The following abstracts were presented as posters at the 2014 NEI Psychopharmacology Congress

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https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

CNS Spectrums (2015), 20, 61–92. © Cambridge University Press 2015
doi:10.1017/S1092852914000765
First published online 10 February 2015

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Congratulations to the scientific poster winners of the 2014 NEI Psychopharmacology Congress!

1st PLACE: Randomized controlled safety and efficacy trials of lisdexamfetamine dimesylate for adults with moderate to severe binge eating disorder (page 14)
2nd PLACE: CNS pharmacology of dextromethorphan (DM): new insights on potential mechanism of action and therapeutic applications (page 30)

Ethical Informed Consent Considerations for Research in Severe Mental Illness

Melinda McCusker, PMHNP

Scott & White Healthcare, Medical University of South Carolina

ABSTRACT: Study Objective: The objective of this integrative review is to update researchers on the clinical and ethical considerations that are shaping the current understanding of informed consent for research participants with a severe mental illness (SMI).

METHOD: A literature search was performed within the last 5 years in the following databases: Legal Collection, MasterFile Premier, MEDLINE, and PsycInfo. Nineteen articles focusing specifically on the ethical issues surrounding conducting research involving individuals with SMI were included.

RESULTS: Individuals with SMI have a greater likelihood to be at risk for incapacity in making informed consent. Informed consent should be based on the clinical features of SMI and on evolving legal understandings of informed consent as an individual's right, regardless of societal or health status. To hold the preconception that individuals with a certain psychiatric disorder do not have decision making capabilities violates their autonomy, re-enforces stigmatization, and unreasonably neglects the potential research contributions of this population. Several instruments can serve as tools to aid in determining capacity in research. Instruments vary by administration length, administrator training, and measurement

OBJECTIVE: Additional strategies to improve capacity include iterative approach, discussion, use of technology, and continuous monitoring of symptoms and severity of the psychiatric illness.

CONCLUSIONS: These strategies enhance the capacity of the participant and reduce the risk for coercion. Based on the information presented, informed consent is highly achievable for SMI research participants.

What is This Lump? Risk of Renal and Salivary Stone Formation with Topiramate (Topamax) Treatment

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ABSTRACT: Topamax, originally approved as an antiepileptic, is being used increasingly for bipolar, migraine, and even weight-loss treatment. Topamax is best recognized for its neuronal inhibitory effect, however it is also a strong inhibitor of carbonic anhydrase. At therapeutic doses this action regularly causes acid/base imbalance and mild metabolic acidosis. It is established that Topamax treatment increases risk of renal lithiasis, however the closely associated sialolithiasis has not been documented.

This case study describes a migraine patient on Topamax treatment who presented with a submandibular sialolith, likely a result of increased calcium deposition in the salivary gland due to increased serum and salivary carbonic acid levels with resulting decreased pH and solubility of calcium.

This case highlights a poorly discussed adverse event profile of Topamax, an agent increasingly used in neurology and even general practice. This report suggests that patients receiving Topamax should be monitored for signs and symptoms of renal and salivary stone formation and other consequences of acid/base imbalance.

Priapism: A Rare but Serious Side Effect of Trazodone

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ABSTRACT: Background: Trazodone is a dose dependent multifunctional drug with variable receptor efficacy at different dosage. It was approved in 1982 for treatment of depression. Currently it is often used as an augmenting agent with SSRIs. It is also the second commonest drug used for treatment of insomnia (Mendelson, 2005). It is usually well tolerated with minor side effects like dizziness, morning drowsiness, headache, fatigue etc. However there are reported cases of prolonged painful penile erection lasting for more than 4 hours resulting in urological emergency.

CLINICAL CASE: 52 year male patient with history of sleep apnea was initially prescribed Paxil for symptoms of persistent depressive disorder. The dose was titrated to 40 mg daily. Patient tolerated it well, without any reported side effects. He complained of continuing sleep difficulty despite using his CPAP machine with proper settings. Trazodone 200 mg at night was added for his insomnia and also augmentation of effect of SSRI. Possible rare instances of priapism were explained to him. After two months he had one episode of prolonged penile erection for four hours which was relieved spontaneously. It was not reported and he did not take trazodone for next two months. However he resumed taking it as it helped him with insomnia. This time, with one dose of 200 mg trazodone he developed prolonged painful erection, sustained for eight hours. He visited emergency room and urology was consulted immediately. He was treated with intracavernosal instillation of total 300 microgram phenylephrine injection to achieve detumescence. Later he was followed up by urology and permanent erectile dysfunction was avoided.

