

The following abstracts were presented as posters at the 2013 NEI Psychopharmacology Congress.

Congratulations to the Scientific Poster Competition winners of the 2013 NEI Psychopharmacology Congress

1st Place: James Arthur Halgrimson, DO. 2nd Place: Michelle Magid, MD; Jason Reichenberg, MD; and Poppy E. Poth, CCRC. 3rd Place: Kathryn D. Moseley, MS, RD; Colleen G. Azen, MS; Martha Jean Ottina, PhD; and Shoji Yano, MD

Poster Titles:

1. Details of P450 Enzymes Role in Metabolism of Pharmaceuticals
2. The Treatment of Depression using Botulinum Toxin A: A 24 week Randomized, Double-blind, Placebo-controlled Study
3. Pilot Study to Evaluate the Effects of Tetrahydrobiopterin on Adult Individuals with Phenylketonuria with Measurable Maladaptive Behaviors

Apathy. Who Cares? An Evolutionary Concept Analysis

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BACKGROUND: There is a lack of proper definition for apathy in the research literature. Apathy has been identified as a separate syndrome than depression, however, continues to be confused with depression.

MATERIALS AND METHODS: A concept analysis utilizing the evolutionary approach was employed. In 2012, a literature search using Cumulative Index of Nursing and Allied Health Literature Plus with Full Text was conducted. Searching the keyword of apathy in all fields retrieved 653 results. Using a systematic approach, results were reduced to 36 publications.

RESULTS: Several advances in the use of the term and clinical applications were discovered. A significant breakthrough was made by an establishment of diagnostic criteria for clinical use. Apathy was defined in terms of comparison to depression, altered motivation, emotionality, activity, interest, initiative, and its pathophysiology.

CONCLUSIONS: Advances of the development of apathy as well as clinical use have been made. Separate treatment approaches have been suggested that are different from the battery of treatment for depression. Further studies are needed to fortify the concept of apathy as well as apply it to clinical use.

Details of P450 Enzymes Role in Metabolism of Pharmaceuticals

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ABSTRACT: Since their discovery in the 1960s, P450 metalloenzymes have long been noted to be a key component in the breakdown of hydrocarbon substrates across all forms of life. Most interestingly, in the human body, 57 specific isoforms of P450 enzymes have been characterized as key components of pharmaceutical metabolism. As research continues to reveal further details of specific interactions between the P450 enzyme superfamily and modern psychopharmacological agents, research continues to demonstrate details of P450 enzyme-drug interactions, and their subsequent effects on overall pharmacological metabolism. This study reveals evidence of key reaction intermediates that have long been hypothesized to exist as a key intermediate in the hydroxylation, epoxidation, sulfoxidation and overall biochemical alteration of psychopharmacological agents in the human body.

Clozapine and Cardiomyopathy: A Case Report

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ABSTRACT: Introduction: With increasing usage of clozapine in treatment resistant cases of schizophrenia,

it is important to shed light on one of the rare side effects of clozapine: cardiomyopathy! A potentially life threatening condition. The purpose of this discussion is to highlight the current prescribing guidelines for initiation of clozapine and the causal relationship between clozapine and cardiomyopathy.

CASE PRESENTATION: This is a case of a 24 y/o healthy man with chronic schizophrenia who has been complaining of distressing auditory hallucinations resistant to many trials of mono and combination antipsychotic therapy. Ultimately, patient was placed on clozapine reaching a maximum daily dosage of 250 mg. One year later, the patient presented to the medicine clinic with palpitations. An EKG showed tachycardia. Echocardiography showed his LVEF to be markedly reduced (25–35%) with moderate to severe global hypokinesis of the left ventricle. A coronary angiogram showed no evidence of CAD. The patient was diagnosed with dilated cardiomyopathy. Clozapine was discontinued but it was re-started at a lower dosage and titrated to 100 mg po daily due to the re-emergence of severe psychotic symptoms. Six months later, there was no improvement in his cardiac MRI with LVEF 30%. One year later, clozapine was discontinued and LVEF in echocardiography increased from 30% to 40–50%.

DISCUSSION: It is highly likely that his cardiomyopathy was caused by clozapine. There was no family history of heart disease. The patient has no CAD risk factors. His EKG prior to clozapine initiation was normal. The patient did not have a baseline echocardiogram which would have been helpful in comparing his heart condition before and after the initiation of clozapine. The patient was placed on a beta blocker and an ACE inhibitor but improvement was noted only after clozapine was discontinued. The patient presented to the medicine clinic with tachycardia which is commonly considered a benign side effect from many antipsychotics. Clinicians should be vigilant that high clinical suspicion with tachycardia in patients taking clozapine warrants a cardiac work up.

CONCLUSION: Clozapine may be associated with fatal myocarditis and cardiomyopathy in physically healthy young adults. The literature shows in some cases that cardiomyopathy improves after clozapine is stopped. For at least the initial four weeks of treatment, patients should be closely monitored for nonspecific symptoms such as fatigue, flu like symptoms, tachycardia with EKG at baseline, vital signs at each visit, and then weekly laboratory testing including CPK, troponins, inflammatory markers, a CBC looking for eosinophilia. A baseline echocardiography is not a must but could be crucial in specific clinical situations. Following the guidelines could serve to alert the clinicians of not yet symptomatic myocarditis which if left untreated, might progress to cardiomyopathy, a life threatening condition.

Vasovagal Syncope After Initial Dose of Quetiapine: A Case Report

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ABSTRACT: Introduction: Side effects of medication often become one of the most important factors in determining course of treatment for psychiatric patients. Doctors must be aware certain side effects, such as vasovagal syncope, can be very dangerous if they occur outside a monitored environment.

CASE DESCRIPTION: This is a report of 27 year old Asian female who recently moved to the United States with no significant past psychiatric or medical history who was brought in to the psychiatric emergency room by her husband because of depressed mood, paranoid ideation and auditory hallucinations. She was started on quetiapine 25 mg and had a vasovagal response to her first dose. The patient was started on aripiprazole 5 mg daily to target the auditory hallucinations and citalopram 10 mg for a depressed mood. Patient was switched from aripiprazole to quetiapine 25 mg Q12 H for more optimal mood stabilization. The patient received her first dose of quetiapine in the late morning. Two hours later, the patient was in the dining area began complaining of blurry vision. She stood up and fell with a brief loss of consciousness. She regained consciousness but was dizzy. Vital signs were checked- BP 47/21 and HR 55. Patient vomited and lost consciousness again. A rapid response team was called. After 5 minutes, the patient was awake and alert with stable vital signs. A medical work up revealed no cause for her vasovagal episode. She was stabilized psychiatrically on citalopram 20 mg daily and aripiprazole 10 mg daily and discharged. She has had no episodes of syncope since.

DISCUSSION: If risk factors for vasovagal syncope as a side effect of quetiapine were able to be identified, physicians could take these into consideration when initiating treatment. A literature review did not reveal any studies however, several patient centered websites mention such a relationship. One such website reported that 717 of 63,381 people reported syncope on quetiapine, with the majority of syncopal episodes occurring within 1 month of starting quetiapine. This may be an underreported phenomenon warranting further investigation.

OBJECTIVES: Identify how commonly vasovagal syncope occurs as a side effect of quetiapine. What are the risk factors for developing this side effect and are there ways to mitigate this risk.

RELEVANCE: Vasovagal syncope is a very serious and potentially dangerous side effect that physicians should be aware of when prescribing quetiapine. This case highlights 1 patient that experienced vasovagal syncope after her first dose of quetiapine which highlights the importance of more research about such a potentially dangerous side effect and any possible risk factors to be aware of that may be considered when prescribing quetiapine.

WORKS CONSULTED: “From FDA reports: Seroquel and Syncope”, <http://www.ehealthme.com/ds/seroquel/syncope>, accessed July 11, 2013.

Neurocardiogenic syncope; *BMJ* 2004 August 7; 329 (7461): 336-341.

Efficacy of Cariprazine on YMRS Single Items: A Pooled Analysis of 3 Randomized, Double-Blind, Placebo-Controlled Trials in Bipolar Mania

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ABSTRACT: Background: Cariprazine (CAR) is an orally active and potent dopamine D3/D2 receptor partial agonist with preferential binding to D3 receptors currently in development for the treatment of mania. Bipolar mania is a debilitating disease for which optimal clinical treatments require broad antimanic efficacy. CAR has demonstrated efficacy in 3 randomized, double-blind, placebo-controlled trials (NCT01058096, NCT01058096, NCT01058096) in bipolar mania. This pooled analysis evaluated the effects of CAR on YMRS single-items to investigate efficacy across mania symptom domains.

METHODS: Data were pooled from 3 cariprazine studies in patients with acute manic or mixed episodes associated with bipolar I disorder. CAR was flexibly dosed (3–12 mg/day) in 2 studies; the third study used a fixed/flexible dose design (3–6 mg/day, 6–12 mg/day). All 3 studies consisted of a washout period of up to 7 days followed by 3 weeks of double-blind treatment. Patients were hospitalized for screening and ≥ 14 days of treatment. Post hoc pooled analysis analyzed change from baseline to Week 3 in individual items of the Young Mania Rating Scale (YMRS) using an MMRM approach.

RESULTS: A total of 1037 patients (CAR, n = 608; PBO, n = 429) were included in the pooled ITT population, defined as patients who received ≥ 1 dose of study medication and had ≥ 1 postbaseline YMRS assessment.

In each of the individual trials, CAR showed significant advantage vs PBO on YMRS total score improvement (LSMD: -4.3 to -7.0 ; $P < .0001$ [all studies]). In the pooled analyses, the LSMD for CAR vs PBO was significant for all YMRS items: elevated mood (-0.38 [95% CI: -0.53 , -0.24], $P < .0001$), increased motor activity-energy (-0.34 [95% CI: -0.49 , -0.18], $P < .0001$), sexual interest (-0.29 [95% CI: -0.42 , -0.17], $P < .0001$), sleep (-0.33 [95% CI: -0.48 , -0.19], $P < .0001$), irritability (-0.85 [95% CI: -1.07 , -0.63], $P < .0001$), speech (-0.69 [95% CI: -0.93 , -0.46], $P < .0001$), language (-0.33 [95% CI: -0.46 , -0.20], $P < .0001$), content (-0.78 [95% CI: -1.05 , -0.51], $P < .0001$), disruptive-aggressive behavior (-0.69 [95% CI: -0.89 , -0.50], $P < .0001$), appearance (-0.23 [95% CI: -0.33 , -0.13], $P < .0001$), and insight (-0.24 [95% CI: -0.34 , -0.14], $P < .0001$). In general, CAR treatment showed at least moderate effect sizes (Cohen's d) on all YMRS items, with estimates ranging from -0.31 (increased motor activity) to -0.55 (irritability).

CONCLUSION: Cariprazine demonstrated efficacy on all individual YMRS items in this pooled analysis. These results suggest that cariprazine has broad efficacy across symptoms in the treatment of acute mania associated with bipolar I disorder.

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Utilizing Computerized Cognitive Training to Enhance Working Memory for Students with Learning and Attention Disorders

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ABSTRACT: Working memory (a component of executive functioning) has been well documented as a significant predictor of academic outcomes (e.g., reading and math achievement as well as general life outcomes). The purpose of this study was to investigate the effectiveness of computerized cognitive training to improve working memory in a school setting. A total of 81 students with a mean age of 12.8 years were recruited from a private school in southern California that specializes in providing education to children with learning disabilities and attention disorders. Participants were assessed for levels of WM and completed a total of 20 hours of computerized cognitive training across 10 weeks. Analysis indicated that students with delayed working memory made gains in both measures of working memory (i.e., verbal and visual working memory) while their typical peers did not. Additionally, it was found that delayed students were able

to approximate the visual working memory abilities of their typical peers at the end of the training. These findings show that computerized cognitive training is an effective intervention for children with working memory deficits, particularly in the area of visual working memory. Implications of these findings are discussed.

Cardiovascular Reactivity: An Unbiased Metric of Chronic Pain in Disability Claimants?

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ABSTRACT: Pain is multifaceted and subjective. Obtaining unbiased ratings of pain severity from validated measures is lacking but needed for clinical evaluation and treatment of chronic pain patients. Historically, accurate ratings of pain severity are confounded by patient “illness behavior,” i.e., symptom magnification from helplessness and fear avoidance on the one hand and by medical examiners who are prone to disbelief on the other. Prior research suggests that impairment in baroreflex regulation of cardiovascular (CV) arousal relates to central mechanisms that control chronic pain severity (1,2,3). These findings suggest that measuring the response to orthostatic stress may generate a valid unbiased science-based measure of pain severity. The assessment protocol is easily administered requiring just the use of an electronic blood pressure recorder. This assessment protocol is based on two previously published procedures (4,5,6).

The main objective of this case study is to find out whether the CV response to orthostasis is associated with chronic pain severity and whether it is useful in the evaluation of disability claimants that are affected by abnormal illness behavior as well as physician examiner bias.

Cardiovascular (CV) data were obtained in 34 men and 16 women (47+/-11 years of age) with chronic pain and litigated injury disability claims. Changes in systolic blood pressure (SBP) were examined in response to postural challenge at two different points in time over the course of a day devoted to completing a standardized psychodiagnostic assessment protocol. SBP was measured 4 times when lying supine with eyes closed for 6–8 min, followed by 4 additional readings after standing up with eyes open for 6–8 min. BP was measured at 1-min intervals. One set of measures were made at the beginning of the day before the standardized psychodiagnostic assessment protocol was initiated (session 1). A second set of measures were made approximately 6 hours later upon completion of the assessment protocol (session 2).

SBP changes were found to discriminate disability claimants according to self-reported pain severity, emotional distress, and pain magnification. Profile analyses (adjusted for sex, age, and BMI) showed that (i) high scores of pain severity are significantly associated with an increase in SBP from session 1 to 2, compared to a decrease for low scores; (ii) high scores of pain magnification are significantly associated with an increase in SBP from a late point of measurement when lying down (supine) to an early point of measurement after standing up when compared with SBP decrease in low scores of pain magnification; (iii) high scores of pain-related emotional distress are significantly associated with a decrease in SBP from early- to mid-measurement after standing up compared to a SBP increase for low scores. Moderation analyses showed that the observed effects of pain measures on cardiovascular arousal changes were independent of each other and of patient “illness behavior” estimated by MMPI-2.

The findings suggest that CV responses to challenging psychosocial (psychodiagnostic assessment) and physical (orthostasis) situations may be a useful assessment in evaluating pain severity in injured workers with chronic pain and litigated disability claims. Further research is needed to validate these findings and to determine how these relationships are affected by litigated disability claims.

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A Safety, Tolerability, and Effectiveness Study of Nuedexta (Dextromethorphan 20 mg/Quinidine 10 mg) for Treatment of Pseudobulbar Affect (PRISM-II)

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ABSTRACT: Study Objectives: Pseudobulbar affect (PBA) is a neurological condition characterized by uncontrollable, inappropriate outbursts of laughing and/or crying, which typically occur several times per day and may be highly distressing to patients and caregivers. PBA symptoms arise from disruption of the neural network regulating emotional expression. Although PBA can be caused by a variety of neurological conditions, including brain injury, stroke, and neuronal degeneration, clinical manifestations and pathology are similar. Dextromethorphan 20 mg/quinidine 10 mg (DMQ) is currently the only FDA-approved treatment for PBA. DMQ safety and efficacy studies were conducted in patients with two distinct neurological conditions: amyotrophic lateral sclerosis and multiple sclerosis. A large, open-label study (N = 553) of patients with PBA due to a variety of conditions provided additional safety data; however, effectiveness was not studied. PRISM II evaluates the safety, tolerability, and effectiveness of DMQ for treatment of PBA in patients with dementia, stroke, or traumatic brain injury (TBI).

METHODS: PRISM-II is a nationwide, open-label, multi-center, 12-week study enrolling up to 750 patients (minimum 200 each with dementia, stroke and TBI) aged ≥ 18 years. Patients must have a clinical diagnosis of PBA and score ≥ 13 on the Center for Neurologic Study-Lability Scale (CNS-LS), an established PBA rating instrument. Patients will be treated with DMQ twice daily. The primary endpoint is mean change from baseline in CNS-LS score. Determination of effectiveness will be based on magnitude of CNS-LS change and comparison with results of previous Phase III studies conducted with DMQ in PBA patients. We will also assess PBA episode counts (laughing and/or crying),

Mini-Mental State Examination, visual analogue scale for quality of life, Clinician Global Impression of Change (CGIC), Patient Global Impression of Change (PGIC), patient treatment satisfaction, and Patient Health Questionnaire (PHQ-9) (to evaluate mood symptoms). Safety measures include adverse event monitoring, concomitant medication usage, and vital signs.

RESULTS: Enrollment status and any preliminary data will be presented.

CONCLUSION: This study intends to provide a prospective assessment of DMQ effectiveness and safety in patients with PBA and dementia, stroke, or TBI.

FUNDING: Avanir Pharmaceuticals, Inc.

Demographics and Clinical Profile of 'Psychiatric Frequent Flyers' to the Emergency Department in Tertiary Care Hospital settings

Varinderjit Parmar, MD, Ewa Talikowska-Szymczak, MD, and Peter Szymczak, MD

ABSTRACT: INTRODUCTION: Worldwide there has been an increasing interest focusing on a group of individuals who contribute a disproportionate number of visits to the ED for psychiatric reasons. Frequent users of the ED services are proven to be a diverse group of patients that provide a challenge to emergency physicians. These "frequent flyers" have been shown to have more psychiatric, psychosocial, and substance abuse issues than the general population.

PURPOSE: This study aims to find out frequent users' demographics, most common presenting diagnosis and emergency services utilization patterns in tertiary care centers. Data obtained from this study may permit for early identification of that patient population and more efficient utilization of PES resources.

METHOD: Data for emergency psychiatric visits at 2 tertiary care hospitals were obtained for a 5-year period from April 2006 to March 2011. The data includes dates, times, gender, marital status, age, and primary diagnosis. Primary Diagnosis was also sorted into eleven diagnostic clusters. Frequent flyers were defined as individuals who attended the hospital 5 or more times during the 5 years of the data sample. The data was coded separately for these individuals to include the number of visits to the ER over 5 years, their average age, and their most common diagnosis given at ER visits. A descriptive analysis was performed to assess the characteristics of 'frequent flyers' and the nature of their hospital visits.

RESULTS: Frequent flyers represented 2.18% of 6919 total attendees to the two emergency departments. Visits by frequent flyers, made up 15.76%. Frequent flyers were found to be 68.9% male and 31.1% female, with an average age of 40.55. The average number of visits made by a frequent flyer was 10.37 visits over 5 years. Approximately 11% of frequent flyers attended the hospital 20 or more times. Substance use was found to be the most common primary diagnosis (58.3%), anxiety disorders (15.2%) and schizophrenia and psychotic disorders begin the (13.2%); mood disorders, adjustment disorders, somatoform and dissociative disorders, personality disorders and childhood disorders accounted for the remaining 13.2% of primary diagnoses.

CONCLUSION: Frequent flyers were much more likely to present with a diagnosis of substance use and of schizophrenia and psychotic disorders and much less likely to have anxiety or mood disorders. Frequent flyers generally came into the emergency room with more than one type of diagnosis. Frequent flyers' visits had much higher instances of arriving in an ambulance, slightly higher chances of being brought in by the police, and a significantly lower chance of being a walk-in visits. Frequent flyers were more likely to have the classification of urgent (triage code status) than the nonfrequent flyer group. The average length of ER visit was not found to be significantly different for frequent flyers compared to nonfrequent flyers.

Effect of Lunar Phase Cycle (Full Moon) on Psychiatric Emergency Room Presentation in Tertiary Care Hospital Settings

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ABSTRACT: Introduction: Even today, many of us think that mystical powers of the full moon induce erratic behaviors, psychiatric hospital admissions, suicides, homicides and emergency room calls. There has long been a perceived correlation between the effect of lunar cycles on human behavior and illness severity. Studies of the effects of moon cycles on mental disorders and psychiatric emergencies have always been of interest, yet, previous studies on the effect of lunar phases on psychiatric admission rates have been inconsistent.

PURPOSE: The purpose of this study is to find the link between full moon phases of the lunar cycle and various psychiatric presentations in tertiary care settings, including patients' gender and age within in a five-year time span.

METHOD: Charts of all psychiatric emergency room patients were reviewed retrospectively. Data for emergency psychiatric visits at 2 tertiary care hospitals was obtained from a five-year period, April, 2006 to March, 2011. Emergency room presentations were divided by ICD -10 criteria into 11 categories. The data was compiled from a computerized log created to record all psychiatric consultations performed by mental health services at these 2 hospitals. Collected data included patients' visit times, dates, genders, ages, and primary diagnosis. The percentage of patients who were evaluated on non-full moon days was compared to the percentage of patients evaluated on full moon days.

RESULTS: In this analysis we compared the clustered diagnoses of participants who presented at the Kingston hospitals during the full moon to those of a control group of patients that did not present on the full moon. Patients were included in the full moon group who presented from 6 pm to 12 am on the first day of the full moon and 12 am to 6 am on the second day of the full moon. A Chi-Squared analysis was used to compare the frequencies of diagnoses in the full moon patients to those of the control group. Age and gender demographics were also observed between the groups.

CONCLUSION: No significant differences were found between the patients presented on full moon night and the control groups, indicating that there is no change in the frequency of presentation of different diagnoses between these groups. A significant difference was found between the different age groups. Patients presented to psychiatric emergency on full moon nights are younger than those who presented on non-full moon nights. There was no significant difference between the gender distribution of the patients presented on full moon and non-full moon nights.

