Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Tracking Referral Patterns of Peripheral Artery Disease to Improve Accuracy of Differential Diagnosis

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Introduction: Peripheral artery disease (PAD) impacts more than 8 million people in the U.S. and over 202 million people globally[1]. PAD occurs when atherosclerotic plaque accumulates in the lower extremities. In atherosclerosis, plaque occludes arteries and results in reduced blood flow to the individual's heart, brain, and extremities. Symptomatic PAD can result in pain while walking, changes in skin color as well, leg numbness, hair loss, slower growth of toenails, and others[2].

Research question: What is the prevalence rate of PAD among patients referred to orthopedic surgery, general surgery, and internal medicine for the evaluation of the lower extremity pain? What are the provider type referral patterns for patients who are newly diagnosed with peripheral artery disease and how can finding patterns of referrals lead to better care for patients?

Methodology: We used the deidentified Cerner Health Facts Database for data analysis. Patients aged 50 years or more who had the main complaint of leg pain, no history of trauma, and no previous history of PAD will be evaluated in this study. Patients would be evaluated by measuring the ankle-brachial index (ABI) by using doppler and pulse volume recording (PVR). A patient will be considered to have PAD if their ABI is below 0.9 or their PVR readings indicate anomalies or both.

Data

Specialty	Number of PAD Referrals
Internal Medicine	50,712
General Surgery	31,256
Orthopedic Surgery	5,354

Conclusion: It is critical that orthopedic surgeons, as well as primary care physicians, should increase their level of wariness for PAD when assessing patients with lower extremity pain, with a both non-traumatic and traumatic history. About a quarter of PAD patients require specialized surgical intervention[3] yet our data clearly shows that only about 10% are getting it at this time.

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Insomnia treatments and on-the-road driving performance: a systematic literature review

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Background: Insomnia involves difficulty falling asleep, maintaining sleep or premature awakening and may increase fatigue and reduce quality of life. Some insomnia treatments impair next day driving performance. Lemborexant is a new dual orexin receptor agonist (DORA) approved for the treatment of insomnia.

Objectives: This systematic literature review compared the impact of lemborexant and other insomnia treatments on next day driving performance.

Methods: Searches were done in Medline and Embase through May 2019, and in clinical trial registries. Randomized controlled trials (RCTs) included measured performance in a standardized on-road driving test in healthy volunteers or people with insomnia, were published in English, and had $\geq$ one group randomized to a recommended dose of benzodiazepines, z-drugs, trazodone, ramelteon or DORAs. Quality of trial was assessed using the National Institute for Health and Care Excellence (NICE) checklist for RCTs. Pairwise random-effects meta-analyses assessed the difference between each active treatment and placebo in standard deviation of lateral position (SDLP). Interpretation of clinical significance was based on the established benchmark equating a difference in SDLP versus placebo of +2.4 cm with a blood alcohol concentration of 0.05%.

Results: A total of 14 studies were included. Publication dates ranged from 1984 to 2019. Clinically significant differences in SDLP compared with placebo were shown in healthy volunteers for zopiclone (10/10 studies) and ramelteon (1/1 study), and in people with insomnia for flunitrazepam (2/3 studies). Premature termination of the driving test was reported most frequently for zopiclone (5/10 studies). Lemborexant 5 mg or 10 mg had no statistically or clinically significant difference from placebo in SDLP, and no premature driving test terminations (1/1 study).

Conclusion: Zopiclone (z-drug), ramelteon and flunitrazepam (benzodiazepine) were associated with impaired driving performance, similar to driving under the influence of alcohol. Premature test termination was reported most frequently for zopiclone. Lemborexant 5 mg or 10 mg had no significant effect on driving performance and no premature test terminations.

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The Role of Extracorporeal Membrane Oxygenation in Corona Virus Disease 19 Associated Acute Respiratory Distress Syndrome

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Introduction: The Corona Virus Disease 19 (COVID-19) Global Pandemic has led to the increase in the number of patients experiencing Acute Respiratory Distress Syndrome (ARDS) across the world. The World Health Organization (WHO) has recognized Extracorporeal Membrane Oxygenation (ECMO), as a therapeutic option for patients with COVID-19 associated ARDS.