DISCUSSION: Priapism is documented as a rare but dramatic and potentially harmful side effect affecting 0.01-0.1% of population on trazodone (Mendelson, 2005). Most of the cases manifest within one month of starting therapy. However there is one reported case of priapism with one single dose of trazodone 100 mg (Jayaram, 2005). Alpha adrenergic blocking effect of the drug is thought to be responsible for the effect. There is possible effect of metachlorphenylpiperazine (mcPP), an active metabolite of trazodone, through its effect on increasing 5HT2C activity to cause priapism. It is very important to weight benefits and risks while choosing an off label medication for insomnia. It is equally important to discuss common and rare but serious side effects of medication. Effective patient informed care can address patient's knowledge about the medication effects and prevent serious health hazards with a positive influence on therapeutic outcome.

Targeted Treatment for Depression: Evaluation of Current Clinical Practices

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ABSTRACT: Objectives: Despite the availability of numerous agents to treat major depressive disorder (MDD), two thirds of patients fail to achieve remission and one third ultimately fail to respond. Both psychiatrists and primary care physicians (PCPs) have difficulty tailoring therapy based on the pharmacologic profiles of available antidepressants. This study's objective was to increase self-awareness among clinicians of their knowledge, skills, practice patterns, and barriers to managing patients with MDD.

METHODS: A 23-question survey was developed to assess the current clinical practices and to identify educational needs of psychiatrists and PCPs. The survey included knowledge- and case-based, multiple-choice questions made available online to healthcare providers without monetary compensation. A logistic regression was used to determine relationships between knowledge, intent to change practice behaviors, and barriers to better patient outcomes. The survey launched on August 28, 2013 and participant responses were collected over the following 4 weeks.

RESULTS: In total, 273 psychiatrists and 245 PCPs completed the survey. Cumulative correct scores averaged 56% among psychiatrists and 45% among PCPs. Psychiatrists scored highest on questions regarding individualizing initial and ongoing treatments for patients with MDD (60% correct responses). PCPs scored highest on questions related to the ability to formulate treatment decisions based on use of scales to assess symptoms (50%). Significant gaps in both groups were observed related to the understanding of the theoretical basis of MDD and integrating this knowledge into treatment selection (44% vs 30%, average correct scores), appropriate use of patient-reported depression rating scales to discern disability or quality of life issues (42% vs 48%), appropriate use therapy in patients with comorbidities (44% vs 43%), and management of treatment-resistant depression (49% vs 33%). When participants were asked about the level of difficulty they encounter in selecting first-line antidepressant therapy based on mechanisms of action, the highest percentage in both specialties indicated difficulty on a level of 4 out of 7.

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

Psychiatrists and PCPs who scored higher on assessment questions related to mechanism of action of antidepressants reported significantly less difficulty in selecting first-line therapies ($P < 0.05$). Those who scored higher on the assessment felt more strongly that the content will impact their practice and that the number of planned practice changes corresponded to a higher number of barriers to better patient outcomes ($P < 0.05$).

CONCLUSIONS: This assessment of clinical practices identified knowledge gaps that support the need to develop educational interventions on MDD, including understanding theoretical causes of MDDs and selecting treatment, incorporating rating scales into practice, and treatment selection taking in patients with comorbidities and treatment-resistant depression.

Improving Knowledge Related to Diagnosis and Treatment of Bipolar Depression: Effect of Online CME

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ABSTRACT: Study objectives: Although bipolar I disorder is characterized by both manic and depressive episodes, at least half of the patients initially present with depression (1). Studies indicate that clinicians have difficulty differentiating between unipolar and bipolar depression and initiating appropriate treatment (2,3). This study's objective was to determine if a video-based online CME activity improved knowledge of psychiatrists about diagnosis and treatment of bipolar depression.