Residential Treatment for Combat Stress: A Comprehensive Approach

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ABSTRACT: STUDY OBJECTIVES: Moncrief Army Community Hospital (MACH) created the Combat Stress and Addictions Recovery Program (CSARP) to meet the comprehensive needs of behavioral health patients suffering from post deployment issues. The

model incorporates a comprehensive, “wrap-around” experience that is patient and family centered and includes local commands as part of the treatment team. While cognitive processing therapy is the core of this model, CSARP also incorporates nutrition, physical therapy, mindfulness meditation, biofeedback, pain management, financial management, spiritual counseling and pharmacotherapy into the program. The CSARP model is innovative because it is the Army’s first residential, multi-disciplinary program that utilizes a holistic approach with active duty soldiers in the Army. Previously utilized outside civilian programs limited the scope of services they offered, preventing patients from addressing all their issues prior to their return to work.

METHOD USED TO EVALUATE THE EFFECTIVENESS: CSARP patients are combat veterans who are in need of intensive treatment for combat stress and other unhealthy behaviors who pose no imminent safety risk. Soldiers complete self-administered outcome measures upon admission and at discharge. The outcome measures used to examine the program’s effectiveness include: The Satisfaction with Life Scale, Purpose in Life Test, Spiritual Attitude Inventory, Occupational Satisfaction Index (OSI-R), Leisure Boredom Scale, Lock Wallace Marital Adjustment Test, Post Traumatic Cognitions Inventory (PTCI), Beck Depression Inventory-II (BDI-II), Epworth Sleepiness Scale, PCL-M, Outcome Questionnaire (OQ-45), WHO-QOL-BREF, Multidimensional Sexual Self Concept Questionnaire and the SF-36 Questionnaire. Predictive Analytics SoftWare, version 18 (PASW) was used to analyze the data. Several Paired Samples T Tests were conducted to compare the means of pre and post-test measures.

RESULTS: There were statistically significant findings on the PCL-M, $t(17) = 3.70$, $p = .002$, the PTCI, $t(17) = 4.50$, $p = .000$, and the BDI-II, $t(11) = 4.51$, $p = .001$, indicating a significant decrease in reported symptoms of PTSD and depression.

CONCLUSIONS: The demand for effective treatment of post-deployment stress continues to grow as troops return home. The CSARP model offers several benefits. The residential component allows for “front loading” of therapies, potentially decreasing the need for outpatient treatment. Soldiers are assimilated into local support networks which they will continue to utilize upon discharge. The program is also cost effective and allows family member participation without any travel expenses or logistical complications. In conclusion, if CSARP patient outcomes continue to mirror the positive findings cited in previous studies, the program

can possibly become the AMEDD model for residential treatment of PTSD.

FUNDING: No Funding sources for this study.

Residual Fatigue During Treatment with SSRI for Major Depressive Disorder: Secondary Analysis of STAR*D

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ABSTRACT: Introduction: Fatigue is one of the most common and incapacitating symptoms of major depressive disorder (MDD) (Fava, 2003). Moreover, it contributes significantly to relapse and disability as well as diminished health-related quality of life (HRQOL) (Menza et al., 2003; Baldwin & Papakostas, 2006; Swindle et al., 2001). Patients who are partial responders to antidepressant treatment identify fatigue as one of the most common and bothersome residual symptoms (Fava et al. 2006). This secondary analysis of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D; Rush et al., 2004; Fava, 2003), a study that comprised a series of real-world treatment trials in a broadly representative group of outpatients with MDD, describes the fluctuations in symptoms of fatigue, and consequences on outcomes, during Level 1 treatment with citalopram.

METHODS: The STAR*D Level 1 database included 2,876 subjects who were eligible for analysis. In this analysis of the public domain database, question 14 (energy level) from the Quick Inventory of Depressive Symptomatology (QIDS-SR16) served as a proxy for fatigue. Patients were grouped into one of four groups by fatigue status: none (no fatigue at Level 1 entry or exit), treatment emergent fatigue (no fatigue at entry, fatigue at exit), remission (fatigue at entry, none at exit), and residual fatigue (fatigue at both entry and exit).

RESULTS: Of the 2,840 patients with complete data, 99 (3.5%) were classified as having no fatigue during Level 1, 59 (2.1%) had treatment emergent fatigue, 954 (33.6%) had fatigue that remitted during treatment, and 1728 (60.8%) had residual fatigue. Within those with residual fatigue, 795 (46.0%) demonstrated some improvement of fatigue, 746 (43.2%) maintained stable

levels, and 187 (10.8%) worsened over the course of treatment. The rate of Hamilton Depression Rating Scale17-defined remission (<8) at Level 1 exit across the residual fatigue groups was significantly different (39.4% from the “no fatigue” group, 20.3% of the “treatment emergent” fatigue group, 56.1% of the “remitted” fatigue group, and 11.6% of those with “residual symptoms” of fatigue ($p < .0001$)). Satisfaction and enjoyment in various domains of functioning (QLES-Q) was also impacted by residual fatigue, with highest outcome scores observed in the groups with no fatigue (63.1 ± 18.9) or remitted fatigue (69.1 ± 19.1) symptoms compared to those with treatment emergent (46.6 ± 16.3) or residual fatigue (46.5 ± 19.0) during treatment ($p < .0001$). Similar results were observed for physical and mental functioning, measured by the SF-12.

CONCLUSIONS: The majority of patients (60.8%) experienced persistent fatigue during depression treatment, despite relief of depression symptoms. Optimal outcomes were more likely to be achieved in patients without fatigue at Level 1 exit. Baseline predictors and outcomes associated with residual fatigue are described further.

FUNDING: This study was funded by Eli Lilly.

Impact of Fatigue on Outcome of SSRI Treatment: Secondary Analysis of STAR*D

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ABSTRACT: Introduction: Fatigue is one of the most common and incapacitating symptoms of major depressive disorder (MDD) (Fava, 2003). Moreover, it contributes significantly to relapse and disability as well as diminished health-related quality of life (HRQOL) (Menza et al., 2003; Baldwin & Papakostas, 2006; Swindle et al., 2001). Patients who are partial responders to antidepressant treatment identify fatigue as one of the most common and bothersome residual symptoms (Fava et al. 2006). The current secondary analysis of data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D; Rush et al., 2004; Fava et al., 2003), a study that comprised a series of real-world treatment trials in a broadly representative group of outpatients with MDD, describes the relationship of baseline fatigue to outcomes of Level 1 monotherapy treatment with citalopram.

METHODS: The STAR*D Level 1 database included 2,876 subjects who were eligible for analysis. In this secondary analysis of the public domain database, question 14 (energy level) from the Quick Inventory of Depressive Symptomatology (QIDS-SR16) served as the proxy for fatigue. The current analysis explores presenting characteristics and outcomes of those with baseline fatigue.

RESULTS: Of the 2,868 with complete data, 158 (5.5%) endorsed the response of “0; no change in usual level of energy”, 657 (22.9%) reported “1; tires more easily than usual”, 1536 (53.6%) endorsed the response of “2; makes significant personal effort to initiate or maintain usual daily activities”, and 517 (18.0%) had a score of “3, unable to carry out most of usual daily activities due to lack of energy.” Being female, unemployed, and having fewer years of education and lower monthly income were associated with higher rates of baseline fatigue (all $p < .0001$). Adjusted analyses indicated that higher levels of fatigue at baseline were significantly associated with a decrease in the likelihood of achieving remission (QIDS-SR score <6) at the end of Level 1 treatment (OR = 0.811, $p = 0.0001$, 95% CI (0.729, 0.903)). Baseline fatigue was also associated with satisfaction and enjoyment in various domains of functioning (Q-LES-Q), with those with higher baseline fatigue experiencing lower satisfaction ($\beta = -2.575$, $p < .0001$). Those with higher scores on baseline fatigue also demonstrated poorer mental and physical functional outcomes, as measured by SF12 Mental ($\beta = -1.283$, $p = .0016$) and Physical ($\beta = -1.058$, $p = .0003$) subscales.

CONCLUSIONS: The current analysis presents baseline demographic and clinical characteristics of patients in STAR*D, by differing levels of baseline fatigue. Groups differed in outcomes experienced from Level 1 treatment with citalopram, with increased levels of fatigue at study entry associated with reduced likelihood of remission, decreased overall satisfaction, and reduced mental and physical function at outcome.

FUNDING: This study was funded by Eli Lilly.

Rechallenging Clozapine after Neuroleptic Malignant Syndrome

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ABSTRACT: Neuroleptic malignant syndrome (NMS) is a potentially fatal manifestation of antipsychotic use

associated with symptoms like mental status changes, muscle rigidity, fever and autonomic dysfunction. It is known to be associated more with typical antipsychotics but atypical antipsychotics like Clozapine are not exempt from this side effect. Clozapine is one of the most effective antipsychotics for refractory schizophrenia, but when patients develop life threatening adverse effects like NMS, treatment options become limited. Here we present a case of a patient who developed typical symptoms of NMS with Clozapine and was rechallenged with Clozapine successfully.

CASE SUMMARY: The patient was a 24 year old female with a diagnosis of schizoaffective disorder, bipolar type, who presented with paranoia, auditory command hallucinations and bizarre behavior. She was tried on three antipsychotics and three mood stabilizers which included Paliperidone. However she did not show improvement and her behavior continued to be disorganized, including but not limited to drinking out of the toilet bowl, taking several cold showers daily and having auditory hallucinations. Clozapine was started and titrated upwards. Five days after commencing Clozapine, at a dose of 100 mg, she developed typical NMS features including muscular rigidity, fever, mental status changes, elevated Creatine Kinase (CK - 3078 U/L), leukocytosis and urinary incontinence. Of note is that the patient was on Lithium concomitantly. She was transferred to the medical service, treated with IV hydration and her psychotropic medications were stopped. The patient was re-admitted to psychiatric unit after her NMS symptoms resolved and she was medically stabilized. No psychotropic medications were started for two weeks and then clozapine was rechallenged at a low dose of 25 mg at bedtime and titrated upwards slowly over a period of 10 days to 200 mg daily totally. Her symptoms improved and she was at her baseline on discharge after an inpatient stay of almost 4 months totally.

DISCUSSION: A review of literature revealed only 5 reports (1991–2001) of patients who had developed typical NMS with Clozapine who were rechallenged with the drug after an average time of 8.5 weeks. In consensus patients who develop NMS with Clozapine can be rechallenged after a reasonable period of time; 2 weeks in our patient. Concomitant use of Lithium has been shown to be associated with increased neurotoxic effects. Rechallenge is usually successful if care is taken to avoid concurrent use of Lithium and other psychotropics, dosing by starting at low doses and titrating upwards slowly while monitoring closely for emerging NMS symptoms. Serial CK levels can be adopted for more close monitoring. Although NMS with Clozapine is rare, physicians should be aware that emergence of NMS should not be a deterrent to rechallenging the drug again, provided slow careful dose titration is done.

Lithium, Hypercalcemia and Hyperparathyroidism - What Psychiatrists Need to Know

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ABSTRACT: Introduction: Lithium has many well known side effects like leucocytosis, hypothyroidism, weight gain, renal abnormalities including diabetes insipidus and cardiac arrhythmias. One adverse effect which is not so much in the forefront in psychiatry is hypercalcemia and sometimes associated hyperparathyroidism. Here, we present a patient who presented with lithium toxicity, altered mental status, hypercalcemia, hyperparathyroidism and also nephrogenic diabetes insipidus with a specific focus on what psychiatrists need to know in managing hypercalcemia and hyperparathyroidism.

CASE REPORT: Mrs.A was a 66 year old Caucasian female with a psychiatric history of schizoaffective disorder. She was admitted for altered mental status and agitation from an outside hospital due to Lithium toxicity. Her lithium level was reported to be 3.4mEq/L initially but was around 1mEq/L on admission. She was found to be in acute renal failure with hypernatremia and hyperthyroidism and was diagnosed with Lithium induced Nephrogenic Insipidus. iCal was critically high at 1.62 mmol/L, total Calcium was 11.2 mg/dl. She was aggressively treated with free water replacement and DDAVP. Lithium was stopped. Further evaluation revealed that PTH was high at 484.8 pg/ml (normal 15–65 pg/ml). In a few days, her mentation improved. Nephrology recommended starting cinacalcet 30 mg daily. A Sestamibi scan did not show any definitive evidence of Parathyroid adenoma but was limited due to patient noncompliance. At this point iCal was 1.54 mmol/L and the total calcium was down at 10.0 mg. She had also been given one dose of IV zoledronic acid. Once the patient had been medically stabilized and her mental status had improved, she was discharged home on cinacalcet 30 mg bid to follow up with nephrology and the medical team.

CONCLUSION: Lithium has been known to cause hypercalcemia by altering the set point of calcium sensing receptors. Hypercalcemia and hyperparathyroidism have been seen in up to 10–15% of people on long term lithium in some studies. Stopping lithium may reverse this finding. If hypercalcemia persists many options exist -careful observation alone, treatment with cinacalcet or parathyroidectomy in patients with parathyroid adenomas. The importance in treating this lies in the fact that many patients whose psychiatric symptoms were not under control reported symptomatic improvement once

their endocrine irregularities were corrected. Prior to starting Lithium, baseline PTH and calcium levels should be established. No standard recommendations exist but some authors suggest that the levels be checked at least on a yearly basis and sooner in patients showing symptoms of hypercalcemia. Psychiatrists have to be aware of hypercalcemia and hyperparathyroidism as a side effect of Lithium use and should incorporate screening and regular checks of parathyroid function as part of their treatment.

Chronic Spinal Pain Primarily Produces Dual Channel Depressive Illness

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ABSTRACT: Study Objective: Determine the nature of major depressive (MD) spectrum illness among chronic spinal pain patients. Specifically, this study sought to assess the proportion of such patients suffering from serotonergic (5HT), nor-adrenergic (NA), or dual channel (co-morbid 5HT and NA) deficiency symptoms of MD illness.

METHOD: One hundred consecutive chronic spinal (cervical and/or lumbar) pain patients with residual MD symptoms who were referred for specialty psychiatric care, were evaluated. All patients had been treated with an anti-depressant by their primary care or pain clinic physician, but continued to exhibit debilitating depression, thus their referral. The evaluations included the Symptom Questionnaire (SQ) and the Clinical Assessment of Depression (CAD), both administered via computer, as well as a structured psychiatric interview designed to a) confirm the presence of an MD illness using DSM4tr criteria and b) determine the presence of 5HT deficiency (e.g. loss of interests, hopelessness, guilt) and NA (low energy, poor concentration/attention, psychomotor retardation) symptoms. Patients were classified according to their having predominantly 5HT deficiency, NA deficiency, or mixed (dual channel 5HT and NA) deficiency symptom clusters.

RESULTS: Of the 100 patients, 56 were male, 44 were female; the age range was 29 to 63, with an average of 44 years. 63 patients suffered from chronic lumbar pain alone, while 23 suffered from cervical pain alone, while 14 suffered from both. All patients had been treated with an appropriate dose of an SSRI antidepressant for an appropriate length of time (60+ days). The most

common agent used was citalopram, followed by escitalopram, and sertraline. 94 patients were found to suffer from MD with dual channel (mixed, 5HT and NA symptoms). Six patients suffered from MD with predominantly 5HT symptoms. All patients obviously continued to exhibit MD despite adequate pharmacotherapy with an SSRI alone. The 94 patients with dual channel MD, were switched to either venlafaxine, desvenlafaxine, or duloxetine (all dual channel antidepressants) and titrated to effect. After an average of 60 days, 91 of these patients attained remission, defined as no longer meeting MD criteria and normalization of previously elevated CAD depression scores. Among the six 5HT deficiency patients, all were placed on supra-therapeutic doses of their original SSRI, and all eventually attained remission.

CONCLUSIONS: The vast majority (94%) of chronic spinal pain patients in this study suffered from dual channel MD, and had not achieved remission, at referral, despite adequate prior treatment with an SSRI. Remission was attained for 91% of the patients after a switch to a dual channel agent. These results indicate the need to assess for MD type in chronic pain patients, and they call for increased use of dual channel antidepressants as first line treatment for such patients.

FUNDING: None.

Treatment of a High Functioning Individual with Traumatic Brain Injury and Subsequent Emotional Volatility with Dextromethorphan/Quinidine

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ABSTRACT: Treatment of a High Functioning Individual with Traumatic Brain Injury and Subsequent Emotional Volatility with Dextromethorphan/Quinidine Pathological laughing and crying, or pseudobulbar affect (PBA) has been described in patients with a variety of neurological disorders, including multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), epilepsy, brain tumors, Alzheimer's disease, and traumatic brain injury since the nineteenth century. PBA is characterized by uncontrollable, inappropriate episodes of laughing or crying after minor stimuli that would not typically cause such an outburst and are embarrassing or socially awkward when they occur for the individual with PBA. Dextromethorphan/Quinidine (DM/Q) has been

demonstrated to be effective in the treatment of PBA in individuals with ALS or MS (Pioro 2010). We report a case of an individual who was assaulted and suffered a TBI and subsequently developed PBA who was successfully treated with DM/Q. This individual had an improvement in not just his PBA, but also ability to manage intrusive memories, when taking DM/Q. This suggests that individuals who have developed PBA as a result of TBI could potentially benefit from DM/Q. It also raises the possibility that there is a neuroanatomical and/or neurophysiological disorder that manifests itself clinically as PTSD that responds to DM/Q. There is no evidence that this individual experienced any adverse effects or harm from taking DM/Q. He was being treated with several medications and receiving cognitive, occupational, vestibular and other therapies at the same time he was treated with DM/Q, so it is not possible to attribute his clinical improvement solely to the DM/Q. However, the fact that he discontinued the medication and then had a worsening of symptoms, and then restarted the medication with improvement of symptoms suggests that he was benefiting from the DM/Q. Further studies are required to determine if DM/Q is effective in the treatment of PBA in TBI.

Pilot Study to Evaluate the Effects of Tetrahydrobiopterin on Adult Individuals with Phenylketonuria with Measurable Maladaptive Behaviors

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ABSTRACT: Objectives: To evaluate the effects of tetrahydrobiopterin (BH4) on maladaptive behavior in patients with PKU.

METHODS: In an effort to determine if BH4 has any effects on the central nervous system, we studied 10 individuals with measurable maladaptive behaviors for one year. Behavioral assessments using the Vineland Adaptive Behavior Scales-Second Edition and a PKU Behavior Checklist were obtained at baseline, six months, and at the end of the study. Biochemical measures including plasma amino acids were obtained quarterly and phenylalanine (Phe) and tyrosine (Tyr) were obtained monthly.

RESULTS: Out of the ten subjects, two were responders to BH4, as determined by a blood Phe reduction >30%. While blood Phe in the eight non-responders did

not change significantly throughout the study, their Tyr levels were significantly higher at six months ($p = 0.012$), but not at 12 months ($p = 0.23$). By the end of the study, eight subjects exhibited fewer maladaptive behaviors on the components of the Vineland Maladaptive Behavior Index and all 10 had lower total scores on the PKU Behavior Checklist.

CONCLUSION: These findings suggest there may be direct effects of BH4 on the central nervous system independent of lowering blood Phe.

FUNDING: BioMarin Pharmaceutical provided the study drug and support for this study.

Synthetic Cannabis "K2" Intoxication and Psychiatric Manifestations

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ABSTRACT: Objective/Background: The emergence of new "designer drugs" has changed in the epidemiology of substance abuse. The synthetic cannabinoid popularly known as "K2" or "Spice", has become a growing health concern. The most common presenting symptoms are severe agitation often accompanied by aggression, tachycardia, panic attacks and psychosis. The objective of this report is to describe symptoms seen with K2 use.

METHOD: For the past 6 months, we identified over 50 patients with K2 intoxication presenting in our psychiatric emergency room. Ingestion is based on patients' admission of usage or report by a family member since we do not test for this drug. All patients presented with severe agitation, disorganized thoughts and assaultive behavior. Most of them were 18-25 year old males who required admission to an inpatient psychiatric unit for stabilization and treatment.

RESULTS: Synthetic cannabis or "K2" has similar but much more potent effects compared to natural cannabis. It is a full agonist at the cannabinoid receptor type 1 (CB1) in the brain. It can have severe neurotoxic effects and there are even reports in the literature of death in healthy adolescents and young adults.

CONCLUSION: K2 intoxication must be considered in the differential diagnosis in patients who present to psychiatric emergency rooms with psychosis, severe agitation or panic attacks even if routine toxicologies

are negative. The long term effect of these new synthetic compounds a unknown and the clinical guidelines for managing symptoms are evolving.

FUNDING: No funding.

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Postictal EEG Suppression During Early Course of ECT (Electroconvulsive Therapy) Predicts Clinical Improvement in Bipolar Disorder

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ABSTRACT: Background and Introduction: Electroconvulsive therapy (ECT) is an effective treatment for major affective disorders and has been used for many decades. In affective disorders the capacity to achieve and sustain remission over lengthy periods of time may indicate less vulnerability to subsequent relapses and /or chronic psychosocial disability. Once the phase of acute treatment is over the goal of treatment is to prevent further episodes of illness by prophylaxis. Lithium, anticonvulsant mood stabilizers and some atypical antipsychotics have been used in this regard as mood stabilizers to sustain remission and to prevent further episodes. The combined use of ECT and anticonvulsants has been a clinical scenario with paucity of literature apart from some open trials and a retrospective chart review. To date there has been little research on the management of psychiatric patients maintained on the anticonvulsant medications who also receive ECT.

METHODOLOGY: In the background of clinical scenarios involving use of anticonvulsants with ECT we conducted a randomized controlled trial - with three limbs wherein the dose of the medication was stopped/halved or continued at full doses. We could ensure that 75% of the sample (i.e. 36 patients) out of 48 patients were given the randomized doses of medications. The number of patients in each limb was as follows - stop group(10), half dose(14) and full dose(24). A blind rater assessed the patients using psychopathology scales - YMRS, HDRS, CGI and cognitive assessment scale - PGI memory scale. ECT was administered using standard equipment. EEG recording was done at every session and analyzed by the blind rater.

