number of subjects (n=58) were rerandomized than planned, likely due to restrictive criteria for re-randomization. Greater overall improvement was seen with PIM relative to PBO on the key secondary endpoint, the Sheehan Disability Scale (LSM difference=–0.8, SE=0.3; P=0.004), and positive results were also seen on 7 of the 11 other secondary endpoints, including responder rate (≥50% reduction in HAMD-17 total; P=0.007), Massachusetts General Hospital Sexual Functioning Index (P<0.001), and Karolinska Sleepiness Scale for daytime sleepiness (P=0.02). Discontinuations due to adverse events were low (PIM 1.2%, PBO 3.2%). One serious adverse event was reported in each treatment group, deemed unrelated to treatment. No deaths were reported. Laboratory assessments, electrocardiography, and changes in vital signs were unremarkable, and no new safety signals were reported.

CONCLUSIONS: Study data provide evidence of the efficacy, safety, and tolerability of adjunctive PIM in treating MDD inadequately responsive to SSRI or SNRI therapy. Efforts to confirm these results are ongoing in a Phase 3 program. Funding Acknowledgements: ACADIA Pharmaceuticals Inc.

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The Brain Becomes What the Brain Does

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ABSTRACT: The lack of current research regarding teacher knowledge about early life stress (ELS) in children needs to be expanded. The purpose of this study was to assess teacher knowledge, educational training levels, and their individual ability to identify signs and symptoms of ELS. Participants were given the Early Life Stress Assessment Survey. The statistical analysis of respondent survey data indicated that 85% of survey participants had little or no knowledge of the topic and have not attended at least one professional training course or seminar. This result was significant, because 96% of participating teachers indicated they had students who have experienced ELS in their classrooms. Additionally, participants were asked to identify signs and symptoms of ELS versus other types of learning disabilities. The average survey score was 58% correct answers.

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Antidepressant Adherence and Alternative Future Options in Pacific Islander Youth

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ABSTRACT: Objectives: To investigate the current response to psychopharmacology and transcranial magnetic stimulation (TMS) in Pacific Islander adolescents with Major Depressive Disorder (MDD).

BACKGROUND: 40-60% of youth with Major Depressive Disorder (MDD) have a limited response to current treatment protocols and require either (a) medications with a wider side effect profile, (b) intensive psychosocial programs that interfere with school, and/or (c) publicly spurned options (electroconvulsive therapy). Such results are tempered further when working with Pacific Islanders, as such youth and families have shown in multiple studies. The aversion to such standard treatment is concerning, as Native Hawaiian adolescents have a higher risk of suicide than other adolescents in Hawaii (12.9/100,000 youth per year). With this in mind, the investigators wondered how a novel, non-pharmacological approach to depression treatment in children, transcranial magnetic stimulation (TMS), would fair.

METHODS: 2 literature searches (utilizing Pubmed, Ovid, Google Scholar, and OneSearch) were conducted on 6/10/19: 1 investigating rTMS in adolescent depression, the other researching rTMS in depression in Native Hawaiian or other Pacific Islander youth.

RESULTS: At this point in time, 10 studies exist testing TMS' effects in children and adolescents with treatment refractory depression. 9 of said studies were open-label trials; 1 was a small (n=2) RCT (with both patients randomized to the active arm). Of those evaluating depression severity through Children's Depression Rating Scale-revised ("CDRS-R") scores, 100% of the trials (8/8) displayed a statistically significant improvement. None of the trials of the 1st series of searches nor the entirety of the 2nd series yielded information as to how TMS fairs in Native Hawaiian or other Pacific Islander youth.

CONCLUSIONS: No studies exist that can verify the efficacy of TMS in youth, of Oceanic origin or otherwise, with the same degree of scrutiny as currently done in adults. Therefore, our group is engaging in a pilot study to evaluate the performance of TMS for the treatment of MDD in Native Hawaiian and other Pacific Islander adolescents aged 12-17; we are planning on then progressing on to a sham-controlled RCT in a larger sample size of the

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same population to test its efficacy in not just Pacific Islanders, but all youth.
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Insulin Sensitivity and Glucose Metabolism of Olanzapine and Combination Olanzapine and Samidorphan: A Phase 1 Exploratory Study in Healthy Volunteers

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ABSTRACT: Background: A combination of olanzapine and samidorphan (OLZ/SAM) is in development for schizophrenia to provide the efficacy of olanzapine while mitigating olanzapine-associated weight gain. The objective of this phase 1 exploratory study was to assess metabolic treatment effects of OLZ/SAM.

METHODS: Healthy, non-obese adults (18–40 years) were randomized 2:2:1 to once-daily OLZ/SAM, olanzapine, or placebo for 21 days. Assessments included oral glucose tolerance test (OGTT), hyperinsulinemic-euglycemic clamp, weight gain, and adverse event (AE) monitoring. Treatment effects were estimated with analysis of covariance.

RESULTS: Sixty subjects were randomized (OLZ/SAM, n=24; olanzapine, n=24; placebo, n=12); 19 (79.2%), 22 (91.7%), and 11 (91.7%), respectively, completed the study. In the OGTT, olanzapine led to significant hyperinsulinemia (P<0.0001) and significantly reduced insulin sensitivity (2-hour Matsuda index) at day 19 vs baseline (P=0.0012), changes not observed with OLZ/SAM. No significant between-group differences were observed for change from baseline in clamp-derived insulin sensitivity index at day 21. Least squares mean weight change from baseline was similar with OLZ/SAM (3.16 kg) and olanzapine (2.87 kg); both were significantly higher than placebo (0.57 kg; both P<0.01). Caloric intake significantly decreased from baseline to day 22 with OLZ/SAM (P=0.015) but not with olanzapine or placebo. Forty-nine subjects (81.7%) experienced ≥1 AE (OLZ/SAM, 87.5%; olanzapine, 79.2%; placebo, 75.0%).

CONCLUSIONS: In this exploratory study, hyperinsulinemia and decreased insulin sensitivity were observed in the OGTT with olanzapine but not with OLZ/SAM or placebo. Clamp-derived insulin sensitivity index and weight changes were similar with OLZ/SAM and olanzapine in healthy subjects during the 3-week study.
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The Safety and Tolerability of Lumateperone 42 mg for the Treatment of Schizophrenia: A Pooled Analysis of 3 Randomized Placebo-Controlled Trials

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ABSTRACT: Introduction: Lumateperone (ITI-007) is in late-phase clinical development for schizophrenia. Lumateperone has a unique mechanism of action that modulates serotonin, dopamine, and glutamate neurotransmission.

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