METHODS: An online CME activity was developed as a 25-minute video discussion with 2 leading experts on diagnostic criteria and the current evidence base for treatment of acute bipolar depression. The activity also included a transcript of the discussion and a downloadable slide deck to highlight key data and recommendations from the video discussion. The effects of education were assessed using a linked pre-assessment/post-assessment study design that separated learners into 3 categories: improved (incorrect pre, correct post), reinforced (correct pre and post), and unaffected (incorrect pre and post).

RESULTS: For psychiatrists who participated in the CME activity, comparison of individually linked pre-assessment question responses to the respective post-assessment question responses demonstrates statistically significant improvements ($N = 304$; $P < .05$). Correct responses on post-assessment questions were significantly higher after CME completion compared with the pre-assessment question responses, with an overall medium effect ($d = 0.493$). While only 31 (10%) participants answered all 4 questions correctly on the pre-assessment, 95 (31%) answered them all correctly on the post-assessment. Between 10% and 33% of participants showed improvement in understanding individual learning concepts, and these concepts were reinforced for between 17% and 82% of learners. The biggest improvement was demonstrated in recognition of risk for antidepressant-induced switch to mania and recognition of side effects for established treatments; the need for further education was seen in awareness of side effects of investigational therapeutic agents.

CONCLUSION: This study demonstrates the impact of a 25-minute, video-based online CME activity, featuring a discussion between 2 leading experts on diagnosis and treatment of bipolar depression. The educational gaps uncovered in this assessment will be used to develop further case-based CME activities, designed to move psychiatrists along the learning continuum by improving competence and performance related to management of bipolar depression.

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Hyponatremia Secondary to Sodium Valproate: An Uncommon Drug to Produce SIADH-Like Syndrome: A Case Report and Review of Literature

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ABSTRACT: Background: Hyponatremia is prevalent in hospitalized psychiatric patients, more so in patients with chronic schizophrenia. Although polydipsia is a common association found amongst these patients, there is a possible additive effect of psychotropic drugs, especially typical antipsychotics causing SIADH. Drug induced SIADH is of specific interest, as discontinuation of the insulting drug can easily revert the electrolyte abnormality.

CASE REPORT: A 51-year-old Caucasian man was bought to the emergency room with complaints of confusion,

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

sluggishness and disorientation. He had a history of paranoid schizophrenia for the last 12 years and had two admissions in the past with a diagnosis of psychogenic polydipsia. Laboratory data at the time of admission was significant for serum sodium 120 mmol/L, urine osmolality 211 MMOL/K and valproic acid level 129 mcg/ml. He was treated with demeclocycline and hypertonic saline with SIADH as the probable diagnosis. Psychiatry was consulted for review of psychotropic medications, which included divalproex sodium, fluvoxamine, and quetiapine. Fluvoxamine was discontinued and divalproex sodium was reduced to 500 mg BID. The patient was transferred to mental health unit after medical stabilization with a sodium level of 130. The following few days his sodium level continued to decline. Initially both psychogenic polydipsia and SIADH were considered to be responsible for declining sodium levels. However, it was observed that his body weight remained relatively constant during this time while sodium levels declined, suggesting that it was not "excess water" that was contributing to the continued drop of sodium level. Our literature search revealed that divalproex sodium could contribute to hyponatremia as well. Divalproex sodium was discontinued and in following three days the sodium level gradually improved to 133 mMol/l. Despite being on demeclocycline, the highest level of sodium was achieved only after discontinuing divalproex sodium. Further, a discussion with primary care physician, revealed he had normal sodium before being started on divalproex sodium, approximately two years back.

DISCUSSION: Valproic acid is hypothesized to cause SIADH via reducing sensitivity of hypothalamic osmoreceptors or by directly affecting tubular cell function. With our patient, sodium valproate was suspected only after excluding the more common purported factors involved in SIADH (Fluvoxamine, hypothyroidism, COPD, and BPH). Although hyponatremia and inappropriate ADH secretion are mentioned in the package insert of sodium valproate, its rare occurrence signifies the high threshold of suspicion among internists about its role in hyponatremia.