All three groups were similar in baseline and ECT variables ensuring adequacy of randomization.

RESULTS: The results showed no significant difference in the scores of patients- both in terms of psychopathology and cognitive domains assessment. Some suggestion towards faster improvement in the group taking full dose of the anticonvulsants was found using RMANOVA. This was seen in the patients who presented with manic symptoms and were assessed with YMRS (40 out of 48 patients). EEG analysis showed an inverse correlation between postictal fractal dimension and CGI scores. Though the study has many strengths in terms of design an important limitation has been the reduction in the sample size due to exclusion of patients.

Cool or Cold? Freon® Abuse - A Case Report and Discussion

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ABSTRACT: Introduction: Freon is the trademark name of a group of hydrochlorofluorocarbons used as refrigerator coolants .They are odorless, colorless, non-corrosive & non-flammable. Even though they are being replaced with less environmentally-harmful hydrocarbons due to concerns of ozone depletion, the name is still used to refer to these coolants. There is very little awareness among physicians about Freon abuse in spite of multiple media reports of deaths due to accidental & intentional coolant exposure. Freon gas abusers typically obtain it from air conditioning units. A small instrument like a key or a spoon is used to depress the valve & release the gas which is either inhaled directly or “bagged”. We present a case of a patient who had cold injuries to the face after recreational freon abuse.

CASE: Mr.D is a 33 year old male diagnosed with schizoaffective disorder and cannabis abuse who presented to ER after his first time huffing Freon gas from an air conditioning unit to “get high”. He had abused nitrous before and was looking for a similar experience. After huffing the gas with his mouth over the opening of the valve, he passed out & woke up sometime later with the gas still freely flowing. Within the hour, he developed increasing swelling & numbness of his lips, mouth & cheek which brought him to the ER. On exam, there was significant swelling of both upper, lower lips & cheeks, desquamation of the lower lip & bleeding of the upper gums. There was no pharyngeal or tongue swelling. The only lab finding was leukocytosis of 18.7.

Laryngoscopy showed no signs of respiratory compromise. He improved with IV steroids & was discharged two days later with oral antibiotics & follow up.

DISCUSSION: Inhalants are often the first drugs of abuse children are exposed to. An NDPS report from 2011 showed 6398 cases of Freon toxicity out of which only 1183 were intentional inhalation. 19 deaths were noted in this report. Access to air conditioner units is easy, inexpensive & requires very little equipment. Gas chromatography is needed to detect the hydrocarbons in specimens as it is undetectable in standard drug screens. Exposure to Freon gas causes a variety of systemic symptoms & cold injuries like blisters & frost bite. Long term effects are impaired cognition, delayed responses & mood instability. Fatalities are mainly by respiratory depression, cardiac arrhythmias & accidental trauma. It is very important for medical providers have to be aware of coolants as a source for inhalant abuse, screen for it and be vigilant in similar scenarios. Children & adolescents need to be educated about the ill effects of huffing Freon. Using locks for the air conditioner compressors also can be another option. As abusers know very little about the ill effects of huffing freon gas, education remains the most important factor in preventing adverse events.

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“Psychosis Post Psychedelic Party” - A Case Study of LSD Induced Late Psychosis in a 19 Year Old Patient

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ABSTRACT: BACKGROUND: Lysergic acid diethylamide (LSD) is a psychedelic drug, which is used for its mind altering properties. It has been reported to induce changes in mood, thought process, judgment as well as sensory perceptions. The effects are highly variable. LSD affects a large number of receptors, including all dopamine receptor subtypes, and adrenoreceptor subtypes. The psychedelic effects of LSD are attributed to its strong partial agonist effects at 5-HT_{2A} receptors; it binds to most serotonin receptor subtypes except for 5-HT₃ and 5-HT₄. Its exact mechanism of action is unknown, but it is thought to work by increasing glutamate release causing excitation. There has been

some literature on LSD induced psychosis and mood instability. We report a case of a 19-year-old woman with no previous psychiatric history who developed psychotic and manic symptoms 4 days after ingestion of LSD.

CASE: The patient is a 19-year-old female with no past psychiatric diagnosis who was brought to the hospital by her father with concerns of bizarre behavior after LSD use. She reportedly consumed an unknown quantity of LSD for the first time 4 days before admission. She was fixated on “Girls, boys, sex and molestation” and stated that she was in the hospital to “see her family”. Per dad, she has been behaving oddly for the last few hours. She was paranoid, having frequent mood swings, talking excessively and responding to internal stimuli. On exam, she maintained an intense stare, was disorganized, had delusions of persecution and auditory hallucinations. She was started on risperidone 1 mg twice daily then increased to 3 mg daily. She developed a dystonic reaction which resolved with Benadryl but her psychosis did not show any improvement. Risperidone was discontinued and olanzapine was added on which the patient showed improvement. She was eventually discharged after 10 days of hospitalization with a recommendation to follow up as an outpatient. Her family had reported a past history of teratoma so a detailed work up was done and was negative for NMDA autoantibody encephalitis.

CONCLUSION: There are very limited studies on the causes, risk factors, pharmacokinetics and dynamics of LSD and its related illnesses. There is some literature mostly between the 1960s and 1970s about LSD induced schizophrenia and similar disorders. It is a speculation that LSD rapidly crosses blood brain barrier by oral ingestion and inhibits the serotonergic systems, which further precipitate mania or depression secondary to the alteration in CNS norepinephrine. Stress can also increase norepinephrine levels, which may be a factor in the case of our patient owing to her social situations. Certainly this is only a hypothesis at this time and warrants further studies and investigation in the cause and the course of the disease.

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Improved Adherence and Cost Savings From a Pharmacogenetic-Based Psychiatric Intervention

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ABSTRACT: Study Objective(s): Tools for more personalized practice of medicine are only just beginning to enter wider clinical use. The utility of this genetic information as it pertains to clinical decision-making, treatment effectiveness, costsavings, and patient perception remains to be fully understood. The objective of this study was to assess the effect of clinician access to patient genetic information on subsequent patient compliance and direct costs.

METHOD: In this retrospective study, we examined health claims data in order to assess the adherence rates and healthcare costs for patients suffering from psychiatric disorders. These patients were analyzed as cases, or patients whose clinicians ordered a genetic test that assists in treatment-based clinical decision-making, versus controls, or patients who did not have the genetic test. Cases and controls were propensity score matched in order to reduce confounding in treatment selection. An initial study of 111 cases and 222 controls was performed for both adherence and healthcare costs, and a replication study of 116 cases and 232 controls was performed in which only adherence was assessed.

RESULTS: Overall, the patients who had genetic testing were significantly more medication adherent ($p = 1.56 \times 10^{-3}$; Cohen's $d = 0.511$) than patients without genetic testing and showed a relative cost savings of 9.5% over a four month observation period (\$562 total cost savings).

CONCLUSIONS: These results suggest that pharmacogenetic testing in psychiatric populations may improve patient adherence while demonstrating cost-effectiveness. Randomized, controlled trials will be necessary to better characterize the direct impact on clinical outcomes, to address potential sources of confounding, and to identify the populations in which this testing may be most useful. Also, more data about the clinician and patient attitudes and experiences with personalized medicine will further refine how pharmacogenomics is used in practice, and could further influence the effectiveness and cost savings of this type of testing in healthcare.

FUNDING: This study was funded by Genomind, LLC.

At Antipsychotic-Like Effective Doses, Cariprazine Displays Potent Dopamine D3 and D2 Receptor Occupancy In Vivo and Efficacy Across Animal Models

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ABSTRACT: Background: Cariprazine (CAR) is an orally active and potent dopamine D3/D2 receptor partial agonist with preferential binding to D3 receptors. Balanced and potent functional blockade of the D3 and D2 receptors may result in benefits on cognitive deficits and augmented effects on mood and negative symptoms. We evaluated the CAR dose relationship between D3 receptor occupancy, functional activity, and efficacy in different animal models.

METHODS: Striatal D2 and cerebellar D3 receptor in vitro affinity and in vivo occupancy in rats was determined using the high affinity agonist radioligand [³H](+)-PHNO. Established rat models of antipsychotic, procognitive, anxiolytic, antidepressant, and anti-manic activity were used to evaluate the effects of CAR, aripiprazole (ARIP), and risperidone (RISP) at various doses in rats.

RESULTS: CAR, ARIP, and RISP demonstrated in vitro affinity for both D2 receptors (K_i [nM]: CAR, 2.65; ARIP 22.7; RISP, 5.61) and D3 receptors (K_i [nM]: CAR, 3.90; ARIP, 243; RISP, 9.17). CAR showed potent antipsychotic-like efficacy on conditioned avoidance response and amphetamine-induced motor activity tests (ED₅₀: 0.8 and 0.1 mg/kg). It was as potent as RISP (ED₅₀: 0.9 and 0.2 mg/kg) and more potent than ARIP (ED₅₀: 18 and 3.9 mg/kg). At antipsychotic-like effective doses, CAR, ARIP and RISP, displayed high in vivo occupancy of D2 receptors (ED₅₀ [% max inhibition]: CAR, 0.23 mg/kg [99.3]; RIP, 7.65 mg/kg [91.9]; RISP, 0.29 mg/kg [89.2]); however, only cariprazine displayed potent in vivo occupancy of D3 receptors (ED₅₀ [% inhibition]: CAR, 0.43 mg/kg [99.3]; ARIP, >30 mg/kg [26.4]; RISP: ~2.3 mg/kg [53.4]). In agreement with this, chronic treatment with cariprazine, but not RISP, at antipsychotic-like effective doses resulted in significant increases in D3 receptor binding level in several brain regions. Additionally, CAR at doses at or below its antipsychotic-like effective doses demonstrated anti-manic-(minimum effective dose, MED: 0.06 mg/kg), antidepressant- (MED: 0.03 mg/kg), anxiolytic-like (MED: 0.2 mg/kg), and procognitive (MED: 0.02 mg/kg) efficacy

in rat models. In mice, procognitive and antidepressant-like effects were shown to be mediated via the D3 receptor as demonstrated using D3 receptor knockout mice studies.

CONCLUSION: At antipsychotic-like effective doses in rats, CAR demonstrated balanced and significant occupancy at both dopamine D2 and D3 receptors; other antipsychotics displayed high D2 receptor occupancy with relatively low D3 receptor occupancy. These results suggest a distinct functional blockade of D3 receptors by CAR not seen with other atypical antipsychotics. Additionally, at antipsychotic-like doses CAR demonstrated efficacy in different rat models of psychosis/mania, mood, anxiety, and cognition. The distinct D3 receptor mechanism of action may provide potential clinical benefits in improving cognitive deficits and mood symptoms.

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Initial 2-Week Outcomes Following 2 Methods of Switching to Iloperidone From Risperidone in Patients with Schizophrenia

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ABSTRACT: Objective: Changing (switching) antipsychotics is a common therapeutic strategy when a patient's current antipsychotic has limited efficacy/tolerability. We report results observed within the first 2 weeks following a switch to iloperidone (ILO) from risperidone (RIS).

METHODS: This analysis used data from a 12-week, multi-center, open-label outpatient trial evaluating 2 approaches (gradual vs immediate) to switching to ILO in adults with schizophrenia exhibiting efficacy and/or tolerability problems with RIS, olanzapine (OLA), or aripiprazole (ARI). 500 Patients (aged 18–64y) diagnosed with schizophrenia and experiencing inadequate efficacy and/or poor tolerability were switched from 1 of 3 preswitch agents: RIS (n = 175), OLA (n = 155), or ARI (n = 170). Patients were randomized 1:1 to either a gradual-switch (ie, dose reductions over the first 2 weeks [to 50% on Day 1, 25% at Week 1, 0% at Week 2]; n = 240) or an immediate-switch group (ie, immediate discontinuation of current

treatment at baseline; n = 260) to open-label ILO (all patients starting on Day 1). ILO was titrated over 4 days to 6 mg BID, followed by increases (≤ 4 mg/d) up to 12 mg BID, if needed. The primary variable was the Integrated Clinical Global Impression of Change (I-CGI-C), rated from 1 (improvement) to 7 (worsening). The primary analysis time point was at Week 12.

RESULTS: For patients switching from RIS, over the first 2 weeks of ILO treatment, discontinuations for any reason occurred in 9.9% of patients in the gradual-switch group and 7.4% in the immediate-switch group. Discontinuations due to treatment-emergent adverse events (TEAEs) were higher in Week 1 vs Week 2 in the gradual-switch group (3.7% to 0%) but not in the immediate-switch group (4.3% to 5.5%). The incidence of spontaneously reported TEAEs was higher during Week 1 compared with Week 2 for both groups (gradual switch, 39.5% to 15.4%; immediate switch, 41.5% to 35.2%). Analysis of ILO's most common TEAE associated with RIS-to-ILO switch (dizziness) revealed lower rates in patients switched from RIS gradually (6.2%) vs immediately (11.7%) during Week 1. At Week 2, both switch groups demonstrated a decline from Week 1 rates (0%, gradual; 4.4%, immediate). In addition, I-CGI-C scores improved for both the gradual- and immediate-switch groups over the first 2 weeks: the percentage of patients with a rating of much or very much improved on the I-CGI-C (ie, responders) was 7.4% (Week 1) and 16.0% (Week 2) for the gradual-switch group and 12.8% (Week 1) and 30.9% (Week 2) for the immediate-switch group.

CONCLUSION: Switching from RIS to ILO either gradually or immediately demonstrated subtle clinical differences regarding clinical response within the first 2 weeks of therapy. Whereas the gradual-switch method (ie, cross-titration) revealed lower initial rates of dizziness, the immediate-switch method appeared to yield a higher percentage of responders within the first 2 weeks.

Tobacco Related Disorders - Hidden Comorbid DSM Diagnoses in Patients with Schizophrenia and Other Psychotic Disorders

Varinderjit Parmar, MD, Ewa Talikowska-Szymczak, MD, Peter Szymczak, MD, and Dianne Groll, PhD

ABSTRACT: LEARNING OBJECTIVES: To find out whether physicians explore nicotine dependence/Abuse/withdrawal in schizophrenic population. To know if physicians document nicotine dependence/Abuse/

withdrawal in schizophrenic population on Axis 1. To highlight the importance of complete nicotine screening in psychiatric population and then documenting it on Axis 1.

INTRODUCTION: The treatment of smoking behavior in psychiatric patients remains a challenge for most mental health professionals. The population of mentally ill persons is being disproportionately affected by the tobacco epidemic. In Canada, about one in five people are affected by mental illness, and an estimated 50% of them (and up to 90% of patients diagnosed with schizophrenia) are smokers. Methods Charts of all psychiatric emergency room patients were reviewed retrospectively. Data for emergency psychiatric visits at the Kingston General hospital and Hotel Dieu Hospital was obtained from a five-year period, April 2006 to March 2011. The data was compiled from a computerized log created to record all psychiatric presentations to the 2 tertiary care hospitals (Kingston General hospital and Hotel Dieu Hospital). Collected data included patients' visit times, dates, genders, ages, and primary diagnosis. Schizophrenic patient population was sorted out and retrospective charts were reviewed done to find out whether nicotine dependence/abuse/withdrawal was explored and documented.

RESULTS: Out of 502 patients diagnosed with schizophrenia and other psychotic disorders, only 43.4% (218 patients) were found to have documented nicotine use status [24% (119 patients) recognized as smokers and 20% (99 patients) as non - smokers] either in their history or in one of their diagnostic Axes. Remaining 56% (284 patients) did not have any signs of their nicotine use status reported, which means that more than a half of the patients had not been assessed in regards to their nicotine usage or results of their assessments have not been documented.

CONCLUSIONS: We found only 43% patients, who were diagnosed with schizophrenia and other psychotic disorders, to have their nicotine smoking status reported in their medical documentation. Even if recognised in the history, there is a lack of appropriate documentation of existing nicotine - related disorders in the diagnostic Axis 1, which results in nicotine related disorders being under diagnosed and overlooked. None of the patients enrolled in our study had their nicotine smoking status documented under Axis I, whereas 88% of patients had it reported only in their history. There is a great need for implementation of appropriate education for all mental health professionals in regards to the appropriate nicotine use and nicotine related disorders recognition and diagnosis.

Seasonal Variations of Psychiatric Emergency Presentations to the Tertiary Care Hospital Settings

Varinderjit Parmar, MD, Ewa Talikowska-Szymczak, MD, Peter Szymczak, MD, and Dianne Groll, PhD

ABSTRACT: BACKGROUND: Referrals to psychiatry account for a large proportion of primary care, and in-hospital medical and paramedical services. Visitations to the ER are often observed to follow certain seasonal patterns. Few studies have focused on seasonal presentations of psychiatric illness in the emergency room setting. No significant studies have focused on gathering data on seasonal presentations of psychiatric illness in an emergency department of a tertiary care center.

OBJECTIVES: To determine seasonal patterns of psychiatric diagnoses presented to the emergency department in tertiary care settings. To examine seasonal variations of basic demographics, such as age and gender, of psychiatry patients presented to emergency room in tertiary care settings. To assist departments of psychiatry to better equip emergency room resources and to better educate the staff and learners based on results of this study.

METHODS: Charts of all psychiatric emergency room patients were reviewed retrospectively. Data for emergency psychiatric presentations from 2 tertiary hospitals was obtained from a five-year period. Emergency room presentations were divided by ICD -10 criteria into 11 categories. The data was first divided according to season (winter, spring, summer, and fall). Seasonal trend of psychiatric diagnoses was studied.

RESULTS: In this study we examined the seasonal difference in emergency room presentations of mental diagnoses. The data was first divided according to season (winter, spring, summer, fall), and then all seasons were compiled to form a baseline rate, which was then used in comparison with individual seasons. A One-Way ANOVA was first used to determine if there were any differences between the total presentations between the seasons, and it was found that there were no significant differences between the number of presentations. To examine the difference in age between the seasonal groups, a One-Way ANOVA was completed that compared the average age of people presenting to the ER between the four seasons.

CONCLUSIONS: Psychiatry patients who presented in the fall were significantly younger than those who presented in all other seasons. As well, psychiatry patients who presented in the summer were significantly

older than those who presented in all other seasons. The Presentation of psychiatry patients in cluster “substance related disorder” was significantly higher during fall seasons as compared to the baseline. As well, clusters “adjustment disorder”, “anxiety disorder” and “others” were significantly lower than baseline during fall seasons. During fall seasons, as compared to baseline, there were less significant decreases in delirium, dementia and other cognitive disorder, schizophrenia and other psychotic disorders, and somatoform and other dissociative disorders. There were no significant differences amongst the number of presentations in all the four seasons.

Switching to Lurasidone in Patients with Schizophrenia: Tolerability and Effectiveness at 6 Weeks and 6 Months

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ABSTRACT: Study Objectives: The objective of these two studies was to evaluate the safety and effectiveness of switching stable outpatients with schizophrenia or schizoaffective disorder to lurasidone.

METHOD: Non-acute patients with schizophrenia or schizoaffective disorder who were candidates for switching from current antipsychotic medication (due to insufficient efficacy and/or safety or tolerability concerns) were randomized to 3 open-label lurasidone switch strategies: a 40/40 group (N = 74) was started on 40 mg/day for 14 days; a 40/80 group (N = 88) was started on 40 mg/day for 7 days, then increased to 80 mg/day for 7 days; and an 80/80 group (N = 82) with 80 mg/day for 14 days. The prior antipsychotic was tapered off over the initial 2-week study period (50% step-down by week 1, discontinuation after week 2). All patients were then treated for 4 weeks with lurasidone flexibly dosed 40–120 mg/day. Time to treatment failure was evaluated as the primary outcome, defined as insufficient clinical response, exacerbation of underlying disease or discontinuation due to an adverse event (AE). Of subjects who completed the 6 week study,

149 (75.3%) enrolled in an extension study and received 6 months of additional open-label, flexible dose treatment with lurasidone (40–120 mg/day).

RESULTS: No clinically relevant differences in safety, tolerability or efficacy were noted when comparing the 3 switch strategies. Time to treatment failure was similar between three lurasidone dosing strategies. Treatment with lurasidone in the short-term study was associated with LS mean (SE) within-group improvement at Week 6 on the PANSS total score (-5.3 ± 0.7 ; LOCF). Among subjects who entered the extension study, treatment with lurasidone was associated with additional LS mean improvement in the PANSS total score, from extension baseline at Month 6, of -3.6 ± 0.9 (OC; -1.5 ± 0.9 , LOCF). Overall, 86.5% of subjects completed the 6-week study and 65.8% of subjects completed the extension study. Discontinuation due to AEs was 7.0% in the 6 week study and 11.4% during the extension study. Minimal changes were observed in lipid and glycemic indices in both the core and extension studies. The proportion of subjects with $\geq 7\%$ increase in weight in the core study was 0.9%, and 16.0% in the extension study. The most frequent AEs during the core 6-week study were insomnia (8.8%), nausea (8.8%), akathisia (8.1%), and anxiety (6.1%). The most frequent AEs during the extension study were nausea (8.8%), dry mouth (4.7%), and vomiting (4.7%).

CONCLUSION: In these two studies, switching to lurasidone was well-tolerated regardless of initial dose or rate of titration. Patients switched to lurasidone generally maintained or improved symptom control during the short-term and extension study. At the end of 6 months of treatment, minimal changes were observed in weight and lipid parameters, consistent with prior longer-term studies of lurasidone.

FUNDING: Sponsored by Sunovion Pharmaceuticals Inc.