Description: ECMO has becoming accepted as part of the therapeutic algorithm in the treatment of traditional ARDS refractory to conventional medical management, including lung protective ventilation, neuromuscular relaxation and proning. With the spread of the COVID-19 Global Pandemic to Europe and North America the utilization of ECMO in COVID-19 associated ARDS has increased exponentially over the past several months. With a limited body of evidence relating to COVID-19 associated ARDS and the use of ECMO, the role of ECMO in treating this disease remains to be defined. However, in environments where this resource can be provided, ECMO continues to be recommended as a therapeutic option, with data collected thus far suggesting promising outcomes. Given the significant morbidity and mortality related to COVID-19 associated ARDS, many ECMO centers have considered revising criteria for determining which patients to place onto ECMO, excluding patients with advanced age, higher BMI and in multi-system failure. Early engagement of Palliative Care Medicine is recommended to facilitate establishing goals of care for patients placed onto ECMO.

Discussion: With its established role in the treatment of traditional ARDS, ECMO has gained increasing acceptance as a treatment modality in COVID-19 associated ARDS refractory to standard medical therapies. As the number of patients receiving ECMO for COVID-19 associated ARDS continues to increase, data not only relating to outcomes, but also to demography would be valuable in identifying disparities to accessing this potentially life-saving treatment modality.

Key Words: ECMO, COVID-19, ARDS, WHO, Pandemic, Proning

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Efficacy and Safety of Lemborexant Across 12 Months in Elderly Subjects With Insomnia Disorder

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Introduction: The dual orexin receptor antagonist lemborexant (LEM) is approved in the United States and Japan for the treatment of insomnia in adults and the elderly (age ≥65y). In pivotal study E2006-G000-303 (Study 303; SUNRISE-2; NCT02952820), LEM showed significant benefit compared with placebo (PBO) on sleep onset and maintenance measures over 6 mo in adults age ≥18y; these benefits continued over 12 mo. This analysis examined efficacy and safety data for LEM across 12 mo from the elderly subgroup of Study 303.

Methods: Study 303 was a 12-mo, randomized, double-blind, PBO-controlled (first 6 mo), global phase 3 study. During the first 6 mo, subjects were randomized to PBO or LEM (5mg, [LEM5]; 10mg, [LEM10]). During the second 6 mo, LEM subjects remained on their assigned LEM dose while PBO subjects were rerandomized to LEM5 or LEM10 (data not reported here). Patient-reported (subjective) sleep outcomes were calculated based on sleep diary data. *P*-values at 6 months were based on mixed-effect model repeated measurement analysis evaluating least squares (LS) geometric mean treatment ratio (sSOL) or LS mean treatment difference (sWASO) for PBO vs LEM.

Results: 949 subjects were in the Full Analysis Set; 262 were age ≥65y (PBO, n=89; LEM5, n=87; LEM10, n=86). In subjects ≥65y, decreases from baseline in median subjective sleep onset latency (sSOL; min) for LEM5 (−21.7; $P<0.0001$) and LEM10 (−26.0; $P<0.01$) were significantly greater vs PBO (−10.8) at 6 mo. Decreases in median sSOL were maintained for LEM5 (−29.3) and LEM10 (−34.3) at 12 mo. Mean (SD) decreased from baseline in subjective wake after sleep onset (sWASO; min) were significantly greater for LEM5 (−54.8 [64.4]; $P<0.01$) and LEM10 (−51.4 [69.3]; $P<0.05$) vs PBO (−26.5 [52.9]) at 6 mo. Mean (SD) decreases in sWASO were maintained for LEM5 (−58.6 [46.0]) and LEM10 (−60.9 [80.4]) at 12 mo. The most common treatment emergent adverse events (>10% in either group) with LEM5 and LEM10, respectively, were somnolence (9.3%, 19.0%), nasopharyngitis (9.3%, 10.7%), and headache (10.5%, 6.0%) over 12 mo.

Conclusion: In subjects ≥65y, LEM demonstrated efficacy at 6 mo vs PBO, which was sustained at 12 mo. LEM was well tolerated in this subgroup.

Support: Eisai Inc.

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Efficacy and Safety of Lemborexant in Subjects Previously Randomized to Placebo for 6 Months

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Introduction: Lemborexant (LEM) is a dual orexin receptor antagonist approved in the US and Japan for the treatment of insomnia in adults. Here, we report sleep-diary outcomes from placebo (PBO) subjects who were rerandomized to LEM during the last 6 months of Study E2006-G000-303 (Study 303; SUNRISE-2; NCT02952820).