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Trazodone Use for Insomnia Resulting in 'Activation,' Two Case Reports

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ABSTRACT: Trazodone belongs to the serotonin antagonist and re-uptake inhibitor (SARI) class of antidepressants and has been shown to possess some anxiolytic and hypnotic activity. Currently, the off-label use of trazodone for the treatment of primary or secondary insomnia is the most frequent reason for its prescription in the USA and it is the second-most commonly prescribed agent for treating insomnia. Here we would like to report two cases which demonstrate its use for insomnia could cause activating symptoms, resulting in, insomnia or a manic switch.

CASE 1: A 71-year-oldfemale was evaluated for continuity of care. She had MDD in partial remission and Anxiety Disorder NOS on evaluation. The PHQ9 was 6 with difficulties with sleep, predominantly with initiation almost every night. She has tried melatonin and alprazolam on a P.R.N basis with minimal success. She was advised to take trazodone, starting at 25 mg QHS and titrating to 100 mg based on her response. Two days later she called the clinic to report that she couldn't sleep after taking trazodone, had slept only 2-3 hrs each night. She reports to have felt activated after taking it although she did not endorse other symptoms of hypomania or mania. Her sleep got adjusted to baseline after stopping trazodone and taking 0.25 mg of Alprazolam the next day.

CASE 2: A 33-year-old female evaluated for continuity of care. She had PTSD and Mood Disorder NOS on evaluation. One of her chief complaint was insomnia, problem with initiating and maintaining sleep. She was started on lamotrigine and trazodone at 25 mg QHS and advice to titrate to 100 mg based on response. After two weeks, she reported using trazodone 50 mg QHS; and having easier time falling asleep, and sleeping about 5 hrs per night. We advised to try increasing the trazodone dose to 100 mg. Two weeks later the patient's affect was euphoric and she endorsed other symptoms of hypomania and was sleeping on average only 3 hrs per night and yet feeling energetic the next day. At this time patient presented additional history, which suggested she was having a switch in mood and was diagnosed with Bipolar Disorder. Trazodone was stopped and she improved over the next 4-5 days and her mood became euthymic to slightly depressed.

DISCUSSION: According to our review of the literature, there are only ten reported case of trazodone associated with onset of hypomanic or manic symptoms. Additionally trazodone causing insomnia possibly via the activating and anxiogenic properties of its metabolites has been mentioned in the literature. In the light of the fact that it's the first drug most psychiatrists would prescribe for insomnia, these two cases demonstrate that psychiatrist's

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

should be aware that it can be 'Activating' and in rare cases it could cause insomnia and make them hypomanic or manic.

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GeneSight Psychotropic Decreases Medication Costs in A Large, Prospective Case-Control Project

Josiah D. Allen, BA; Joseph C. Carhart, MA; Andrew G. Marshak, BA; Alexander J. Spivak, BA; Charles A. Altar, PhD; and Bryan M. Dechairo, PhD

ABSTRACT: Objective: GeneSight Psychotropic, a combinatorial pharmacogenomic decision support tool, has demonstrated improved outcomes in four published clinical trials. Our objective was to examine whether prospective use of GeneSight Psychotropic could decrease total medication spending in a large case-control project.

METHODS: The project was performed in association with Medco Research Institute (now Express Scripts). Medco members were eligible for the project after switching to or augmenting with another antidepressant or antipsychotic ("index medication") within 90 days after starting their first antidepressant or antipsychotic medication (defined as one or more of the 26 medications covered by GeneSight Psychotropic at the time of the project commencement). GeneSight-tested patients (n = 2,166) were propensity matched to a non-tested, treatment-as-usual (TAU) group (n = 10,880) on gender, age, index medication, primary diagnosis and temporality. Pharmacy data were tracked for 180 days prior to and 365 days following entrance into the project. Medication costs were tabulated for the pre- and post-testing periods for both groups. In a secondary analysis, patients within the GeneSight arm were stratified into one of three advisory categories (green, yellow, red) based upon the interaction of their genetic profile and their medication regimen. Patients were excluded from this analysis due to lack of follow up data (n = 34) or if they were not on a GeneSight medication at any time during the post-testing period (n = 468), reducing the sample size for the secondary analysis to 1,664.