Short- and Long-Term Treatment with Lurasidone or Quetiapine XR in Patients with Schizophrenia: Effect on Metabolic Syndrome

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ABSTRACT: Study Objectives: Schizophrenia is associated with high risk for cardiovascular morbidity and mortality, with many individuals meeting National Cholesterol

Education Program (NCEP) criteria for metabolic syndrome (MetS). This study evaluated the effect of short- and long-term treatment with lurasidone and quetiapine XR (QXR) on the prevalence of MetS.

METHOD: The effects of fixed doses of lurasidone (80 mg/d; 160 mg/d), QXR (600 mg/d), and placebo on the prevalence of MetS were evaluated in subjects with schizophrenia enrolled in a double-blind, placebo-controlled 6 week study, and a subsequent 12 month, double-blind, flexible-dose continuation study with lurasidone (40–160 mg/d) and QXR (200–800 mg/d). NCEP criteria with MetS defined as meeting ≥ 3 of the following were used: waist circumference (male, ≥ 102 cm; female, ≥ 88 cm), triglycerides (≥ 150 mg/dL), HDL-cholesterol (male, < 40 mg/dL; female, < 50 mg/dL), blood pressure ($\geq 130/85$ mmHg), or plasma glucose (≥ 110 mg/dL). Between-group differences were tested for significance using Fisher's exact test (LOCF for 6 week; observed cases for 12-month data).

RESULTS: At baseline, the prevalence of MetS was similar for lurasidone 24/246 (9.8%), QXR 13/119 (10.9%) and placebo 14/121 (11.6%) groups. After 6 weeks of treatment, the prevalence of MetS was lower in subjects receiving lurasidone and placebo (12.3% and 12.8%) compared with subjects receiving QXR (21.7%; $p < 0.05$ for lurasidone vs. QXR). For the subgroup with MetS at baseline, the following median changes were observed at Week 6-LOCF in weight (lurasidone, +0.2; QXR, +1.3; placebo, +0.3 kg), triglycerides (lurasidone, -40.0; QXR, -3.0; placebo, -62.0 mg/dL), and glucose (lurasidone, +0.0; QXR, +10.5; placebo, +1.0 mg/dL). Among subjects who entered the 12-month continuation study, the proportion meeting NCEP criteria for MetS at baseline of the 12-month study was similar for subjects treated with lurasidone 16/151 (10.6%) or QXR 8/85 (9.4%). At 12 months, the proportion meeting NCEP criteria for MetS was lower for the lurasidone group vs. QXR group (2/76 [2.6%] vs. 4/33 [12.1%]; $p = 0.046$).

CONCLUSIONS: Treatment with lurasidone was associated with significantly lower rates of MetS when compared with quetiapine XR at both 6 weeks and 12 months. In the subgroup of patients with MetS at baseline, 6 weeks of treatment with lurasidone was associated with improvement in lipid parameters, and minimal change in weight.

CLINICAL TRIALS REGISTRATION: clinicaltrials.gov identifier: NCT00789698.

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Effect of Lurasidone on Metabolic Indices in Bipolar I Depression: Data from Monotherapy and Adjunctive Therapy Studies

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ABSTRACT: Study Objectives: Patients with bipolar disorder are at a higher risk of cardiovascular disease and mortality. A recent meta-analysis (Vancampfort et al, Am J Psych 2013;170:265–74) found that individuals with bipolar disorder treated with an antipsychotic medication had a 1.7-fold higher risk of developing metabolic syndrome compared with untreated subjects. The objective of the current analysis was to evaluate the effect of short-term treatment with lurasidone on weight and metabolic parameters.

METHOD: Safety results were analyzed from two 6-week, double-blind, placebo-controlled studies that evaluated the efficacy and safety of lurasidone as monotherapy (20–60 mg/d or 80–120 mg/d vs. placebo) or as adjunctive therapy (20–120 mg/d) to lithium (Li) or valproate (VPA), in patients with nonpsychotic bipolar I depression, with or without rapid cycling (DSM-IV-TR). Changes from baseline to week 6 in metabolic parameters were assessed by rank ANCOVA (LOCF), adjusted for baseline values. All metabolic parameters were obtained under fasting conditions per protocol.

RESULTS: In the monotherapy study, the proportion of subjects with a clinically significant ($\geq 7\%$) increase from baseline to Week 6 in weight was low for lurasidone (2.4%) and placebo (0.7%). For monotherapy with lurasidone and placebo, respectively, comparable median changes were observed at Week 6 in total cholesterol (-0.5 vs. -3.0 mg/dL), LDL cholesterol (-2.0 vs. -2.0 mg/dL), triglycerides (+1.5 vs. +8.0 mg/dL) and glucose (0.0 vs. +0.5 mg/dL). In the adjunctive therapy study, the proportion of subjects with a clinically significant increase in weight was low for lurasidone (3.1%) and placebo (0.7%). For adjunctive therapy with lurasidone and placebo, respectively, comparable median changes were observed at Week 6 in total cholesterol (-4.0 vs. 0.0 mg/dL), LDL cholesterol (-3.0 vs. -3.0 mg/dL), triglycerides (+4.5 vs. -4.0 mg/dL) and glucose (+1.0 vs. +1.0 mg/dL).

CONCLUSIONS: In these two placebo-controlled studies in subjects with acute bipolar I depression, short-term treatment with lurasidone, either as monotherapy, or as adjunctive therapy to Li or VPA, was associated with minimal changes in weight, lipid parameters, or

measures of glycemic control. Further studies are needed to assess the long-term metabolic profile of lurasidone in patients with bipolar disorder.

TRIAL REGISTRATION: clinicaltrials.gov identifier: NCT00868699 and NCT00868452.

FUNDING: Sponsored by Sunovion Pharmaceuticals Inc.

Evaluation of Quality of Life Assessments Among Patients with Schizophrenia Switched to Lurasidone From Other Antipsychotics

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ABSTRACT: Study Objectives: Patients with schizophrenia frequently switch between antipsychotics, underscoring the need to ensure that important treatment outcomes such as health-related quality of life (HRQL) are achieved and maintained following the switch. This analysis evaluated changes in overall health-related quality of life among patients with schizophrenia switched from current antipsychotic treatment to lurasidone.

METHOD: Stable, but symptomatic outpatients with schizophrenia were switched from their current antipsychotic to lurasidone, in a 6-week, open-label trial, conducted in the US. The Personal Evaluation of Transitions in Treatment (PETiT) is a validated 30-item instrument measuring self-reported overall quality of life outcomes among patients with schizophrenia. In addition, PETiT assesses 2 domain scores on psychosocial functioning and adherence related attitude. Each item of PETiT is assigned a rating of 2, 1 or 0 where 2 denotes positive change and 0 denotes negative change. Higher scores on PETiT denote better HRQL. PETiT scale was administered at baseline and study endpoint. Changes from baseline to study endpoint in PETiT total score (overall HRQL) and subscale scores on medication attitude, social functioning, activity, patient perception of cognition and dysphoria were compared using ANCOVA with BL score and pooled site as covariates.

RESULTS: Of the 240 subjects with schizophrenia or schizoaffective disorder who received at least one dose of study medication, 235 subjects with available data on the PETiT scale were included in the current analysis. Mean PETiT total scores at baseline was 35.3 and at study endpoint was 38.5. Mean change from baseline to the study endpoint in the PETiT total score was 3.2, change in

psychosocial functioning domain score was 2.5, and change in adherence domain score was 0.7, significant in all patients ($p < 0.001$). Changes from baseline in the mean scores of each PETiT domain scores were (mean [SD], p -value): social functioning (0.1 (1.40), 0.96), activity (0.7 [2.7], 0.0002), patient perception of cognition (0.9 [2.50], < 0.0001) and dysphoria (0.8 [2.3], < 0.0001).

CONCLUSIONS: The findings from this study indicate that patients switching from other antipsychotics to lurasidone experienced improvement in quality of life assessments within 6 weeks of treatment. Statistically significant improvements were observed in the overall QoL as well as subscales for medication attitude, activity, patient perception of cognition and dysphoria as assessed by the PETiT scale. Further investigation regarding the effects of longer-term lurasidone treatment on quality of life and patient reported perceptions of switch to lurasidone is warranted.

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Changes in Cardiometabolic Parameters and Metabolic Syndrome Status in Patients with Schizophrenia Switching From Other Antipsychotics to Lurasidone

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ABSTRACT: Study Objectives: Atypical antipsychotics are associated with various degrees of cardiometabolic risks including weight gain, hyperglycemia, hypertension and lipid abnormalities. An effective treatment of schizophrenia with minimal cardiometabolic risks remains a key unmet medical need. Changes in cardiometabolic parameters and metabolic syndrome status in patients with schizophrenia switching from other antipsychotics to lurasidone were examined in this analysis.

METHOD: Clinically stable, but symptomatic outpatients with schizophrenia and schizoaffective disorder were switched from their current antipsychotic to lurasidone in a randomized, 6-week, open label trial, conducted in the US. An increase in cardiometabolic parameters was defined as: BMI ≥ 30 kg/m², triglycerides (≥ 150 mg/dL), fasting plasma glucose (FPG ≥ 100 mg/dL), blood pressure (systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg) and HDL cholesterol (< 40 mg/dL in males

and <50 mg/dL in females). Metabolic syndrome was defined by the International Diabetes Federation as those with a BMI ≥ 30 kg/m², plus ≥ 2 of the above four factors. Cardiometabolic parameters and presence of metabolic syndrome were assessed at study baseline (BL) and endpoint.

RESULTS: Of the 244 subjects switching to lurasidone, the analysis included subjects (n = 220) with a BL and ≥ 1 post-BL value for any cardiometabolic parameter. At BL, proportions of patients with elevated cardiometabolic parameters were: n = 104 (47.3%) with BMI ≥ 30 kg/m², n = 55 (30.1%) with raised triglycerides, n = 84 (35.9%) with raised blood pressure, n = 35 (19.0%) with raised FPG, and n = 34 (18.6%) with reduced HDL cholesterol. At study endpoint, the proportion of patients with elevated cardiometabolic parameters was: n = 100 (45.5%) with BMI ≥ 30 kg/m², n = 45 (24.6%) with raised triglycerides, n = 83 (35.5%) with raised blood pressure, n = 33 (17.9%) with raised FPG, and n = 33 (18.0%) with reduced HDL cholesterol. Metabolic syndrome frequency was n = 34 (15.5%) at BL and n = 28 (12.7%) at study endpoint.

CONCLUSION: In this 6-week, open-label study, an improvement in cardiometabolic parameters and a reduction in metabolic syndrome rate was observed in adult patients switched from other antipsychotic agents to lurasidone. The safety profile found in this study was similar to other lurasidone studies. Effects of long-term switch to lurasidone on metabolic parameters warrants further investigation.

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Lurasidone Monotherapy of Bipolar Depression: Influence of Baseline Thyroid Function on Treatment Response

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ABSTRACT: Objective: Treatment response of bipolar depressed subjects to lithium and antidepressant therapy has been reported (Cole et al. *Am J Psychiatry* 2002;159:116-21; Chakrabarti, *J Thyroid Res* 2011;

1-13) to be sensitive to baseline thyroid status, with poorer response observed in patients with lower free thyroxine index values and higher TSH values, even within normal reference ranges. This post-hoc analysis evaluated whether thyroid function level influenced treatment response to lurasidone in subjects diagnosed with bipolar I depression.

METHODS: Subjects meeting criteria for bipolar I depression, with a MADRS score ≥ 20 , were randomized to 6 weeks of once-daily, double-blind treatment with either lurasidone 20-60 mg, lurasidone 80-120 mg (combined in the current analysis, n = xxx) or placebo (n = 505). Patients receiving ongoing thyroid hormone treatment (n = 27; 5.3%) were excluded from the analysis. Baseline levels of thyroid-stimulating hormone (TSH; normal reference range, 0.35-1.8 μ IU/mL) and free thyroxine (free T₄; normal reference range, 0.35-5.5 ng/dl) were obtained at screening. Patients were first stratified by median split in baseline TSH (high-normal TSH group, lurasidone n = 159; placebo, n = 81; and a low-normal TSH group, lurasidone n = 159; placebo, n = 79), and then further stratified into 1 of 4 baseline thyroid function categories based on a median split of high-normal vs. low-normal free T₄; patients receiving placebo (n = 160) were similarly stratified. Efficacy was assessed using baseline to week 6 change in MADRS (LOCF, ANCOVA).

RESULTS: At baseline, the median TSH was 1.6 μ IU/mL, the median free T₄ was 1.01 ng/dl, and the mean MADRS was 30.5. Mean MADRS scores at baseline were similar for the high- and low-normal TSH groups for both lurasidone and placebo. The LS mean change from baseline in MADRS was significant for lurasidone (vs. placebo) in both the high-normal TSH group (-14.4 vs. -9.8; $p < 0.01$) and the low-normal TSH group (-13.4 vs. -10.1; $p < 0.05$). The proportion of subjects meeting responder criteria ($\geq 50\%$ reduction in MADRS; LOCF-endpoint) was also significantly higher for lurasidone vs. placebo in both the high-normal TSH group (54.5% vs. 36.7%; $p < 0.05$) and the low-normal TSH group (49.0% vs. 26.7%; $p < 0.01$). Based on a further stratification by median free T₄ values, subjects with lower baseline thyroid function (high-normal TSH + low-normal free T₄) had greater LS mean MADRS improvement on lurasidone than subjects with higher baseline thyroid function (low-normal TSH + high-normal T₄): -16.1 vs. -12.8.

CONCLUSIONS: The results of the current post-hoc analysis suggests that the antidepressant effect of lurasidone in bipolar depressed individuals is not sensitive to baseline thyroid status, at least within the normal range. Further research is needed to confirm

this finding, including bipolar depression patients treated with lurasidone adjunctive to mood stabilizers.

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Efficacy of Lurasidone in the Treatment of Agitation Associated with Acute Schizophrenia

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ABSTRACT: Study Objectives: Agitation is a common presentation among patients hospitalized for an acute exacerbation of schizophrenia. Rapid and effective control of agitation is an important early treatment goal. The objective of this post-hoc analysis was to evaluate the efficacy of lurasidone in reducing agitation in patients who were hospitalized for an acute exacerbation of schizophrenia.

METHOD: This analysis was performed on pooled data from five 6-week, double-blind, placebo-controlled trials, in subjects with an acute exacerbation of schizophrenia who were randomized to fixed, once-daily, 40–160 mg oral doses of lurasidone. Efficacy assessments were PANSS total score and the PANSS Excited Component (PEC) subscore recorded on Day 3/4 and Day 7 (and weekly thereafter) in the group of patients (n = 773) experiencing clinically relevant levels of agitation, which was defined as a PEC score ≥ 14 at baseline (Citrome, J Clin Psych 2007;68:1876–1885). A low agitation group was defined as a PEC score < 14 at baseline.

RESULTS: In the high agitation group, the mean PANSS total and PANSS-EC scores at baseline were similar for lurasidone (100.7 and 16.7; n = 530) and placebo (101.1 and 16.8; n = 243). In the low agitation group, the mean PANSS total and PANSS-EC scores at baseline were lower for both lurasidone (91.2 and 10.9; n = 500) and placebo (91.3 and 10.7; n = 254). In the high agitation group, treatment with lurasidone was associated with a significantly lower attrition rate compared with placebo (36.0% vs. 48.1%; $p < 0.01$). Treatment of the high agitation group with lurasidone was associated with significantly greater improvement in PANSS-EC scores at Days 3/4 (–1.6 vs. –1.0; $p < 0.001$), Day 7 (–2.3 vs. –1.6; $p < 0.001$), and at Week 6 endpoint (–5.5 vs. –3.8; $p < 0.001$; effect size,

0.43) compared with placebo. Treatment of the high agitation group with lurasidone was also associated with significantly greater improvement in PANSS total scores at Days 3/4 (–5.1 vs. –4.0; $p < 0.001$), Day 7 (–9.0 vs. –6.5; $p < 0.001$), and at Week 6 endpoint (–27.2 vs. –18.4; $p < 0.001$; effect size, 0.57) compared with placebo. Higher endpoint responder rates ($\geq 20\%$ improvement in PANSS total) in favor of lurasidone vs. placebo were observed in both the high agitation group (64.3% vs. 43.4%; $p < 0.01$) and in the low agitation group (62.2% vs. 46.5%; $p < 0.01$).

CONCLUSIONS: In this post-hoc analysis of pooled data from five short-term trials in subjects with an acute exacerbation of schizophrenia, treatment with lurasidone significantly reduced agitation as early as Day 3, with improvement maintained through week 6 endpoint. Treatment with lurasidone was associated with significant improvement in PANSS total and CGI-Severity scores from Day 7 onward in subjects with high and low agitation at baseline. In the high agitation group, treatment with lurasidone was associated with a lower discontinuation rate compared with placebo.

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Effect of Lurasidone on Weight and Metabolic Parameters: A Comprehensive Analysis of Short- and Long-Term Trials in Schizophrenia

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ABSTRACT: Study Objectives: Patients with schizophrenia are at significantly higher risk for diabetes, dyslipidemia, hypertension, and obesity, contributing to increased mortality. Antipsychotic medication may add further cardiometabolic risk, with significant differences in effects on weight, glucose and lipids reported among atypical antipsychotics. The objective of the current pooled analysis was to evaluate the effect of lurasidone on weight and metabolic parameters.

METHOD: Short-term data were pooled from seven double-blind, placebo-controlled, 6-week treatment studies of patients who met DSM-IV criteria for schizophrenia with an acute exacerbation. The short-term safety analysis consisted of patients treated with lurasidone (20–160 mg, N = 1508); haloperidol 10 mg

(N = 72); olanzapine 15 mg (N = 122); risperidone 4 mg (N = 65); quetiapine XR 600 mg (QXR; N = 119); or placebo (N = 708). Longer-term data (6–22 months) were pooled from 5 open-label studies in patients taking lurasidone 20–120 mg/day.

RESULTS: In the short-term studies, subjects experiencing $\geq 7\%$ increase/decrease in weight was 5.4%/3.1% for combined lurasidone doses, 7.0%/7.0% for haloperidol, 40.2%/0% for olanzapine, 6.2%/4.6% for risperidone, 15.3%/0% for QXR, and 4.3%/3.9% for placebo; and the mean change in BMI (kg/m²) was +0.1, 0.0 +1.4, +0.1, +0.7, and 0.0 for lurasidone, haloperidol, olanzapine, risperidone, QXR, and placebo, respectively. Median endpoint change in lipids were: triglycerides (mg/dL), -4.4 for combined lurasidone, -2.7 for haloperidol, +24.8 for olanzapine, +3.5 for risperidone, +9.7 for QXR, and -6.2 for placebo; total cholesterol (mg/dL), -5.0 for lurasidone, -8.1 for haloperidol, +7.7 for olanzapine, +6.6 for risperidone, +6.2 for QXR, and -5.0 for placebo; similar trends were recorded for changes in LDL for lurasidone, QXR and olanzapine. Median glucose (mg/dL) was unchanged (LOCF-endpoint) for lurasidone (0.0) and placebo (0.0), and was somewhat higher for haloperidol (+2.0), olanzapine (+4.0), risperidone (+3.0), and QXR (+3.0). Minimal-to-no changes were observed at Week 6 LOCF-endpoint in HbA1c. In the longer-term treatment sample, mean change in weight at Month 12 was -0.59 kg for the lurasidone group (observed case); and the median changes (mg/dL) in metabolic parameters at Month 12 were: -3.9 for total cholesterol and -6.2 for triglycerides (observed case).

CONCLUSION: In this comprehensive analysis of short- and longer-term studies, treatment with lurasidone was associated with minimal increases in weight in short-term trials, and small decreases in weight in longer-term trials. In the combined lurasidone dosage groups there was a baseline-to-endpoint decrease in mean total and LDL cholesterol, and triglycerides during both short-term and longer-term treatment.

FUNDING: Sponsored by Sunovion Pharmaceuticals, Inc.

Residential Treatment for Combat Stress: A Holistic, Comprehensive Approach

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ABSTRACT: **STUDY OBJECTIVES:** Moncrief Army Community Hospital (MACH) created the Combat Stress and Addictions Recovery Program (CSARP) to meet the comprehensive needs of behavioral health patients suffering from post deployment issues. The model incorporates a comprehensive, “wrap-around” experience that is patient and family centered and includes local commands as part of the treatment team. While cognitive processing therapy is the core of this model, CSARP also incorporates nutrition, physical therapy, mindfulness meditation, biofeedback, pain management, financial management, spiritual counseling and pharmacotherapy into the program. The CSARP model is innovative because it is the Army’s first residential, multi-disciplinary program that utilizes a holistic approach with active duty soldiers in the Army. Previously utilized outside civilian programs limited the scope of services they offered, preventing patients from addressing all their issues prior to their return to work.

METHOD USED TO EVALUATE THE EFFECTIVENESS: CSARP patients are combat veterans who are in need of intensive treatment for combat stress and other unhealthy behaviors who pose no imminent safety risk. Soldiers complete self-administered outcome measures upon admission and at discharge. The outcome measures used to examine the program’s effectiveness include: The Satisfaction with Life Scale, Purpose in Life Test, Spiritual Attitude Inventory, Occupational Satisfaction Index (OSI-R), Leisure Boredom Scale, Lock Wallace Marital Adjustment Test, Post Traumatic Cognitions Inventory (PTCI), Beck Depression Inventory-II (BDI-II), Epworth Sleepiness Scale, PCL-M, Outcome Questionnaire (OQ-45), WHOQOL-BREF, Multidimensional Sexual Self Concept Questionnaire and the SF-36 Questionnaire. Predictive Analytics SoftWare, version 18 (PASW) was used to analyze the data. Several Paired Samples T Tests were conducted to compare the means of pre and post-test measures.