Methods: Study 303 was a 12-month, randomized, [1].double-blind, global phase 3 study of insomnia disorder in adults (≥18y). Subjects were randomized to PBO or LEM (5mg [LEM5]; 10mg [LEM10]) for the first 6 months (Period 1). During the second 6 months (Period 2), PBO subjects were rerandomized to LEM5 or LEM10; LEM subjects remained on their assigned treatments. Changes from Period 2 baseline (calculated after PBO completion) in patient-reported (subjective) sleep onset latency (sSOL) and wake after sleep onset (sWASO) are reported for rerandomized subjects.

Results: For PBO subjects (n=318) at study baseline, median sSOL (min) was 55.9 and mean sWASO (min) was 132.5 (80.2). The Period 2 baseline values for PBO-LEM5 (n=133) and PBO-LEM10 (n=125) subjects, respectively, were: median sSOL, 31.2, 34.3 and mean (SD) sWASO, 105.1 (80.6), 100.1 (84.6). Decreases (improvements) from the Period 2 baseline in median sSOL were observed at 1 month (PBO-LEM5, −3.2; PBO-LEM10, −2.9) and 6 months (PBO-LEM5, −2.7; PBO-LEM10, −5.0). Additionally, decreases (improvements) from the Period 2 baseline in mean (SD) sWASO were observed after 1 month (PBO-LEM5, −8.5 [49.4]; PBO-LEM10, −5.7 [36.1]) and 6 months (PBO-LEM5, −8.2 [49.0]; PBO-LEM10, −10.0 [58.8]). Overall incidence of treatment-emergent adverse events (TEAEs) was similar during treatment with PBO (62.7%) and with LEM (PBO-LEM5, 54.9%; PBO-LEM10, 57.7%). TEAEs were consistent with those reported in the first 6 months of treatment for subjects randomized initially to LEM at study baseline.

Conclusions: In a 12-month Phase 3 study, LEM efficacy vs PBO was observed by the first week of treatment and sustained across 6 months of LEM treatment. PBO subjects rerandomized to LEM for the second 6 months displayed additional sleep outcome improvements beyond their PBO-related response during the first 6 months. LEM was well tolerated in these subjects.

Support: Eisai Inc.

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Stent Thrombosis Among Polysubstance Use Patients

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Background: While the role of antiplatelet therapy and statins in preventing thrombosis after stent placement have been established, other factors such as substance use have also been found to be important. For example, several case studies report a higher risk of thrombosis following cocaine use [1], [2] and one small study showed an increased rate of thrombosis on long term follow up [3]. To our knowledge, there is no US-based national level study that explores substance abuse both in general and broken down to specific substances and its relationship with thrombosis after stenting. Given the possible reluctance of clinicians to proceed with coronary artery stenting for concerns of thrombosis in this particularly high-risk group, it is important to examine and quantify this risk. Our study attempts to bridge this gap by investigating thrombosis after stenting among polysubstance abuse patients relative to the general population.

Methods: We used the National Inpatient Sample database (2005-2014) to identify patients who had a history of percutaneous coronary intervention (PCI) and their rate of thrombosis, demographic characteristics, and comorbidities were explored. We then compared the proportion of individuals using various substances grouped by the occurrence of thrombosis, and the rate of thrombosis by substance used. Finally, we performed a logistic regression using stent thrombosis as the primary outcome and substance abuse as the primary exposure while controlling for age, gender, race, medical comorbidities, and the total number of substances used.

Results: Of 2,261,263 patients with a history of PCI, 45,132 (2%) had thrombosis after stenting. Most of the patients were male (61%) and white (69%). Only 36537 (1.62%) had a history of substance abuse. 51,641(2.28%) and 12,995(0.57%) had a history of alcohol and cocaine abuse respectively. Multivariate regression with substance abuse as the primary exposure was not statistically significant. However using the individual substances as the primary exposure, we found the odds of stent thrombosis was 2.53 ($p<0.01$) times higher respectively among cocaine and cannabis users compared to non-users. However, the odds of thrombosis were lower among alcohol and opioid users (0.69 and 0.70 respectively) compared to non-users.

Conclusion: Stent thrombosis is increased among cocaine and cannabis users but we found no increased risk among alcohol and opioid users.

Table 1. Summary characteristics

Variable	n	%
Age (mean)	68.91	
Sd	12.56	
Gender		
Female	878447	38.85
Male	1382708	61.15
Race		
White	1566803	69.29
Black	181323	8.02
Hispanic	119329	5.28
Asian or Pacific Islander	32800	1.45
Native American	11022	0.49
Other	48948	2.16
NA	301038	13.31
Thrombosis		
Yes	45132	2.00

continued…

[1] As defined by the NIS data variable, "cm_drug".