RESULTS: Patients who received GeneSight testing saved $1,035.60 on total medication costs annually vs. the TAU group. This was due to a mean increase from the pre- to post-testing period of $143.77 in medication costs per member per month (PMPM) in the TAU group ($p < 0.0001$), compared to a mean increase of only $57.47 PMPM in the GeneSight group ($p < 0.0001$). The resulting cost differential PMPM between the two groups was $86.30. Among those eligible for the secondary analysis, 24.8% of patients were placed in the 'green' category, 46.5% were placed in the 'yellow' category, and 28.7% were placed in the 'red' category. Patients stratified into the red category spent $2,050.12 more on medications over the 365 day period after GeneSight testing compared to those stratified into the green or yellow categories ($p = 0.0005$), thus increasing the mean costs of the GeneSight group by $587.77.

CONCLUSION: Patients who received GeneSight testing saved, on average, over $1,000 in medication costs annually. If the 28.7% of patients taking red category medications were switched to more genetically concordant medications, the overall annual savings of the GeneSight group would increase by an estimated $588. Results from these analyses demonstrate that use of GeneSight Psychotropic can result in cost savings of between $1,000 and $1,600 annually compared to treatment as usual.

Pharmacogenetic Testing Shows Utility for Psychiatric Patients

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ABSTRACT: Study Objective(s): Underlying genetic differences may be an important factor in variable responses to psychiatric medications. This study aimed to demonstrate the effectiveness of genetic testing using patient and clinician reported outcomes, and to demonstrate the impact of genetic testing on clinician treatment decisions.

METHODS: This was a naturalistic unblinded, prospective analysis of the Genecept Assay (Genomind, Inc, Chalfont, PA). Study subjects included patients and their clinicians who ordered the saliva-based test. Ten genes were tested: 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). An analytic results report was provided to the clinician and clinical support was available for report interpretation. Clinicians were asked to complete a baseline survey which included assessment of the patient's medications,

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

psychiatric history, and severity of illness using the Clinical Global Impressions-Severity (CGI-S) scale. A second survey was completed after results were received, capturing treatment changes guided by the assay. The clinician assessed the patient's improvement at 3 months using the Clinical Global Impressions-Improvement (CGI-I) scale. Patients were asked to complete self-assessments of depression, anxiety, medication side effects, and quality of life at three time points (baseline, 1 month, and 3 months).

RESULTS: Data related to 685 patients was collected. Approximately 70% had a mood disorder and 29% had an anxiety disorder. Seventy three percent of patients were treatment resistant, having failed two or more treatment trials prior to genetic testing. Clinician-reported CGI-I data indicated that 87% of patients showed clinically measurable improvement post-Genecept. Strikingly, 91% of the treatment resistant patients also showed clinically measurable improvement. Patient reported data demonstrated significant increases in quality of life, as well as decreases in depression, anxiety, and medication side effects; response rates exceeded those reported in the seminal STAR*D trial at all levels.

CONCLUSION: The data strongly support the utility of pharmacogenetic testing in improving treatment outcomes in psychiatric patients. Response rates were superior to those seen with standard treatment and were considerably higher than placebo response rates. Response to psychiatric treatment is highly variable and often involves a number of failed medication trials. Personalized therapies informed by genetic data can ease this burden and improve patient outcomes.

FUNDING: This study was funded by Genomind.