RESULTS: There were statistically significant findings on the PCL-M, $t(17) = 3.70$, $p = .002$, the PTCI, $t(17) = 4.50$, $p = .000$, and the BDI-II, $t(11) = 4.51$, $p = .001$, indicating a significant decrease in reported symptoms of PTSD and depression.

CONCLUSIONS: The demand for effective treatment of post-deployment stress continues to grow as troops return home. The CSARP model offers several benefits. The residential component allows for “front loading” of therapies, potentially decreasing the need for outpatient

treatment. Soldiers are assimilated into local support networks which they will continue to utilize upon discharge. The program is also cost effective and allows family member participation without any travel expenses or logistical complications. In conclusion, if CSARP patient outcomes continue to mirror the positive findings cited in previous studies, the program can possibly become the AMEDD model for residential treatment of PTSD.

FUNDING: No Funding sources for this study.

An Open Label Study of Pharmacogenomic Based Treatment of Depression and Anxiety

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ABSTRACT: Study Objective(s): Response to psychiatric medication is highly variable, and genetic contributions to this variability are widely accepted. Therapies informed by a patient's genetic data have the potential to produce superior outcomes. Collecting data from subjects in actual practice settings poses challenges relative to typical research studies. This study offers a unique design to overcome these challenges, including an electronic consent form and secure online capture of study questionnaires as well as automated email and SMS reminders to reduce attrition. Study aims include: (1) demonstration of the efficacy of genetic testing through patient and clinician report outcomes (2) characterization of patients selected for pharmacogenetic testing by clinicians as well as (3) demonstration of the impact of genetic testing on clinician treatment decisions.

METHODS: This is an open label, prospective analysis of clinicians who order the Genecept Assay (Genomind, LLC, Chalfont, PA), and patients for whom the test is ordered. Both patients and their treating clinicians are enrolled as study subjects. Genes tested by the Genecept Assay are the serotonin transporter (SLC6A4), voltage-gated calcium channel (CACNA1C), Ankyrin G protein (ANK3), dopamine receptor subtype two (DRD2), catechol-O-methyl transferase (COMT) and methylenetetrahydrofolate reductase (MTHFR), as well as cytochromes P450 2D6 (CYP2D6), 2C19 (CYP2C19), and 3A4 (CYP3A4). Analytic results reports are provided to clinician participants, who will be asked to complete a baseline survey which asks about current medications, psychiatric history, and severity of illness using the Clinical Global Impressions-Severity (CGI-S) scale. Clinicians are asked to complete an additional survey after receiving the genetic results noting

any medication changes prompted by genetic results. A follow up assessment occurs at 3 months from the time of genetic testing, which includes an assessment of improvement of illness severity using the Clinical Global Impressions-Improvement (CGI-I) scale. Subjects are asked to complete assessments for depression, anxiety, medication side effects, and quality of life at three time points (baseline, 1 month, and 3 months).

RESULTS: This study began enrolling patients in April of 2013. Data from the first group of subjects are currently being analyzed.

CONCLUSION: Psychiatric treatment typically utilizes a trial and error process, often involving a significant number of failed medication trials. Targeted medication therapy informed by genetic data may ease this burden and improve patient outcomes. Results from this prospective study will provide data to corroborate the utility of genetic information in clinical practice.

FUNDING: This study is being funded by Genomind.

Transcranial Magnetic Stimulation (TMS) for Patients with Pharmacoresistant Major Depression: Durability Over 1-Year and Comparison to Antidepressants

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ABSTRACT: Objective: This study was designed to assess the acute and long-term clinical outcomes of patients treated with NeuroStar TMS Therapy® in naturalistic clinical practice compared to a propensity-matched group of patients who participated in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.

METHODS: 307 patients with a primary diagnosis of unipolar, non-psychotic major depressive disorder who had failed to receive benefit from prior antidepressant treatment received TMS treatment in clinical practice (67.7% women, 48.3 ± 14.3 years) at 42 clinical practice sites. TMS was provided as determined by the evaluating physician, consistent with labeled use. 257 patients consented to long-term follow up over 52 weeks and were evaluable for statistical analysis. Clinical assessments (CGI-S, PHQ-9 and IDS-SR) were obtained at 3, 6, 9, and 12 months. Groups were matched by gender, age, income level, treatment resistance staging, symptom burden (QIDS-16 scores), and functional status (SF12 physical and mental component scores). Propensity score matching was performed using a Greedy

Algorithm to select a STAR*D comparison group with baseline characteristics matched to the NeuroStar TMS patient population. Clinical outcomes between groups were compared at a standard time point of 6 weeks.

RESULTS: Compared with baseline, there was a statistically significant reduction in mean [SD] CGI-S, PHQ-9 and IDS-SR total scores at the end of acute treatment (5.0 [0.9] vs. 3.0 [1.4], 18.0 [5.3] vs. 8.8 [6.7], and 44.9 [11.1] vs. 25.7 [15.5], all $P < 0.0001$), which was sustained throughout the 52 week follow-up (2.8 [1.5], 8.6 [6.9], and 25.6 [15.8], all $P < 0.0001$), respectively. The proportion of patients in remission at conclusion of the long term phase was similar to that observed at the end of acute treatment (end of acute/end of long term: CGI-S 41.2%/45.1%; PHQ-9 31.1% /37.0%; IDS-SR 29.7% /29.3%.) Propensity score matching of the NeuroStar TMS and STAR*D patients demonstrated no statistically significant baseline differences between the two groups with mean standardized differences after matching less than 0.25 for all variables. The mean (SD) QIDS-16 score at the 6-week time point was 10.4 (6.18) vs. 13.0 (4.57) for the NeuroStar TMS and STAR*D groups, respectively ($p < 0.0001$). At baseline, 69.4% of the NeuroStar TMS and 72.2% of the STAR*D patients were categorized as severely ill or worse (QIDS-16 > 15). At the six week time point 27.0% of the NeuroStar group vs. and 5.2% of the STAR*D group were categorized as with no symptoms (QIDS-16 < 6).

CONCLUSIONS: TMS demonstrates a statistically and clinically meaningful durability of acute benefit over 52 weeks under a regimen of continuation antidepressant medication and access to TMS reintroduction for symptom recurrence. TMS achieved a greater proportion of patients with full symptom benefit at 6 weeks compared to medication treatment as usual.

Changing Negative Core Beliefs with the Trial-Based Thought Record: A Randomized Study

Irismar Reis de Oliveira, MD, Thaís Delavechia Bonfim, Érica P. Duran, Maria Amélia Penido, Lina Sue Matsumoto, Fernanda Coutinho, and Michella Lopes Velasquez

BACKGROUND: Trial-Based Cognitive Therapy (TBCT) is a recently developed psychotherapeutic approach whose foundation is in cognitive therapy (CT), and inspired in the work of Franz Kafka. It differs from standard CT in that it has its own conceptualization, and simulates legal trials in which the patient role-plays the different characters in a tribunal, namely, prosecutor, defense attorney, juror, witnesses, etc. The Trial-Based Thought

Record (TBTR) is the main technique used in TBCT. As CT postulates that changing negative core beliefs (CBs) is the best prevention against relapses in several psychiatric disorders, an investigation was undertaken by means of the downward arrow technique to uncover and restructure negative CBs, conceptualized as “self-accusations” (e.g., “I am a loser”), in patients having any psychiatric diagnoses. TBTR may be conducted using the empty chair format – an experiential approach derived from Gestalt Therapy in which the patient moves to different chairs to role-play different characters –, or in the static format, in which the patient remains in the same chair during the session.

OBJECTIVES: To confirm previous findings on the efficacy of the TBTR in decreasing the attachment of the patients to their self-critical negative CBs and corresponding emotions, and to assess the differential efficacy of the TBTR employed in the empty chair relative to the static format.

METHOD: This is a parallel-group, randomized study, of patients ($n = 39$) having any psychiatric diagnosis (mood and anxiety disorders, psychosis, etc.). They were submitted to a 50-minute, one-session, simulation of a legal trial and their adherence to negative CBs and corresponding emotions after each step of the TBTR technique first use were assessed. The TBTR comprises 7 steps: the identification of the CB (investigation), prosecutor’s plea, defense attorney’s plea, prosecutor’s second plea, defense attorney’s second plea, jury’s verdict, and preparation for the appeal. Comparisons involved the TBTR used in the empty chair format relative to the static format. Statistical analyses involved a repeated measures mixed ANOVA and an ANCOVA, having the initial values (investigation) as the covariate.

RESULTS: Results of the mixed ANOVA indicated a significant main effect, meaning that significant reductions in percent values both in the credit given to the CBs and in the intensity of the emotions were observed at the end of the session ($p < .001$), relative to baseline (investigation phase). There was no significant interaction between time and treatment. The ANCOVA showed a significant difference in favor of the empty chair approach for both the belief credit and the emotion intensity ($p = .04$).

CONCLUSIONS: The TBTR may help patients reduce the attachment to negative CBs and corresponding emotions, confirming our preliminary observations.⁴ However, contrary to our previous observation, in this study, the empty chair format was more efficacious than the static format in reducing the intensity of corresponding emotions.

EDUCATIONAL OBJECTIVES: After reading this poster, the participant should be able to recognize the importance of CBs in psychiatric disorders and the importance of restructuring such cognitions.

FUNDING: This research was not funded.

Lurasidone in the Treatment of Early-Stage Schizophrenia: A Post-Hoc Analysis of Three Pooled Acute Treatment Studies

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ABSTRACT: Study Objectives: Lurasidone has demonstrated efficacy in the treatment of patients with schizophrenia, typically with a high degree of chronicity. Because lurasidone is well-tolerated and has a relatively favorable safety profile, with a low propensity for weight gain and metabolic abnormalities, it may be a useful agent to treat patients in the early stages of schizophrenia, since evidence suggests that this subgroup may be particularly vulnerable to adverse effects of antipsychotics. The objective of this post-hoc analysis was to evaluate the efficacy of lurasidone in subjects with early-stage schizophrenia (ESS).

METHOD: This was a pooled analysis of ESS subjects who had participated in three 6-week, randomized, placebo-controlled, phase 3 trials evaluating the efficacy of once-daily, 40-160 mg fixed-doses of lurasidone. ESS was defined as onset of illness within 3 years prior to study entry. Efficacy was evaluated using a mixed-model repeated-measures (MMRM) analysis of change from baseline to Week 6 in PANSS total score and CGI-Severity score. Treatment response was defined as $\geq 20\%$ improvement from baseline in PANSS total score. Cohen's *d* effect sizes, and number needed to treat (NNT) values were calculated for key efficacy outcomes.

RESULTS: In this pooled analysis, 848 and 358 subjects were randomized to lurasidone and placebo respectively, and 102 (12.0%) subjects in the lurasidone group, and 44 (12.3%) subjects in the placebo group had ESS (onset of illness within 3 years). Baseline characteristics were similar for ESS and chronic (non-ESS) subjects, including a mean PANSS total score of 97, with the exception that the mean age of ESS subjects was 10 years younger. There was a slightly lower overall

discontinuation rate in ESS vs. chronic subjects treated with lurasidone (26.5% vs. 32.3%). In ESS subjects, treatment with lurasidone was associated with significantly greater improvement at Week 6 on the PANSS total score (-25.9 vs. -17.3 ; $p < 0.05$). For PANSS change at Week 6, the lurasidone vs. placebo effect size (0.42 vs. 0.39) was similar for ESS vs. chronic subjects. Six weeks of treatment with lurasidone was associated with significant higher responder rates compared with placebo in the ESS group (69.0% vs. 48.0%; $p < 0.01$; NNT = 5) and the chronic group (65.0% vs. 48.0%; $p < 0.001$; NNT = 5). A higher incidence of parkinsonism (21.6% vs. 13.1%), nausea (18.6% vs. 9.5%), and vomiting (15.7% vs. 7.0%) was recorded in ESS vs. chronic subjects treated with lurasidone. Lurasidone was generally well-tolerated, with a low rate of discontinuation due adverse events in the ESS vs. chronic groups (3.9% vs. 6.0%).

CONCLUSIONS: The results of this post-hoc analysis indicate that lurasidone is efficacious and well-tolerated in patients with early stage schizophrenia. Follow-up is needed to more fully evaluate long-term outcomes in subjects with early stage schizophrenia.

FUNDING: Sponsored by Sunovion Pharmaceuticals Inc.

Lurasidone Treatment for Bipolar I Depression: Effects on Quality of Life and Patient Functioning

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ABSTRACT: Study Objectives: The objective of this secondary analysis was to evaluate the effect of treatment with lurasidone (both monotherapy and adjunctive therapy with lithium [Li] or valproate [VPA]), on quality of life and functioning in patients with bipolar I depression (BPD).

METHOD: Patients meeting DSM-IV-TR criteria for BPD, with or without rapid cycling, with a MADRS score ≥ 20 , were randomized, in 2 multi-regional trials (combined $n = 853$), to 6 weeks of once-daily, double-blind treatment with lurasidone adjunctive to lithium (Li) or valproate (VPA); or double-blind treatment with lurasidone monotherapy. In the adjunctive therapy study, patients received either lurasidone 20-120 mg/day or placebo, in combination with either Li or VPA. In the monotherapy study, patients received either lurasidone

20–60 mg, lurasidone 80–120 mg, or placebo. In both studies, the primary outcome was change in depressive symptoms, assessed by the MADRS. Functioning was assessed using the Sheehan Disability Scale (SDS) total and subscores. Quality of life was assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire, Short Form (Q-LES-Q-SF). SDS and Q-LES-Q-SF outcomes were evaluated using analysis of covariance with last observation carried forward (LOCF), and logistic regression.

RESULTS: In the adjunctive therapy study, treatment with LUR20-120 resulted in significantly greater reduction in MADRS total score at week 6 compared with PBO (−17.1 vs. −13.5; $p = 0.005$). Significantly greater week 6 reduction in the SDS total score was observed on adjunctive lurasidone vs. placebo (−9.8 vs. −6.3; $p < 0.001$). Significantly greater improvement in the lurasidone group (vs. placebo) was also observed on 2 of the 3 SDS subscores (social life and family life), and in the Q-LES-Q-SF total score. A significantly higher proportion of subjects shifting from below normal to normal (≥ 52.3) Q-LES-Q-SF scores (64.3% vs. 44.1%; $p = 0.001$). In the monotherapy study, treatment with lurasidone significantly reduced MADRS total score at week 6 for both the LUR20-60 group (−15.4; $p < 0.001$) and the LUR80-120 group (−15.4; $p < 0.001$) vs. PBO (−10.7). Significantly greater week 6 reduction in the SDS total score was observed for both the LUR20-60 group (−9.5; $p = 0.003$) and the LUR80-120 group (−9.8; $p < 0.001$) vs. PBO (−6.3). Significantly greater improvement in both lurasidone groups was also observed on each of the 3 SDS subscores, and in the Q-LES-Q-SF total score. A significantly higher proportion of subjects shifted from below normal to normal Q-LES-Q-SF scores for the LUR20-60 group (55.3%; $p < 0.001$) and the LUR80-120 group (54.2%; $p < 0.001$) vs. PBO (32.9%).

CONCLUSIONS: In this analysis of data from two 6-week studies, treatment of bipolar I depression with LUR, whether monotherapy or adjunctive to Li or VPA was associated with significant improvement in quality of life and functioning as measured by patient-rated scales.

FUNDING: Sponsored by Sunovion Pharmaceuticals Inc.

Repetitive Transcranial Magnetic Stimulation as a Treatment for Depression: Outcomes and Adverse Effects in a Community Psychiatric Practice

Robert Dolgoff, MD, Rick Trautner, MD, Melissa Ayers, BA, and Vaidahi Patel, BS

OBJECTIVES: rTMS aims directly to influence abnormal brain circuits. The FDA cleared the Neuronetics Neurostar device in 2008 for the treatment of Major Depressive Disorder. We wanted to know if stimulation of the left dorsolateral prefrontal cortex utilizing the protocol which led to FDA clearance would provide clinical benefit and whether it would be well tolerated in a real world community setting.

METHOD: After screening and after obtaining informed consent we treated 72 depressed patients. Most were highly treatment resistant; 69 (96%) had failed to respond to five or more medications although not all of the trials were adequate. Prior to treatment the average MADRS score was 33, the BDI 36, and the PHQ-9 20. 57 of the patients (79%) had Major Depressive Disorder, the other 15 had Bipolar Disorder I or II. We explained to the bipolar patients that TMS is not an approved treatment for Bipolar Disorder and that they were being treated off label. All patients were treated with high frequency (10hz) stimulation of the left DLPFC, 3,000 pulses per treatment 5 days a week for four to six weeks on average although some patients had more and some had fewer treatments. Many but not all of those who had not improved after two to four weeks of treatment were treated with more pulses (e.g. 4,000) or were given bilateral treatment, usually 2,500 stimulatory pulses to the left DLPFC and 1,500 inhibitory pulses (1 Hz) to the right DLPFC. A MADRS and either a BDI or a PHQ-9 was given to all patients each week. Each patient also had a clinical interview with a psychiatrist each week, usually of 25 minutes duration.

RESULTS: Using a definition of remission as MADRS or BDI < 10 or PHQ-9 < 5 35% of patients remitted. 25% responded (MADRS, BDI, or PHQ-9 decreased by >50%). 21% had a partial response (score decreased by >25%), and the remaining 14% had no response. One patient developed acute mania. One patient committed suicide at a point in treatment when he had become less depressed. Some patients experienced mild to moderate scalp or facial discomfort; in most cases this subsided after the first few treatments. Several patients experienced pain during the treatment or headache that persisted after each treatment and one dropped out because of pain. Most patients had no discomfort at all after the first few treatments.

CONCLUSIONS: Even though the patients were highly treatment resistant rTMS provided impressive benefit and was generally well tolerated. We believe it will be widely utilized.

FUNDING: Limited funding was provided by Neuronetics, Malvern PA.

The Treatment of Depression Using Botulinum Toxin A: A 24 Week Randomized, Double-blind, Placebo-Controlled Study

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ABSTRACT: Study Objective: To determine whether a single treatment of Botulinum Toxin A in the forehead (glabellar) region can improve symptoms of depression.

METHOD: This was a 24-week randomized, double-blind, placebo-controlled study treating people who suffer from depression (and who also had moderate to severe frown lines in forehead region) with Botulinum toxin A (BTA) injections. Thirty participants were randomized to receive either placebo or BTA injections in the forehead. Female participants received 29 units of BTA; male participants received 39 units. At week 12, the groups were switched and those receiving BTA received placebo and vice versa. Participants were evaluated at week 0,3,6,12,15,18, and 24 for improvement in depression symptoms using PHQ-9, BDI, and HAM-D 21 objective measurement scales. The primary outcome measure was a full response to treatment as measured by a >50% reduction in Ham-D scores.

Secondary outcome measures included 1) remission to treatment as measured by a Ham-D score of ≤ 7 and a BDI score of ≤ 9 . 2) full response to treatment as measured by a >50% reduction on BDI. 3) partial response to treatment as measured by a 25% to 49% reduction in score on Ham-D and BDI.

RESULTS: Patients who received BTA had a statistically significant reduction in depression symptoms as compared to placebo.

Moreover, it was noted that the group that received BTA first continued to have improvement in depression symptoms throughout the 24 weeks. This is particularly interesting given that the cosmetic effects of Botox last approximately 12–16 weeks.

The Ham-D 21 response rate was 0% in the placebo group, 55% in BTA first group, and 24% in BTA second group. Remission rate was 0% in the placebo group, 18% in BTA first group, and 18% in BTA second group. Partial response rate was 5% in the placebo group, 73% in BTA first group, and 65% in BTA second group.

The BDI response rate was 5% in the placebo group, 45% in BTA first group, and 33% in BTA second group. Remission rate was 5% in the placebo group, 27% in BTA first group, and 33% in BTA second group. Partial response rate was 32% in the placebo group, 73% in BTA first group, and 56% in BTA second group.

CONCLUSIONS: Botulinum toxin injection to the glabellar region may be an effective, safe, and sustainable intervention in the treatment of depression. Preliminary data provides support for the concept that the facial musculature not only expresses, but may also regulate mood states. This may be due to social factors (i.e. people are more likely to engage with us if we have a positive facial expression) or biological factors (i.e. peripheral feedback from facial movements is altered by BTA injections, thereby breaking a feedback loop of negative neurochemical changes causing negative emotional states) or a complex interaction of both.

FUNDING: The study was funded by The Brain and Behavior Research Foundation Young Investigator Award

Effect of Lurasidone Monotherapy or Adjunctive Therapy on Anxiety Symptoms in Patients with Bipolar I Depression

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ABSTRACT: Study Objectives: Over half of patients diagnosed with bipolar I depression (BPD) experience clinically significant anxiety, and over one-third will be diagnosed with an anxiety disorder in their lifetime. This analysis evaluated the efficacy of lurasidone as monotherapy or adjunctive therapy to lithium (Li) or valproate (VPA) in treating symptoms of anxiety in patients with BPD.

METHOD: Patients meeting DSM-IV-TR criteria for BPD, with or without rapid cycling, with a Montgomery Åsberg Depression Rating Scale (MADRS) score ≥ 20 , were randomized, in 2 large, parallel-group, multi-regional studies (combined $n = 853$), to 6 weeks of once-daily, double-blind treatment with lurasidone adjunctive to lithium (Li) or valproate (VPA); or as monotherapy. In the adjunctive therapy study, patients received either lurasidone 20–120 mg/day or placebo, in combination with either Li or VPA. In the monotherapy study, patients received either lurasidone 20–60 mg, lurasidone 80–120 mg, or placebo (both treatment arms were combined in the current analysis). In both studies, the primary outcome was change in depressive symptoms, assessed by the MADRS. Symptom severity of

anxiety was determined using the Hamilton Anxiety Scale (HAM-A).

