controls to identify new fractures treated in a hospital. Our primary outcome was any fracture. We also considered fracture type and TBI. We compared frailty level between cases and controls. We used logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between trauma and PD after adjusting for the following covariates: selected medical comorbidities, age, sex, race/ethnicity, smoking, and use of care. We used Cox regression to estimate hazard ratios (HRs) and 95% CI for trauma in cases compared to controls using the same covariates. RESULTS/ANTICIPATED RESULTS: Compared to controls, PD patients who developed a fracture were more likely to have a history of falls (OR = 2.20, 95% CI 2.08–2.34) and difficulties in walking (OR = 2.66, 95% CI 2.50–2.82). Compared to controls with a fracture, PD patients with a fracture were more likely to be moderately frail (OR = 1.43, 95% CI 1.25–1.64). PD cases had a higher risk of all fracture types, including hip (OR = 1.93, 95% CI 1.85, 2.01), spine (OR = 1.90, 95% CI 1.79, 2.02), upper extremity (OR = 1.69, 95% CI 1.58–1.80), and other traumas such as a TBI (OR = 2.14, 95% CI 1.88–2.43). PD patients had greater mortality following a fracture (HR = 1.18, 95% CI 1.13–1.24) than controls. DISCUSSION/SIGNIFICANCE OF IMPACT: The burden of trauma in the first

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