ABSTRACT: Study Objectives: Sexual dysfunction occurs in 40%-60% of patients with major depressive disorder (MDD), due to either the illness itself and/or the effects of antidepressant treatment. The phase-2 CLARITY trial recently demonstrated the efficacy of adjunctive pimavanserin (PIM) for MDD when added to ongoing selective serotonin or serotonin–norepinephrine reuptake inhibitor (SSRI/SNRI) treatment. No new safety observations were reported in this study. This post-hoc analysis examines the potential impact of PIM treatment on sexual function.

METHOD: Study methodology has been presented previously (APA 2019). Adult male and female patients with moderate-to-severe MDD were randomized to PIM 34 mg/day (n=51) or placebo (PBO, n=152) added to ongoing SSRI/SNRI treatment. Massachusetts General Hospital–Sexual Functioning Inventory (MGH-SFI) and Hamilton Depression Rating Scale, 17-item version (HAMD-17) item 14 (sexual interest) scores were examined by analysis of covariance.

RESULTS: Adjunctive PIM resulted in significantly greater 5-week reduction (improvement) relative to SSRI/SNRI treatment plus placebo on mean MGH-SFI scores (difference –0.634, SE 0.167; P<0.001; effect size [ES], Cohen's d 0.614). Similarly, PIM resulted in greater improvement compared with placebo on individual MGH-SFI items that applied to both males and females: Interest in Sex (P=0.006; ES=0.483), Ability to Get Sexually Aroused/Excited (P=0.001; ES=0.560), Ability to Achieve Orgasm (P<0.001; ES=0.609), Overall Sexual Satisfaction (P=0.003; ES=0.524). HAMD-17 item 14 scores were also significantly more reduced (improved) with PIM (P<0.001; ES=0.574).

CONCLUSIONS: These results underscore the potential of adjunctive PIM for improving sexual function in patients with MDD and inadequate response to SSRIs/SNRIs. Potential benefits should be confirmed in further studies. Funding Acknowledgements: ACADIA Pharmaceuticals Inc.

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A Phase-2 Sequential Parallel Comparison Design Study to Evaluate the Efficacy and Safety of Adjunctive Pimavanserin in Major Depressive Disorder

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ABSTRACT: Study Objectives: Depression is the leading cause of disability worldwide, with fewer than 50% of treated patients achieving full remission. This study ("CLARITY," ACP-103-042: NCT03018340) examined the 5-HT2A inverse agonist pimavanserin (PIM) as a potential adjunctive treatment for major depressive disorder (MDD).

METHOD: Adult female and male subjects with a DSM-5 primary diagnosis of a major depressive episode as part of MDD, inadequate response to ongoing SSRIs or SNRIs of adequate dose and duration as confirmed by the Massachusetts General Hospital Antidepressant Treatment History Questionnaire, and a MADRS total score >20 were randomized to PIM 34 mg/day or placebo (PBO) added to their SSRI/SNRI treatment. A sequential parallel comparison design was used, consisting of two 5-week stages. PBO nonresponders in Stage-1 who met prespecified criteria were re-randomized to PIM or PBO for the second period (Stage-2). The primary efficacy measure was the weighted average of Stage-1 and Stage-2 total scores of the HAMD-17.

RESULTS: Of the 207 patients enrolled, 52 received PIM, and 155 received PBO in Stage 1. Mean age was 46.2 years, and 72.9% of patients were female. Baseline MADRS total (mean [SD]: 31.5 [0.4]) and HAMD-17 total scores (22.2 [0.3]) indicated a moderate overall severity of illness. PIM met the primary endpoint, reducing the weighted Stage-1/Stage-2 HAMD-17 total score relative to PBO (least-square means [LSM] difference, –1.7; standard error [SE], 0.9; P=0.04). Stage-1 PIM patients demonstrated highly significant 5-week improvement on the HAMD-17 (LSM difference=–4.0, SE=1.1; P<0.001; effect size, Cohen's d: 0.626), separating from placebo by the end of Week 1 (LSM difference=–1.7, SE=0.8; P=0.04). Stage-2 results showed no significant separation among Stage-1 placebo nonresponders (P=0.69). In Stage 2, a substantively smaller

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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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