RESULTS: Overall, 33% of patients met criteria for moderate-to-severe anxiety (HAMA ≥ 18) at baseline. In the adjunctive therapy study, treatment with lurasidone combined with Li or VPA, significantly reduced HAM-A total score compared with placebo (-8.0 vs. -6.0 ; $p < 0.01$; LOCF); significant improvement vs. placebo was also observed for the HAM-A psychic ($p < 0.01$) and somatic ($p < 0.01$) factors. Treatment with lurasidone was associated with higher endpoint anxiety responder rates ($\geq 50\%$ reduction in HAM-A) compared with placebo in both the moderate-to-severe anxiety group (68.8% vs. 45.1%; $p < 0.01$) and in the group with lower baseline anxiety (HAM-A < 18 ; 57.0% vs. 38.8%; $p < 0.01$). In the monotherapy study, treatment with lurasidone significantly reduced HAM-A total score compared with placebo (-6.6 vs. -4.6 ; $p < 0.001$); significant improvement vs. placebo was also observed for the HAM-A psychic factor ($p < 0.01$), but not the somatic factor ($p = 0.108$). Treatment with lurasidone was associated with significantly higher endpoint anxiety responder rates compared with placebo in the lower baseline anxiety group (53.9% vs. 28.0%; $p < 0.001$), but the difference was not significant in the moderate-to-severe anxiety group (51.0% vs. 37.3%). Incidence of adverse events, and discontinuation due to adverse events was not influenced by the severity of baseline anxiety.

CONCLUSIONS: The results of this secondary analysis suggest that short-term treatment with lurasidone is effective in treating symptoms of anxiety in subjects with bipolar I depression. Short-term treatment with lurasidone was well-tolerated regardless of baseline anxiety severity.

FUNDING: Sponsored by Sunovion Pharmaceuticals, Inc. clinicaltrials.gov identifier: NCT00868699 and NCT00868452

Lurasidone for the Treatment of Bipolar I Depression: Treatment Outcomes in the Presence of Subsyndromal Hypomanic Features

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ABSTRACT: Study Objectives: In patients with bipolar I depression, low or subsyndromal levels of hypomanic symptoms are clinically relevant and are associated with an increased risk of treatment-emergent mania (Berk et al. *J Affect Disord* 2008;153-8; Frye et al. *Am J Psych* 2009;166;164-72). This post-hoc analysis evaluated effect of subsyndromal hypomanic features on efficacy and safety outcomes with lurasidone in the treatment of bipolar I depression.

METHOD: All subjects met DSM-IV-TR criteria for nonpsychotic bipolar I depression, with or without rapid cycling, with a Montgomery Asberg Depression Rating Scale (MADRS) score ≥ 20 and a Young Mania Rating Scale (YMRS) score ≤ 12 . Subjects were randomized to 6 weeks double-blind, once-daily treatment with either lurasidone 20-60 mg, lurasidone 80-120 mg, or placebo. For the current analysis, the lurasidone groups were combined. The presence or absence of subsyndromal hypomanic symptoms at baseline was defined using the YMRS based on two criteria: (1) patients above or below the median baseline YMRS score of 4; and (2) patients with a score of ≥ 2 for two or more YMRS items.

RESULTS: Treatment with lurasidone ($n = 182$), compared with placebo ($n = 90$), was associated with significantly greater reduction in MADRS scores in subjects with subsyndromal hypomanic symptoms (-15.73 vs. -10.93 ; $p < 0.01$; MMRM; for the group with YMRS ≥ 4); and in subjects ($n = 213$) without subsyndromal hypomanic symptoms (-15.16 vs. -10.75 ; $p < 0.01$; MMRM for the group with YMRS < 4). When analyzed using criterion 2 (≥ 2 YMRS item scores with a severity ≥ 2 at baseline), treatment with lurasidone, compared with placebo, was associated with significantly greater reduction in MADRS scores in subjects with subsyndromal hypomanic symptoms (-16.29 vs. placebo -10.93 ; $p < 0.01$); and in subjects without subsyndromal hypomanic symptoms (-14.63 vs. -10.08 ; $p < 0.001$). Statistical interaction terms (lurasidone X hypomanic subgroup) were nonsignificant for both analyses, supporting the absence of a significant influence of subsyndromal hypomanic symptoms on lurasidone's efficacy in bipolar I depression. For subjects with vs. without subsyndromal hypomanic symptoms (YMRS ≥ 4 criterion), treatment with lurasidone and placebo were both associated with reduction at Week 6 in mean YMRS scores (-2.4 vs. -2.3). Discontinuation rates due to adverse events were comparable in subjects with and without subsyndromal

hypomanic symptoms for lurasidone (7.5% vs. 4.8%) and placebo (5.3% vs. 6.8%).

CONCLUSIONS: In this short-term study, the superior efficacy of lurasidone monotherapy vs. placebo in bipolar I depression was observed in adults presenting with and without clinically significant subsyndromal hypomanic features. In the subsyndromal hypomania group, treatment with lurasidone was well-tolerated, and was associated with a small reduction from baseline in hypomanic symptomatology.

FUNDING: Sponsored by Sunovion Pharmaceuticals Inc.

Switching to Lurasidone in Patients with Schizoaffective Disorder: Safety, Tolerability and Effectiveness

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ABSTRACT: Study Objectives: Lurasidone is an atypical antipsychotic approved for the treatment of schizophrenia. Limited information is available describing the safety, tolerability and effectiveness of lurasidone in schizoaffective patients. The objective of this post-hoc analysis was to evaluate the safety, tolerability, and effectiveness of switching stable patients with a diagnosis of schizoaffective disorder to lurasidone utilizing three different switch strategies.

METHOD: Non-acute patients with a diagnosis of schizophrenia or schizoaffective disorder who were considered to be appropriate candidates for switching current antipsychotic medication were randomized to three open-label lurasidone switch strategies: a 40/40 group (N = 74) was started on 40 mg/d for 14 days; a 40/80 group (N = 88) was started on 40 mg/d for 7 days, then increased to 80 mg/d for 7 days; and an 80/80 group (N = 82) was started on 80 mg/d for 14 days. The prior antipsychotic was tapered off (50% step-down at the end of week 1; discontinuation after week 2). All patients were then treated for 4 weeks with lurasidone 40–120 mg/d. The primary outcome variable, treatment failure, was prospectively defined as any occurrence of: insufficient clinical response, exacerbation of underlying disease or discontinuation due to an adverse event.

RESULTS: Of the 244 patients randomized, 91 (37%) met DSM-IV-TR criteria for schizoaffective disorder; mean age of initial onset was 26 years, and mean age at onset

of the current episode was 39 years; over half had a history of ≥ 4 hospitalizations. 81.1% of all patients (N = 244), and 82.4% of schizoaffective disorder patients (75/91) completed the 6-week study. Of these 91 patients, 6.6% (6 patients) discontinued due to adverse events. No schizoaffective disorder patient discontinued due to insufficient clinical response and no clinically meaningful differences in completion rates were observed between the three initial dosing strategies employed in this study. Two schizoaffective disorder patients experienced treatment failure in each group, for an overall treatment failure rate of 6.7% (6/89). The five most commonly reported adverse events in patients with schizoaffective disorder were nausea (22.5%), insomnia (14.6%), akathisia (12.4%), vomiting (10.1%), and headache (9.0%). The mean PANSS total score at baseline in the schizoaffective disorder population was 72.1, with an LS Mean change at Week 6 of -6.3 (95% CI: -8.1 ; -4.5 ; LOCF); similarly, CGI-S scores showed a LS mean change at Week 6 of -0.3 (95% CI: -0.4 ; -0.2).

CONCLUSIONS: Lurasidone was effective and well-tolerated in stable patients with a diagnosis of schizoaffective disorder who were switched from other antipsychotic agents. Study completion rates and treatment failure rates were similar across the three switch strategies.

FUNDING: Sponsored by Sunovion Pharmaceuticals Inc.

TRIAL REGISTRATION: clinicaltrials.gov identifier: NCT01143077.

Initial 2-Week Outcomes Following 2 Methods of Switching to Iloperidone from Aripiprazole in Patients with Schizophrenia

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ABSTRACT: Objective: Changing (switching) antipsychotics is a common therapeutic strategy when a patient's current antipsychotic has limited efficacy/tolerability. We report results observed within the first 2 weeks following a switch to iloperidone (ILO) from aripiprazole (ARI).

METHODS: This analysis uses data from a 12-week, multicenter, open-label outpatient trial evaluating 2 approaches (gradual vs immediate) to switching to ILO in adults with schizophrenia exhibiting efficacy and/or tolerability problems with risperidone (RIS), olanzapine (OLA), or ARI. 500 Patients (aged 18–64y) diagnosed with schizophrenia and experiencing inadequate efficacy and/or poor tolerability were switched from 1 of 3 preswitch agents: RIS (n = 175), OLA (n = 155), or ARI (n = 170). Patients were randomized 1:1 to either a gradual-switch (ie, dose reductions over the first 2 weeks [to 50% on Day 1, 25% at Week 1, 0% at Week 2]; n = 240) or an immediate-switch group (ie, immediate discontinuation of current treatment at baseline; n = 260) to open-label ILO (all patients started on Day 1). ILO was titrated over 4 days to 6 mg BID, followed by increases (≤ 4 mg/d) up to 12 mg BID, if needed. The primary variable was the Integrated Clinical Global Impression of Change (I-CGI-C), rated from 1 (improvement) to 7 (worsening). The primary analysis time point was at Week 12.

RESULTS: For patients switching from ARI, over the first 2 weeks of ILO treatment, discontinuations for any reason occurred in 8.7% of patients in the gradual-switch group and 11.1% in the immediate-switch group. Over the first 2 weeks of ILO treatment, discontinuations due to treatment-emergent adverse events (TEAEs) were higher in Week 1 vs Week 2 in both the gradual-switch (5.0% to 0%) and immediate-switch (10.0% to 4.7%) groups. The incidence of spontaneously reported TEAEs was higher during Week 1 vs Week 2 for both groups (gradual switch, 58.8% to 25.0%; immediate switch, 54.4% to 31.8%). Analysis of a common TEAE associated with ARI-to-ILO switch (dizziness) revealed lower rates in patients switched from ARI gradually (10.0%) vs immediately (16.7%) during Week 1. At Week 2, both switch groups demonstrated a decline from Week 1 rates (1.3%, gradual; 2.4%, immediate). In addition, I-CGI-C scores improved for both the gradual- and immediate-switch groups over the first 2 weeks: the percentage of patients with a rating of much or very much improved on the I-CGI-C (ie, responders) was 7.6% (Week 1) and 20.0% (Week 2) for the gradual-switch group and 13.3% (Week 1) and 27.8% (Week 2) for the immediate-switch group.

CONCLUSION: Switching from ARI to ILO either gradually or immediately demonstrated subtle clinical differences regarding clinical response within the first 2 weeks of therapy. Whereas the gradual-switch method (ie, cross-titration) revealed lower initial rates of dizziness, the immediate-switch method appeared to yield a higher percentage of responders within the first 2 weeks.

Narcissism: A Novel Concept to Integrate into Obesity Prevention and Treatment Efforts

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ABSTRACT: Study Objective: With obesity reaching epidemic proportions, health care professionals must create new and creative solutions to reduce obesity, and to assist this vulnerable population. Since the factors that lead to obesity are behavioral in nature, i.e. overeating and inactivity, arming patients with positive mental outlooks of their situations could be beneficial in their efforts to reduce bodyweight and improve health. Thus, this research aims to ascertain if narcissism, a term generally viewed as negative, can be instilled in patients in small, healthy doses to lead to positive lifestyle habits associated with maintaining positive self-image.

METHODS: A multi-disciplinary literature review was conducted to ascertain if there was any evidence that narcissism could be applied to lifestyle for positive outcomes in health and appearance, while limiting the negative effects of excessive love with one's appearance.

RESULTS: Behavioral science research, anecdotal evidence of past bodybuilders, as well as fitness culture advocates demonstrates that people who have an interest in how they appear will lead healthy lifestyles to support their physique goals. This suggests that small doses of narcissism can be useful in treating obesity from a behavioral standpoint.

CONCLUSIONS: Many personality traits are viewed on a spectrum, instead of an all-or-nothing perspective. This presentation argues that narcissism should also be placed on a spectrum, with the usual excessive narcissism being self-defeating on one pole, and little to no self-love being dangerous in its own right on the other pole. Health care professionals should encourage their overweight or obese patients to assume a more narcissistic, or self-loving role in their body recomposition efforts. This should be approached with caution, but since the literature supports the concept, this form of behavioral therapy could be beneficial in treating obesity in clinical practice.

FUNDING: There was no funding for this study.

An Axis I and II Survey of Patients with Fibromyalgia

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ABSTRACT: Study Objectives: The impact of comorbid rheumatologic disease and psychiatric illness has been investigated previously and shows an overall negative impact on patient's quality of life, function, and mortality. Fibromyalgia (FM) has a particularly close relationship with concurrent diagnoses of Axis I and Axis II psychiatric disorders. Despite this, there is a paucity of reported evidence in this area, and this poster further investigates the association between Axis I/II disorders and FM. We hypothesized a high rate of comorbidity in this patients ample.

METHODS: A survey was conducted of 49 subjects who were recruited from an ongoing drug trial for FM pain treatment. Written informed consent was obtained after local IRB approval. Axis I and Axis II psychiatric diagnoses were ascertained by means of PDSQ and PDQ-4 subjective rating scale use respectively.

RESULTS: The average duration of FM was 91.76 months. The average age of subjects was 49.29 years. Forty-one (85.41%) patients with fibromyalgia had an Axis I. The current rate of mood disorder was 61.70% and anxiety disorder was 68.75%. The most common Axis I disorders were somatic disorder (75%) and dysthymic disorder (54.16). Twenty-seven (56.25%) patients presented with personality disorder. Avoidant personality disorder (27.08%) was the most common followed by paranoid personality disorder (22.91%). Data from two subjects were not analyzed due to rating scales not being fully completed.

CONCLUSIONS: In our patient sample, 85.4% of patients had a coexisting Axis I disorder and 56.3% of patients had a coexisting Axis II disorder. According to the National Institute of Mental Health, the lifetime prevalence of any mood disorder in people age 45-59 is 22.9%, as opposed to our finding of 61.7% in the FM population. Most striking is the discrepancy between the prevalence of dysthymic disorder in the general population versus that in our patient population, namely 3.7% (ages 45-59) compared to 54.16% in our FM sample. These large discrepancies suggest the need for further exploration and ideally mutually beneficial treatment strategies may be studied in an outcome based manner. Further studies will be necessary in order to explore the hypothesis that treating concurrent Axis I and Axis II disorders with the standard psychotropic medications and psychotherapy should provide benefit to patients who suffer from FM comorbid with psychiatric disorder. Theoretically, in the CNS there should be overlap between symptoms experienced by FM and psychiatric disorder patients, and given this, there may be overlap in treatment responses and these types of outcome studies warrant future investigation.

FUNDING: None. This poster was created as a research project by a second year psychiatry resident who is planning to attend the Congress.

Management of Resistant Catatonia

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ABSTRACT: Catatonia as a phenomenon has been well described with a schizophrenic illness, severe mood disorders or periodic catatonia disorder. Benzodiazepines trial should be considered in patients with suspected psychogenic catatonia as long as no contraindication exists such as seriously increasing risk of respiratory or hepatic failure. There have been no studies specifically designed to address the benzodiazepine treatment response of persistent catatonic states. Catatonic patients who do not recover immediately with lorazepam may respond to a longer course or higher doses of the medication after failure of ECT. In this case response to Lorazepam suggests that a certain group of patients may require long-term treatment with lorazepam, especially those who may have down-regulation of GABA-A receptors.

CASE DESCRIPTION: 38 year old African-American male with a history of Schizophrenia, disorganized type for 20 years, transferred from medical floor to psychiatric unit for suicidal ideation, auditory and visual hallucinations, disorganized speech, anxiety and posturing. Also patient was pacing, unresponsive to commands, selectively mute and ambivalent. Past psychiatric history: first onset of psychosis at age 17 with multiple psychiatric admissions. For the past three month patient has had multiple psychiatric hospitalizations for disorganized behavior, selective mutism and auditory and visual hallucinations with unsuccessful trial of different neuroleptics. Prior to that patient was able to maintain full time job.

MEDICAL HISTORY: Hypertension, diabetes mellitus type 2, hyperlipidemia. At the time of admission CBC, BMP, TFTs, UDS, ECG, and CT scan of the head all within normal limits. RPR negative. Course of hospital stay: He was started on ziprasidone 60 mg twice a day, sertraline 50 mg gradually titrated up to 150 mg daily, lorazepam 1 mg every 12 hours titrated up to 2 mg three times a day. On this regiment patient developed tachycardia and high blood pressure. Per medicine recommendation, ziprasidone was changed to risperidone M-tabs 1.5 mg every 12 hours without any significant improvement. When patient did not respond to trials of different

neuroleptics, ECT was considered. He received ten ECTs without an improvement of psychosis. Trial of colzapine was initiated but discontinued after patient's WBC count dropped below 3000. Once again lorazepam was considered to manage catatonia in addition to olanzapine for psychosis treatment. Patient's catatonic symptoms improved but he still remains psychotic. Other challenge in this case was concurrent metabolic syndrome.

We can conclude that for some patients, who do not respond to neuroleptics and ECT, long-term lorazepam treatment may be the only solution for catatonia management. Further research is needed to explore effectiveness of long-term lorazepam for treatment of resistant catatonia.

Agomelatine Trial in Depression in Community Psychiatric Setting

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ABSTRACT: Background: Agomelatine is an antidepressant of novel mode of action. Its efficacy and tolerability was tested in an open labile study in a community psychiatric outpatient setting.

METHODS: Patients who attended outpatient clinic covering Billericay and Wickford which are in semirural affluent South of England were tried on agomelatine if they failed to respond to two antidepressants (one is SSRI and the other is SNRI), or suffered from side effects with other antidepressants for a period of nine months. They were reviewed regularly every 6–12 weeks. Liver function tests were done before start, and after, 6, 12, 24 weeks. Results were input to a Excel Microsoft sheet and analysed.

RESULTS: 48 patients were recruited.

20 males, 29 females.

5 patients stopped after a few days to a few weeks because of side effects.

10 patients stopped after a few weeks because of lack of effects.

6 patients needed to be topped up to 50 mg.

6 patients needed mirtazapine 15 mg as an add on treatment.

No patient developed abnormal liver function test.

No patient switched into manic episode.

DISCUSSION: Agomelatine has its place as antidepressant. It is not used as a first line antidepressant. This study has shown that patients response about 30% had to stop it because of lack of efficacy and side effects. Patients who continued on it didn't develop abnormal

liver enzymes. 24% needed either to go to 50 mg to fully respond or to add mirtazapine.

CONCLUSION: Current antidepressants are still lacking the efficacy in all types of depression. Agomelatine has got its place to treat some patients who don't respond to first line antidepressants, but it still have its side effects and some patients don't respond to it.

Three Prospective Clinical Studies Demonstrate Improved Clinical Outcomes with GeneSight Psychotropic, A Pharmacogenomic Decision Support Product

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ABSTRACT: Study Objectives: Antidepressants are among the most widely prescribed medications, yet MDD continues to generate the greatest economic and resource burden and only half of patients remit following an initial antidepressant trial. This study evaluated GeneSight Psychotropic, a pharmacogenomic (PGx) test, for its ability to predict outcomes and improve therapeutic efficacy in treating major depressive disorder (MDD).

METHODS: In 3 depression studies, DNA from patient buccal swabs was sent to the AssureRx Health CLIA and CAP accredited laboratory. Allelic variations in genes for CYP2D6, CYP2C19, CYP1A2, the serotonin transporter (SLC6A4) and the serotonin receptor (HTR2A) were analyzed to generate the GeneSight Psychotropic report. The report stratified 26 FDA-approved antidepressant and antipsychotic medications utilizing the PGx data for each patient. Test results were used by clinicians at their discretion in supporting medication type and/or dose changes with patients in the GeneSight-directed group, while results were not sent to clinicians of patients in the treatment as usual (TAU) group.

RESULTS: The GeneSight test increased the odds of clinical response (50% reduction in HAM-D17) by 2.3-fold in the 3 case-control studies of 258 patients with resistant depression ($p = 0.004$). Clinical improvement was greater in the GeneSight group versus TAU ($p < 0.0003$). Among the 183 patients who completed two of the prospective studies, 22% were identified as being on at least one "red" drug categorized as "Use with caution and more frequent monitoring". After eight weeks, the 23 TAU patients on red status drugs

showed the smallest symptom improvement compared to the 51 TAU yellow drug status patients (“Use with caution”; $t = 2.65$, $p = 0.009$), the 76 TAU pooled green and yellow drug status patients ($t = 2.25$, $p = 0.03$), and the 18 red drug patients who received the GeneSight report ($p = 0.02$). Symptom improvement was greatest for PGx-directed patients who had been prescribed two or more red drugs ($p < 0.01$).

CONCLUSION: GeneSight Psychotropic can augment antidepressant responses when clinicians incorporate test results to support their medication selections, and can predict patients who may show significant clinical improvements.

FUNDING: Two of the three studies were fully funded by the Mayo Clinic Discovery Translation Grant. The third study was fully funded by AssureRx Health, Inc. AssureRx Health, Inc. provided in-kind services consisting of shipping of buccal samples, sample genotyping, and GeneSight report provision. Data analysis personnel were provided by AssureRx Health, Inc.

Vortioxetine, A Multimodal Investigational Antidepressant: Modulation of GABA and Glutamate Neurotransmission in Rat Models of Depression and Cognitive

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ABSTRACT: Background: Vortioxetine is 5-HT₃, 5-HT₇ and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and 5-HT transporter inhibitor. Vortioxetine increases brain extracellular 5-HT, dopamine, norepinephrine and acetylcholine levels in freely-moving rats, has antidepressant activity in behavioral models, and restores cognitive function in preclinical behavioral models and as shown by quantitative EEG. The neurobiological substrate for depression and cognitive function is complex, involving monoamine and GABA and glutamate neurotransmission.

OBJECTIVES: To assess the modulation of GABA and glutamate neurotransmission by vortioxetine in rat models.

METHODS: We used patch-clamp recordings of CA1 pyramidal cells and theta-burst-induced LTP in hippocampus slices, in vivo LTP recording in CA1 in dorsal

hippocampus in acutely stressed rats, 5-HT₃ receptor agonist-induced GABA increase in the PFC of freely-moving rats, forced swim test in a progesterone withdrawal model of depression (where dysfunction of GABA neurotransmission plays a key role), and executive function in the extra dimensional set shifting task after subchronic PCP (NMDA receptor antagonist).

RESULTS: In rat hippocampal slices, vortioxetine blocked 5-HT-induced increase in sIPSC in pyramidal neurons (possibly through blockade of 5-HT₃ receptors on GABA interneurons) and enhanced theta-burst-induced LTP (most likely by decreasing inhibition of pyramidal neurons). In vivo, vortioxetine prevented stress-induced decrease of hippocampal LTP. Vortioxetine inhibited 5-HT₃ receptor agonist-induced increases in extracellular GABA levels in the PFC. In the progesterone withdrawal model, vortioxetine (but not fluoxetine or duloxetine) significantly reduced depression-like behavior after chronic (2 weeks) or acute (2 days) treatment. Neither brain 5-HT nor plasma tryptophan levels were altered by progesterone withdrawal. Vortioxetine dose-dependently restored PCP-induced impairment of extra-dimensional set shift performance to vehicle control levels.

CONCLUSIONS: These findings support the hypothesis that modulation of GABA and glutamate neurotransmission may significantly contribute to vortioxetine's effects in preclinical models of depression and cognitive function.

A Double-Blind, Placebo-Controlled, Multicenter Trial of Adjunctive Armodafinil for Major Depressive Episodes Associated with Bipolar I Disorder

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ABSTRACT: Study Objective: To evaluate the efficacy and safety of armodafinil as an adjunctive therapy for major depression associated with bipolar I disorder.

METHODS: Patients 18–65 years of age with BP I disorder currently experiencing a major depressive episode while taking 1 or 2 of the following: lithium, valproate, olanzapine, aripiprazole, risperidone, lamotrigine, or ziprasidone (ziprasidone only in combination with lithium or valproate) were randomized to armodafinil 150 mg, 200 mg, or placebo. The primary efficacy

assessment was the mean change from baseline to week 8 in the 30-item Inventory of Depressive Symptomatology-Clinician-Rated (IDS-C30) total score.

RESULTS: Of 786 patients screened, 433 were randomized (n = 199 placebo, n = 201 armodafinil 150 mg, n = 33 armodafinil 200 mg). Randomization to the 200 mg armodafinil group was discontinued early in the study by protocol amendment. There was a significantly greater decrease at week 8 for the 150 mg armodafinil group compared with placebo for LS mean (SEM) IDS-C30 total score (-21.7 [1.1] vs -17.9 [1.1]; P = 0.0097). The percentages of IDS-C30 responders ($\geq 50\%$ decrease from baseline) were significantly greater in the 150 mg armodafinil group vs placebo at week 8 (55% [83/150] vs 39% [61/155]; P = 0.0084) and final visit (46% [91/197] vs 34% [67/196]; P = 0.0147). Discontinuations due to adverse events (AEs) were 4% (7/199) for placebo, 6% (11/198) for armodafinil 150 mg, and 6% (2/32) for armodafinil 200 mg. AEs observed in $>5\%$ of either the 150 mg armodafinil or placebo group and more frequently in the 150 mg armodafinil group were diarrhea, 9% (17/198) vs 7% (13/199), and nausea, 6% (11/198) vs 5% (9/199), respectively. Headache, 22% (7/32), insomnia, 13% (4/32), and nausea, 9% (3/32) were the 3 most common AEs for the 200 mg armodafinil group. At final visit, 5% (9/183) of patients in the placebo group, 2% (3/186) of the 150 mg group, and 4% (1/28) of the 200 mg group had clinically relevant ($\geq 7\%$) weight gain from baseline. Young Mania Rating Scale, Hamilton Anxiety Scale, and Insomnia Severity Index scores decreased from baseline to final visit in all groups.

CONCLUSION: Armodafinil 150 mg significantly improved symptoms of a major depressive episode associated with bipolar I disorder when given as adjunctive treatment compared with placebo. Safety data indicate that adjunctive armodafinil 150 mg was generally well tolerated.

FUNDING: Teva Pharmaceuticals.

Case Report

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MB is a 16 year old Latina woman who was referred to Reproductive Psychopharmacology by her psychiatrist at 12 weeks gestation. She was first diagnosed at age 13 with symptoms with DSM-IV major depressive disorder. She had a suicide attempt at age 13, was adopted and the pregnancy was unintended. She lives at home with her family that is very supportive.

Prior pharmaceutical treatment included trials of Lithobid at therapeutic doses, Fluoxetine, Alprazolam

and Vyvanse. When she became pregnant, she was on Lithobid and Fluoxetine 40 mg. The Lithobid was tapered and discontinued by week 4 of gestation. She experienced an increase in her depressive and anxiety symptoms as indicated by her Beck score of 20 and Hamilton-D score of 60 while on Prozac monotherapy. She presented to reproductive psychopharmacology and was placed on L-Methylfolate 15 mg while continuing Fluoxetine. Fluoxetine was discontinued after 3 weeks of TMS therapy. TMS therapy was begun within 48 hours after initial contact with our office corresponding with 12 weeks gestation. She received 30 treatments over a 6 week period, and then treatment once weekly throughout gestation, carried out until 6 weeks postpartum. Parameters for TMS were 85% MT, PPS 5, stimulations time 14 second, interval 39 seconds and TX (ramp) 5. She showed response in 2 weeks and remission in 4 weeks. External fetal monitoring was begun at 34 weeks gestation. Monitoring began 10 minutes prior to initiation of TMS and continued for 55 minutes post TMS treatment. There were at least 4 accelerations while TMS was being administered.

Sonographic findings at 37 weeks: AFI: 34 mm $< 2.5\%$, oligohydramnios, and symmetrical intrauterine fetal retardation. Induction of labor was begun; clear amniotic fluid and epidural anesthesia were done. Live born male infant was delivered, APGAR 9/10, 6 lbs. 8 oz., normal head circumference. Pediatric evaluation revealed no abnormalities and the baby was handed back to the mother.

SUMMARY: TMS was effective in sustaining euthymia from week gestational week 13–6 weeks postpartum. Only the medical food L-Methylfolate had been taken. One cannot say anything about congenital anomalies from this case as TMS was begun 12 weeks. This treatment was devoid of maternal and fetal complications. TMS treatment was effective in treating symptoms of depression, facilitated maternal/infant bonding as he was taken from mother to either the observations nursery or NICU. It is likely that this treatment helped prevent postpartum depression, shortening hospitalization and cost savings to the insurer. TMS has been shown to be effective in both intrapartum depression and postpartum depression in previous studies. A significant finding was a reactive fetal non-stress test during treatment with TMS.

There remains much controversy of the use of psychotropics in pregnancy documented in multiple studies. These complications range from autism slowed infant motor activity, maternal fetal bonding, pulmonary hypertension, Ebsteins anomaly, decreased infant head size and low birth weight. There was no evidence of postpartum depression at 6 weeks postpartum.

At present there is no evidence of these concerns with TMS. I would suggest trials in the early first trimester to answer the questions of anomalies. There is an abundance

of literature showing the efficacy of TMS in the treatment of major depression awaiting FDA approval. Since TMS is a local, non-invasive and non-systemic treatment, there is less chance of systemic complications that may affect pregnancy and postpartum.

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Cariprazine in Acute Exacerbation of Schizophrenia: A Fixed-Dose Phase III, Randomized, Double-Blind, Placebo- and Active-Controlled Trial

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ABSTRACT: Objective: Cariprazine (CAR), an orally active and potent dopamine D3/D2 receptor partial agonist with preferential binding to D3 receptors, is in development for the treatment of schizophrenia and bipolar mania. CAR has demonstrated efficacy in patients with schizophrenia in Phase II (NCT00694707) and Phase III (NCT01104779) studies. This Phase III trial (NCT01104766) further evaluated the efficacy, safety, and tolerability of CAR in patients with acute exacerbation of schizophrenia.

METHODS: This was an international, double-blind, placebo (PBO)- and active-controlled, fixed-dose study of 9 weeks duration (up to 7-day washout, 6-week double-blind treatment, 2-week safety follow-up). Patients with schizophrenia (minimum of 1 year; current episode <2 weeks) were randomized to CAR 3 mg/d, CAR 6 mg/d, aripiprazole (ARI) 10 mg/d (active control), or

PBO. Patients were hospitalized at screening and for at least 4 weeks of double-blind treatment. Primary efficacy parameter was change from baseline to Week 6 in PANSS total score analyzed using a mixed-effects model of repeated measures (MMRM) and adjusting for multiple comparisons; secondary efficacy parameter was change from baseline in Clinical Global Impressions-Severity (CGI-S) score. Safety was evaluated by adverse events (AEs), laboratory values, vital signs, ophthalmology assessments, electrocardiograms (ECGs), and extrapyramidal symptom (EPS) scales.

RESULTS: A total of 617 patients were randomized and received treatment (PBO, 153; CAR 3 mg/d, 155; CAR 6 mg/d, 157; ARI, 152) (Safety Population); 66% completed the study. Change from baseline to Week 6 on PANSS total score was significantly greater for both CAR groups vs PBO (LSMD vs PBO: CAR 3 mg/d = -6.0, P = .0044; CAR 6 mg/d = -8.8, P < .0001); both CAR groups also showed significantly greater improvement on CGI-S scores relative to PBO (LSMD: CAR 3 mg/d = -0.4, P = .0044; CAR 6 mg/d = -0.5, P < .0001). ARI was significantly superior to PBO on both measures (LSMD: PANSS = -7.0, P = .0008; CGI-S = -0.4, P = .0001; not adjusted for multiple comparisons). Treatment-emergent AEs (TEAEs) were reported in 67%, 61%, 71%, and 66% of PBO, CAR 3 mg/d, CAR 6 mg/d, and ARI patients, respectively. Common TEAEs (≥5% and twice the rate of PBO) were akathisia in the CAR 6 mg/d group, and abdominal discomfort and nausea in the ARI group; most TEAEs were mild to moderate in severity. Patients in the CAR and ARI groups relative to PBO had greater EPS (parkinsonism) and akathisia as determined by SAS and BARS, respectively.

CONCLUSION: CAR 3 mg/d and 6 mg/d demonstrated significant improvement relative to PBO on PANSS total score and CGI-S. CAR was generally well tolerated, although the incidence of EPS and akathisia was greater for CAR than PBO.

SOURCE OF FUNDING: Forest Laboratories, Inc. and Gedeon Richter Plc.

A Preliminary Report of a University Hospital Behavioral Crisis Response Team LED by Psychiatry

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ABSTRACT: Background: Violence in health care settings is an escalating public health issue. Assault rates for health care workers are higher than in the private sector. Evidence suggests that violence in the work place impacts individuals' physical and mental well-being and may result in organizational problems like declined productivity. Additionally, health care settings have an obligation to maintain patient safety. Reports demonstrate a need for preventive strategies, yet few approaches have been studied to determine effective implementation. A few evaluative studies support effectiveness of preventive strategies, but actually fail to evaluate implementation. Other issues (e.g., under-reporting) are overlooked. New Jersey passed The Violence Prevention in Health Care Facilities Act (2008) that resulted in the development of an inter-professional highly trained and experienced Behavioral Crisis Response Team (CRT) at an inner city tertiary care University Hospital.

OBJECTIVES: To determine utilization of the CRT and document completion and to characterize incidents, team response, interventions and outcomes to further improve violence prevention strategies.

METHODS: There were 304 CRT calls between June 2010 (initiation of CRT) and April 2012. Associations between possible predictor variables (type of incident, time, location, etc.) & document completion compliance (indicating knowledge & understanding of the CRT policy) were evaluated using bivariate (Chi-Square) and then multiple sequential logistical analyses. SAS was used for all analyses. Use of medication or restraints were also tracked.

RESULTS: CRT utilization increased over time. Most calls were for instances of physical abuse from male patients under 40 years old during the night shift (7pm-7am). Sixty percent of calls were completely documented and that was significantly associated with location ($p < 0.05$). Medical Surgical units were 10 times more likely to document incidents than the emergency department. Physical abuse was most common, followed by threatening behavior and verbal abuse. In 16% of incidents no medication was used; 27% of incidents did not require restraints of any type.

DISCUSSION: Despite an increase in documentation compliance over time, overall compliance needs improvement. Maximizing staff awareness when new policies are implemented, development of additional strategies and strengthening effective ones, improved accessibility and facility of documentation with emphasis on documentation relevance, and the importance of having information may enhance compliance. Training and educational programs for nurses and other responsible health care workers can

be targeted to the highest risk areas, locations with high volume of incidents and most trouble with documentation. Future program evaluations should include employee observations of operational practicality and associated impact of violent incidents on employee health and well-being, as well as, patient safety.

Advanced Generation Folate Therapy Completely Addresses the Needs of the Remethylation and Transsulfuration Cycles

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² Strategic Edge Communications, Inc.

ABSTRACT: Demonstrate that EnLyte contains the optimal blend of ingredients to address the needs of the remethylation and transsulfuration cycles, maximizing production of neurotransmitters and reducing homocysteine.

Artist Talent and Mental Illness... Inhibition or Synergism??

Hellme Abdullah Najim, MBCh, B FRCPsych

ABSTRACT: Introduction: Relationship between creativity and mental illness has been noted since Aristotle. It has been postulated that this relationship can be a positive one through one of four mechanisms. Either through inspiration through illness, altered creativity, identity under threat or troubled personalities.

BACKGROUND AND METHODS: One of those clear examples is Dostoyevsky. By going through his life and concentrating on stressful events and his illness, I will try to give examples of his work and letters to his doctor and to his brother and friends, how he used both as inspirational material to produce his very original literary classics.

DISCUSSION: Dostoyevsky suffered from physical and mental illness. He had very traumatic events in his childhood. He was sentenced to death, then it was reduced to imprisonment in Siberia. He suffered from epilepsy and he was a gambler. His novels are full of characters who describe their feelings and symptoms of epilepsy, they were his account about this intriguing illness. He gave us a very lucid and clear account of epilepsy. In fact, he was very accurate in describing the ecstatic aura to a degree where he described it before it was coined by neurologists.

In this talk I try to elucidate the status of epilepsy as an illness in the nineteenth century from the scientific point of view and Dostoyevsky's role in describing symptoms and phenomena which helped later on in defining and explaining this illness.

This talk is going to give examples of Dostoyevsky's characters, his letters to his doctors and friends and also his behavior.

CONCLUSION: I will conclude by stating the influence of creative artist in highlighting their illnesses and helping their doctors in describing the symptoms, which will help doctors and patients with future treatment. It will also help to combat the stigma of that illness and the concept of mental illness.

Efficacy of Risperidone Long Acting Injectable Depot (RLAI) as a Maintenance Treatment of Patients Suffering from Schizophrenia

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ABSTRACT: Background: Adherence to treatment is a major issue in relapse prevention in schizophrenia. Injectable depot has been claimed to improve covert and overt non-adherence. A study in the North of England has shown that risperidone long acting injectable form has reduced number of admissions and number of days stayed in hospital. Our study aimed to replicate the previous study in the South of England.

METHODS: A retrospective study was conducted in South Essex Foundation University NHS trust which selected every fifth patient who is on the Hospital Pharmacy list for RLAI. The following information was collected. Age, sex, diagnosis and medication, regular follow up, investigation of each patient which included weight, FBS, S. lipid and hormones at the start of treatment, at three months and six months intervals. Reasons for starting RLAI were recorded: Number of antipsychotics before RLAI, chronicity of the illness. Number of admissions and days stayed in each episode before and after RLAI. Patients were included if they stayed for one year or on RLAI. Mirror image analysis was carried out.

RESULTS: 65 notes were reviewed. 70% males. 70% between 18–50 years. 80% had the illness more than 5 years and 50% more than 10 years. 50% had comorbidity with physical illness. Non-adherence to oral medication was the most common reason for starting on RLAI.

Number of admission and number of days stayed in each admission were reduced after RLAI in a statistically significant manner.

CONCLUSIONS: RLAI has reduced number of admission and number of days stayed in hospital in a statistically significant manner. Adherence has improved and it may be the cause of preventing relapse in these patients.

Harnessing the Synergy of Intravenous Ketamine and Electroconvulsive Therapy in Treatment-Resistant Depression

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ABSTRACT: Introduction: An intravenous slow infusion of the glutamate NMDA/AMPA receptor antagonist ketamine has emerged as an effective, safe and rapidly acting antidepressant. Its efficacy is reported in treatment-resistant recurrent major depression and bipolar depression. Electroconvulsive therapy is widely recognized as an effective modality for treatment-resistant depression.

OBJECTIVES: The purpose of the present paper is to explore whether there are clinical situations wherein the two strategies can be safely combined to provide a synergistic effect.

METHOD: The authors present their experience of combining intravenous slow infusions of ketamine in patients who failed to respond to successive trials of antidepressant medications and were scheduled to receive a course of electroconvulsive therapy. Following informed consent the patients received a standardized intravenous dose of 50 mg of ketamine infused slowly over 50 minutes immediately following the ECT stimulus. The ketamine infusions continued during recovery from anesthesia, under close observation in the post-anesthesia care unit.

RESULTS: Ketamine infusions have been employed by the authors for about 2 years. They are utilized in 3 clinical situations: a) in patients with profound hopelessness, nihilism and suicidal ideation, with no expectation of recovery from depression, b) in patients receiving a course of ECT who display only a modest response to the initial 2–4 treatments, and c) in patients receiving maintenance ECT, wherein the duration of antidepressant response was less than 4 weeks. Of the many patients who have received intravenous infusions over the past 2 years, an immediate therapeutic benefit

has been observed in half of the cases. One patient complained of transient perceptual changes. Another patient experienced brief hypomanic symptoms. Two patients experienced transient anxiety. Several patients have received repeated infusions, without adverse effects.

CONCLUSIONS: An intravenous slow infusion of ketamine is a safe and effective adjunct to electroconvulsive therapy. It may serve to reduce the number of ECT treatments required and diminish memory loss. Conversely, the simultaneous use of two effective interventions may obscure the measure of therapeutic benefits derived from either one. This is particularly relevant considering the short-lived benefits reported with IV ketamine. Abbreviating a course of ECT with adjunctive ketamine may produce a more robust but less enduring therapeutic benefit.

Measuring the Effectiveness of Multiple Dose Progesterone on Sleep Quality: A Case Study

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¹SleepImage

ABSTRACT: : Difficulty sleeping and lack of restorative sleep are common complaints which can be troublesome and disabling to many. This is particularly challenging in women of peri- and menopausal age when hormone imbalances can contribute to impaired sleep quality. Both estrogen and progesterone play key roles in promoting healthy sleep and an imbalance in either significantly contributes to poor sleep quality and sleep-specific disorders (i.e. sleep disordered breathing and Restless Legs Syndrome). Progesterone administration has been associated with a decrease in sleep disturbances and an improvement in sleep quality.

STUDY OBJECTIVE: This case study aimed to measure sleep quality and determine appropriate dose of progesterone at night, in a menopausal woman.

METHODS: A busy executive, 50 year old female with sleep and anxiety issues was examined. Patient was taking growth hormone (0.2 mg), Lexapro (5 mg in the a.m.), regular Ambien (5 mg), magnesium (1 g), melatonin SR (5 mg) and melatonin IR (15 mg). Patient also was taking progesterone (25 mg). During 3 day wash-out period patient continued to take all medications except for progesterone. A baseline sleep quality test was performed for one night. Four nights later, patient took 50 mg of progesterone and a sleep quality test was performed. Six nights later, patient took 100 mg of progesterone and a sleep quality test was performed.

RESULTS: Patient was not sleeping well previous to baseline. Attempted to manage stress with meditation at night, along with sleep aids. Baseline night (no progesterone) revealed a Sleep Quality Index (stable vs. unstable sleep) of 0.88 (poor). The second study (50 mg progesterone) reported a Sleep Quality Index of 1.45 (better, but room for improvement) and patient stated that her sleep was ‘significantly improved’. On the third and final night (100 mg progesterone), the Sleep Quality Index dropped to 0.66 (poor), and the patient reported feeling ‘more stressed’.

CONCLUSIONS: Based on results from three nights without and with two different doses of progesterone, it was determined that sleep quality improved significantly during the night when 50 mg of progesterone was taken vs. 100 mg or no progesterone. Therefore, in this case, the optimal dose for positive patient outcome was 50 mg, both for sleep promotion and overall well-being. Furthermore, these independent measures provide an unbiased report of patient physiology while monitoring clinical therapeutic success.

FUNDING: Sleep quality monitoring device was given in-kind by SleepImage for patient testing.

Lisdexamfetamine Dimesylate (LD) in Adult Attention Deficit Hyperactivity Disorder (ADHD)

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ABSTRACT: Objectives: LD is a unique prodrug stimulant. After oral administration, LD is rapidly absorbed from the gastrointestinal tract and converted by hydrolytic activity of red blood cells to dextroamphetamine, which is responsible for its activity. LD was approved initially for the treatment of ADHD in children under the age of 12 up to 70 mg/day. Later, LD was approved for adults with ADHD at the same dose as for children. Our center would like to report about adult patients with ADHD needing above the recommend dose approved by United States of America Food and Drug Administration (FDA).

DESIGN AND METHODS: 11 Adult out-patients ages 30 to 60; 7 women and 4 men, were diagnosed with ADHD using the ADHD- IV scale and were treated with LD at initial dose of 70 mg/ day. Due to the lack of response; this dose was increased up to 280 mg/ day which is above the recommended dosage. Patients were closely monitored during their monthly visit for weight, blood pressure and pulse.

RESULTS: There was a marked improvement in the core of symptoms of ADHD when pre-treatment ratings were compared to post-treatment. There were no changes in vital signs. Some patients did lose some weight initially.

CONCLUSION: LD in adults with ADHD was well tolerated above the recommended dose of 70 mg/day with positive improvement in ADHD.

The use of LD above 70 mg is not approved by USA-FDA. This study is supported in part by the Minnesota Medical Foundation and Clinical Psychopharmacology funds.

Twelve Month Outcomes with Buprenorphine Implants for Opioid Dependence

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ABSTRACT: Background: An implantable formulation of buprenorphine (BPN) has been developed that delivers constant, low levels of BPN for up to six months and offers potential advantages over sublingual BPN by ensuring patient compliance and limiting diversion. Five studies have demonstrated that treatment with buprenorphine implants is well tolerated and effective. The main objective of the current study was to assess longer-term safety; secondary efficacy and treatment satisfaction evaluations were also conducted.

METHODS: 85 opioid-dependent subjects who had completed 6-months of double-blind treatment with either BI (n = 57), placebo implants (PI) (n = 8), or open-label sublingual BPN/naloxone (SL BPN) (n = 20) at 18 US sites were enrolled in a second 6-month phase in which all subjects received 4–5 buprenorphine implants (open-label).

RESULTS: No treatment-emergent adverse events led to discontinuation or were considered related to study drug. The most common adverse events reported were headache (12%), upper respiratory infection (8%), back pain (6%), and urinary tract infection (6%). Opioid withdrawal symptoms and craving were well-controlled, with 79% of subjects completing the second 6 months of treatment. Among subjects who completed the study, the majority agreed (somewhat or strongly) with positive statements and disagreed (somewhat or strongly) with negative statements about their treatment experience over 12 months. Patients treated with placebo or SL

BPN during the initial 6-month phase decreased their self-reported drug use by 25% and 20%, respectively, during the 6-month open-label phase when switched to buprenorphine implants.

CONCLUSION: Buprenorphine implants were well tolerated and effective for up to 12 months, with high rates of treatment satisfaction reported by subjects who completed the study.

The Use of a Novel Urine Drug Monitoring Test to Help Assess How Well Clinicians Predict Antipsychotic Medication Non-Adherence

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¹Ameritox, Ltd

ABSTRACT: Introduction: Prior research has established the critical role of maintenance antipsychotic pharmacotherapy in the management of schizophrenia, schizoaffective disorder, and bipolar disorder. Yet adherence to these drugs is a significant challenge for treating clinicians, and studies show that 50% of patients with these disorders do not take their antipsychotics consistently. Despite the key role of the prescribing psychiatrist in identifying and addressing non-adherence, relatively few studies have addressed how well psychiatrists and other prescribers are able to detect non-adherence. Furthermore, most of these studies relied on indirect measures such as pill counts, pharmacy refills and electronic monitoring.

METHODS: The current study utilizes a novel drug monitoring test to detect the presence of antipsychotic drugs and metabolites in urine and reports on the results of a pilot study comparing behavioral health clinicians' assessment of whether or not their patients were taking the antipsychotic(s) they prescribed as directed with the results of the urine monitoring test. Three psychiatrists and two psychiatric nurse practitioners working in a community mental health setting recorded their assessments for patients prescribed long-term antipsychotic medication. Subsequently, urine drug samples were obtained from these patients and analyzed for the presence of any of seven different antipsychotics using liquid chromatography/tandem mass spectrometry. The urine test result was then compared to the prescriber's assessment for the presence or absence of prescribed antipsychotic(s).

RESULTS: Of the 47 patient samples, 37 were classified as coming from patients the clinicians predicted would

have the antipsychotic medication present in their urine and 7 were classified as coming from patients where the clinician suspected non-adherence. Three samples had no clinician impression of status recorded. Of the 37 samples from patients believed to be taking their antipsychotic medication, drug was detected in only 28 samples. Thus, clinicians misclassified 9 out of 37 samples. Additionally, 15% (7/47) of samples also had a non-prescribed medication detected in the urine, while 17% (8/47) of the samples contained illicit drugs and/or alcohol. Overall, 43% of the samples evidenced some abnormality.

CONCLUSION: Utilizing a novel laboratory technology that directly detects the presence of antipsychotic in urine, this study produced findings consistent with existing literature regarding the relatively poor accuracy of clinical assessment of antipsychotic non-adherence. Given the serious consequences of antipsychotic non-adherence, the use of an easily administered, highly sensitive laboratory test may afford clinicians a new tool to more accurately identify antipsychotic non-adherence. Ameritox funded this research and will pay for the author's travel expenses and poster production.

Cognitive Behavioural Therapy (CBT) Via Email in General Anxiety Disorder

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ABSTRACT: Introduction: Generalized anxiety disorder (GAD) is characterized by excessive worrying, uneasiness and fear. Patients experience severe difficulty in controlling their worries and this significantly affects their functioning. Cognitive Behavioural Therapy (CBT) has been shown to yield clinical improvements in GAD that are superior to no treatment and nonspecific control conditions. However there are some barriers in delivering CBT treatment. These barriers include immigration to and living in another country where CBT in the same language is not available and the patient and the therapist have different cultural back-grounds which effects the rapport necessary to start a therapeutic relationship. Long waiting lists, therapist shortage and lack of access to therapist in remote areas are another problems in receiving CBT. Therefore using alternative methods to overcome these barriers seems necessary. With internet use ever rising, we designed this research to investigate the efficacy of CBT through email in GAD.

METHOD: All people who volunteered to take part in the study were assessed by an online chat interview.

62 subjects met the DSM-IV criteria for GAD and were all asked to complete the Beck Anxiety Inventory (BAI). All the participants were Farsi-speaking and lived inside or outside Iran. 31 participants were randomly assigned to 12 email-based CBT sessions and rest of the participants were put in the control group. Participants had to leave the study in case they started receiving treatment through other resources. BAI scores were again measured after treatment and at a 6-month and 1 year follow-up.

RESULTS: ANOVA was used to analyze the data. The BAI scores among these two groups were not significantly different before the treatment but significantly reduced in the group who received CBT both following 10-12 weeks of treatment and at 6-month and 1 year follow-ups. There was no significant changes in BAI score in the control group.

CONCLUSION: Our study showed that CBT by email is an alternative method of delivering CBT in anxiety disorders when in-person interaction is not possible due to barriers.

Effect of Posttraumatic Stress Disorder on Sleep Architecture in Patients with Obstructive Sleep Apnea

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ABSTRACT: Objective: Both Obstructive sleep apnea (OSA) and Posttraumatic stress disorder (PTSD) are conditions individually associated with sleep disruption and sleep architectural abnormalities. Comorbid PTSD in OSA patients adversely affects treatment of OSA as reported by Hurwitz T et al. Recent studies have established the association between PTSD and OSA in terms of higher co-prevalence. However, the effects of PTSD on sleep architecture and sleep characteristics in OSA patients need to be further evaluated. Therefore we conducted a case control study.

METHODS: A retrospective chart review of all veterans diagnosed with OSA in past 3 years by polysomnography (PSG) studies was conducted. Individuals with OSA and PTSD were assigned to cases (OSA with PTSD, n = 63) and similar number of consecutive charts selected as controls (OSA without PTSD, n = 63). The demographic variables (age, gender), data from PSG studies; total sleep time (TST), sleep efficiency, Apnea-Hypopnea index (AHI), REM.AHI, sleep architecture (Percent of time spent in Stage I, Stage II, Stage III, Stage IV and

REM sleep), Arousal Index, sleep and REM Onset, Periodic Limb Movement (PLM) Index (PLMI) and Arousal Index (PLMAI) were registered. Documented medical diagnosis affecting sleep; gastro-esophageal reflux (GERD), benign prostatic hypertrophy (BPH), asthma and medications affecting random eye movement (REM) sleep were extracted from medical records. Linear regression analysis was performed to determine if there was a significant difference between the OSA with PTSD and OSA without PTSD groups for each of the sleep characteristics.

RESULTS: There were no statistically significant differences between the two groups (OSA with PTSD and OSA without PTSD) for total sleep time (288.6 ± 63.03 vs. 300 ± 50.61 , minutes $p = 0.26$), sleep efficiency (77.53 ± 26.31 vs. 78.36 ± 12.26 , % $p = 0.74$), and OSA severity, as measured by AHI (28.63 ± 15.79 vs. 25.94 ± 19.73 $p = 0.40$). Also no difference was noted for sleep architecture (% of time spent in stage I, stage II, or stage III/IV sleep), the arousal index (18.1 ± 14.2 vs. 16.9 ± 13.6 , per hour $p = 0.62$) and sleep onset, REM, PLMD and PLMAI ($p > 0.05$). But the OSA with PTSD group had less REM sleep as a percentage of TST (11.49 ± 7.83 vs. 15.03 ± 7.52 , % $p = 0.01$).

CONCLUSION: Based on polysomnographic data no significant difference was observed in the sleep characteristics, OSA severity, arousal index and sleep architecture between the groups studied (OSA with and without PTSD) except that in OSA with PTSD group, less REM sleep was noted as a percentage of TST.

FUNDING: No funding.

Initial 2-Week Outcomes Following 2 Methods of Switching to Iloperidone from Olanzapine in Patients with Schizophrenia

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ABSTRACT: Objective: Changing (switching) antipsychotics is a common therapeutic strategy when a patient's current antipsychotic has limited efficacy/tolerability. We report results observed within the first 2 weeks

following a switch to iloperidone (ILO) from olanzapine (OLA).

METHODS: This analysis used data from a 12-week multicenter, open-label, outpatient trial evaluating 2 approaches (gradual vs immediate) to switching to ILO in adults with schizophrenia exhibiting efficacy and/or tolerability problems with risperidone (RIS), OLA, or aripiprazole (ARI). 500 Patients (aged 18–64y) diagnosed with schizophrenia and experiencing inadequate efficacy and/or poor tolerability were switched from 1 of 3 preswitch agents: RIS ($n = 175$), OLA ($n = 155$), or ARI ($n = 170$). Patients were randomized 1:1 to either a gradual-switch (ie, dose reductions over the first 2 weeks [to 50% on Day 1, 25% at Week 1, 0% at Week 2]; $n = 240$) or an immediate-switch group (ie, immediate discontinuation of current treatment at baseline; $n = 260$) to open-label ILO (all patients started on Day 1). ILO was titrated over 4 days to 6 mg BID, followed by increases (≤ 4 mg/d) up to 12 mg BID, if needed. The primary variable was the Integrated Clinical Global Impression of Change (I-CGI-C), rated from 1 (improvement) to 7 (worsening). The primary analysis timepoint was at Week 12.

RESULTS: For patients who switched from OLA, over the first 2 weeks of ILO treatment, discontinuations for any reason occurred in 7.6% of patients in the gradual-switch group and 11.8% in the immediate-switch group. Discontinuations due to treatment-emergent adverse events (TEAEs) were higher in Week 1 vs Week 2 in both the gradual-switch (5.1% to 2.6%) and immediate-switch (6.6% to 1.4%) groups. The incidence of spontaneously reported TEAEs was higher during Week 1 compared with Week 2 for both groups (gradual switch, 41.8% to 39.0%; immediate switch, 63.2% to 20.5%). Analysis of ILO's most common TEAE associated with OLA-to-ILO switch (dizziness) revealed lower rates in patients switched from OLA gradually (10.1%) vs immediately (14.5%) during Week 1. At Week 2, both switch groups demonstrated a decline from Week 1 rates (2.6%, gradual; 2.7%, immediate). In addition, I-CGI-C scores improved for both the gradual- and immediate-switch groups over the first 2 weeks: percentage of patients with a rating of much or very much improved on the I-CGI-C (ie, responders) was 1.3% (Week 1) and 16.5% (Week 2) for gradual-switch group and 6.6% (Week 1) and 18.4% (Week 2) for immediate-switch group.

CONCLUSION: Switching from OLA to ILO either gradually or immediately demonstrated subtle clinical differences regarding clinical response within the first 2 weeks of therapy. Whereas the gradual-switch method (ie, cross-titration) revealed lower initial rates of dizziness,

both switch methods yielded a similar percentage of responders after the first 2 weeks.

Cannabis: Neurobiological Model of Transition to Psychosis

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ABSTRACT: Cannabis is risk factor for the development of schizophrenia, although the exact biological mechanisms remain unclear. Purpose of this presentation is to explore trajectory for psychosis due to cannabis based upon a neurobiological model. A selective Pubmed search was carried out to construct a neurobiological model of pathway based upon our hypothesis. The hypothesis for this conceptual paradigm is that neurobiological changes exist and cannabis metabolites modulate these changes in a sequential manner from genetic expression, environmental and biological interaction and neurochemical dysfunctions leading to cognitive dysmatia. Dopamine remains a final common pathway which leads to core symptom manifestation of affective dysphonia. This symptomatic state unfolds into a psychotic state of affective symptoms due to acute consumption of cannabis in adolescence and post adolescence period. We conclude that a model of pathways based upon neurobiological changes can be conceptualized to explain complex process of cannabis leading to psychotic state. Construction of biological model for psychosis in relation to cannabis.

Factors Associated with Outcomes in Severely Emotionally Disturbed Children who Received Intensive Community Based in Home Mental Health Service

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ABSTRACT: Vieux U, Passman C, Morrissey J, Teploukhava O, Gomez S, Medeiros D, Ahmad, N.

OBJECTIVE: The purpose of this study was to explore demographic, clinical, and service utilization factors associated with treatment outcome among children with severely emotionally disturbed (SED) diagnosis

who enrolled in a community- based in-home mental health service.

BACKGROUND: The Home and Community Based Services - Waiver program (HSBC-W) was initiated in New York State in 1996 as a means of increasing access to intensive mental health services to youth who were at risk for being placed in residential treatment or institutionalized. The general Medicaid waiver provides medical assistance to children and adolescents who meet the eligibility criteria for Serious Emotional Disturbance and also reimburses several community-based services not previously in Medicaid reimbursement.

METHODS: Conducted within the St. Luke's-Roosevelt Hospitals Child and Family Institute, Children's Community Mental Health Services, (HCBS-W) collected de-identified information from 250 medical records of children and adolescents (aged 5-18 years) enrolled between 2004-2008. Clinical and service utilization factors included age, race/ethnicity, use of medication, and length of time in HCBS-W. Descriptive analyses were used to characterize the sample. Bivariate analysis (chi-square and t-tests) and a multinomial logistic regression model were used to examine associations between independent factors and program outcome (defined as success, failure, or neutral). Significant bivariate associations ($p < .15$) were included in the multinomial logistic regression model.

RESULTS: Ages ranged from 5-18 years old ($M = 12.3$, $SD = 3.24$); 62.8% of the participants were male ($n = 157$). The ages were divided into three age groups (5-8, $n = 19$, 9-12, $n = 47$, 13-18, $n = 70$). Race/ethnicity was distributed as follows: 48.4% Latino/Hispanic, 35.2% African American, 7.2% Euro-American, 8.4% Multi-racial, and .4% Asian/Pacific Islander. There were two significant bivariate associations with treatment outcome: length of stay ($X^2 = 17.6$, $p = .007$) and receiving medication at enrollment ($X^2 = 10.3$, $p = .006$). Length of stay, medication, and age ($X^2 = 6.6$, $p = .159$) were included in the regression model. Age and medication were significant predictors of treatment outcome in the logistic regression. Compared to successes, neutrals were on average younger ($X^2 = 6.4$, $p = .01$) and less likely to be on medication ($X^2 = 4.2$, $p = .04$). Length of stay was no longer a significant predictor of outcome.

CONCLUSION: Length of stay in the HCBS-W was associated with better outcomes; however this finding was not significant in the regression model. Being older and prescribed medication was associated with better outcome (but only comparing neutral to successful outcomes). Findings highlight potential treatment target areas, but additional research with more rigorous

measurement is needed to better characterize this population of children.

Aripiprazole Once-Monthly for the Treatment of Schizophrenia: A Double-Blind, Randomized, Noninferiority Study Versus Oral Aripiprazole

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ABSTRACT: Study Objective: To evaluate the efficacy and safety of aripiprazole once-monthly (AOM)-an extended-release injectable suspension vs oral aripiprazole (ARI) for the treatment of schizophrenia in a double-blind, randomized, noninferiority study.

METHOD: Eligible patients required chronic antipsychotic treatment. Patients not receiving ARI were cross-titrated to ARI over 4–6 weeks (Phase 1). Patients then entered an 8–28-week stabilization phase (Phase 2) with ARI 10–30 mg/d. Patients already receiving ARI entered at Phase 2. Patients meeting stability criteria (8 consecutive weeks) were randomized (2:2:1) to 38 weeks of double-blind treatment (Phase 3) with AOM 400 mg (AOM-400), ARI 10–30 mg/d, or AOM 50 mg (AOM-50; for assay sensitivity).

PRIMARY ENDPOINT: Proportion of patients meeting criteria for estimated relapse by Week 26 (noninferiority of AOM-400 vs ARI).

RESULTS: Week 26 estimated relapse rates (N = 662 randomized in Phase 3) were 7.1% for AOM-400, 21.8% for AOM-50, and 7.8% for ARI; the difference between AOM-400 and ARI (–0.6%; 95% confidence interval: –5.3, 4.0) excluded the predefined noninferiority margin of 11.5%. AOM-400 and ARI were superior to AOM-50 ($P \leq 0.001$). All-cause discontinuation with AOM-400 was superior to both ARI and AOM-50. There was a statistically significant difference between treatment groups in Kaplan-Meier time to discontinuation favoring AOM-400 vs ARI ($P < 0.05$) and vs AOM-50 ($P < 0.0001$). Insomnia, akathisia, headache, weight decrease, or weight increase were reported by 9–12% of patients who received AOM-400. Mean changes in weight were similar between groups (range, –1.1 to 0.7 kg). No relevant changes in metabolic parameters or extrapyramidal symptoms occurred.

CONCLUSIONS: AOM-400 was noninferior to ARI in estimated relapse rate, and superior to both ARI and AOM-50 in reducing all-cause discontinuations.

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Effects of Aripiprazole Once-Monthly vs. Placebo on Domains of Personal and Social Performance in Younger and Older Patients with Schizophrenia

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ABSTRACT: Study Objective: To evaluate if younger patients (≤ 35 years) showed a different pattern of changes on personal and social performance (PSP) scale line items than older patients (> 35 years) receiving aripiprazole once-monthly (ARI-OM) vs. placebo in the treatment of schizophrenia.

METHOD: This was a 52-week, double-blind, placebo-controlled study assessing the efficacy and safety of ARI-OM vs. placebo. The study had 4 phases: Phase 1: oral conversion, patients were cross-titrated from other antipsychotic(s) to oral aripiprazole; Phase 2: oral stabilization with aripiprazole; Phase 3: ARI-OM stabilization, with co-administration of oral aripiprazole in the first 2 weeks; and Phase 4: randomized, double-blind, placebo-controlled maintenance phase. The PSP scale score is based on each of 4 domain scores in a 6-point scale (0–5; absent to very severe). Severity scores in the 4 domains and clinical judgment determine the total PSP score (10-point intervals; 0–100 scale). Exploratory post-hoc analyses were performed in subpopulations of younger patients (≤ 35 years) and older patients (> 35 years) at endpoint (52 weeks) comparing treatment differences between ARI-OM and placebo in mean change from baseline on PSP Total, and the 4 domain scores within each subpopulation using last observation carried forward (LOCF) and ANCOVA.

RESULTS: 403 subjects entered Phase 4 of which 394 had baseline PSP evaluations (younger patients: ARIOM n = 93, placebo n = 47; older patients: ARI-OM n = 171, placebo n = 83). The treatment differences (mean change from baseline at Week 52 [LOCF] for ARI-OM-placebo) showed that younger (5.62; $p = 0.01$) and older (3.54; $p = 0.01$) patients receiving ARI-OM demonstrated statistically significant differences in favor of ARI-OM versus placebo in PSP Total scores, with a greater treatment difference in younger patients. The

treatment differences for the PSP “socially useful activities” domain (younger patients: -0.32 , $p = 0.05$; older patients: 0.02 , $p = \text{non-significant}$), PSP “personal and social relationships” domain (younger patients: -0.39 , $p = 0.01$; older patients: -0.23 , $p = 0.05$) and PSP “disturbing and aggressive behaviors” domain (younger patients: -0.44 , $p = 0.01$; older patients: -0.26 , $p = 0.001$) also showed numerically greater differences in favor of ARI-OM for younger compared with older patients. The treatment differences for the PSP “self-care domain” were -0.12 ($p = \text{non-significant}$) in younger patients and -0.26 ($p = 0.01$) in older patients.

CONCLUSION: Treatment differences on the PSP Total score and three social PSP domains suggest that younger patients (≤ 35 years) with schizophrenia may be more sensitive to preservation of function than older patients (> 35 years) after treatment with ARI-OM. Further prospective studies are warranted to confirm the preliminary results based on post-hoc exploratory analysis.

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