Psychosis and Seizure Disorder: Challenges in Diagnoses and Treatment

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ABSTRACT: Background: The association between schizophrenia and seizure disorders has long been a matter of interest to both psychiatrists and neurologists. Psychosis resembling schizophrenia is 6-12 times more likely to occur in patients with epilepsy than in the general population (1). Psychosis related to seizures can mimic the symptoms of schizophrenia, or be comorbid with the disorder. Characteristic EEG findings are evident in some forms of seizure related psychosis. EEGs of patients with epilepsy can be less abnormal when behavioral changes deteriorated. This phenomena is called "forced" or "paradoxical" normalization. This is especially relevant because the optimum treatment for a seizure-related psychosis differs significantly from standard of care for schizophrenia. Many of the antipsychotics, especially clozapine and first generation drugs have a tendency to lower seizure threshold (2). Some of the anticonvulsants like phenytoin, carbamazepine (1) and vigabantrin (2) have been reported to cause psychosis.
Case Report: A 56 year old African American male with a past diagnosis of schizophrenia, who was relatively stable on risperidone 2 mg daily for more than fifteen years presented with a complaint of "being in a daze". On several occasions he was found by the family members to be confused, mute, staring vacantly with bizarre behavior. The episodes lasted for few hours to few days. There was no bowel or bladder incontinence, jerky limb or trunk movement, tongue biting, or unconsciousness. He was admitted to inpatient psychiatry four times in last six months with a similar clinical presentation. He was seen to be staring vacantly, with some lip smacking movements and complained of a churning feeling in his stomach. He would not be able to recognize his room on a few occasions and would refer to religion frequently. He was not seen to be responding to internal stimuli. Risperidone was increased to 2 mg twice daily without any change symptom change. Neurology was consulted for possible organic cause of change in mental status and EEG revealed sharp wave activity over left temporo-parietal at P3-01 channel with phase reversal at F7-T3 with intermittent diffuse slow wave activity throughout the recording. Subsequently patient was treated successfully with a combination of topiramate and risperidone with slow titration.

DISCUSSION: In the presented case, seizure disorder was established as a co-existent disease in a patient who was diagnosed with schizophrenia. Imprecision in the diagnostic criteria for epilepsy-related psychoses remains a barrier to understanding the differentiation and interplay between the two disorders. In the context of epileptogenic potential of antipsychotic medications, and psychotic side effects of anticonvulsant drugs, it will be very useful to have a better level of collaboration between two specialties for a successful treatment of this neuropsychiatric symptom constellation.

Moyamoya Disease and Depression: A Case Report

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https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

ABSTRACT: Moyamoya Disease is a very rare, progressive vascular disease that leads to stenosis of intracranial arteries around the circle of Willis. "Moyamoya" is a Japanese word meaning puffy, obscure, or haze like puff of smoke in the air and the term was used to describe the smoky angiographic appearance of the vascular collateral network. The most common clinical symptoms of the disease are sudden onset hemiplegia, headaches, vertigo, seizures, and cognitive and neuropsychological dysfunction. However, further research is needed to confirm these findings and establish a relationship between the two diseases. There is limited information on the associated cognitive and emotional sequelae, particularly presenting in a psychiatric setting.

We present a patient that presented is a 30-year-old Caucasian female admitted voluntarily with symptoms of depression and post suicidal thoughts of few months duration and progressively increasing since the last two weeks. Patient had a certificate from the University Hospital Psychiatric ED stating that she was referred by her therapist to the ED with complains of, symptoms of depression and anxiety, and suicidal thoughts and planning. Her disorder manifested itself only as depression and some behavioral abnormalities. A previous case report stated that lesions to the basal ganglia could lead to a variety of cognitive and behavioral abnormalities. Apathy, disinhibition and a major affective disturbance characterized the behavioral change in past studied patients. Abulia, memory dysfunction and confusion are also very common with strokes in the putamen or the globus pallidus area. Milandre *et al.* in 1995 reported another case report of a patient with moyamoya disease who exhibited the so-called "athymhormic syndrome" after sustaining ischemic lessons in the right globus pallidus and left lentiform nucleus with no involvement of the caudate. This syndrome consists of apathy, lack of drive and motivation and total flatness of affect. Through the striatum, cross five cortico-striato-thalamo-cortical circuits. This is the reason why lesions in this area can present with widespread motor, cognitive and emotional effects. Through these circuits, the striatum receives input from sensory, motor and limbic regions of the cortex. Interruption in any of these pathways has been implicated in the production of psychiatric symptoms and behavioral disturbances.

An assumption can be made, from the history and the presentation of the our patient, that probably the patient has suffered a lesion in the area of the basal ganglia leading to her chronic emotional and behavioral problem. Moyamoya disease is relatively rare outside of Asia. A total of 239 cases of Moyamoya disease had been reported in the United States as of 1996. Further research is needed to support the relationship of Moyamoya disease and Depression, so we can develop protocols to manage these patients appropriately.

A Study of Methylphenidate Extended-Release Capsules in a Randomized, Double-Blind, Placebo-Controlled Protocol in Children and Adolescents with ADHD

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ABSTRACT: Objective: To determine whether MPH-MLR's ratio of immediate/extended-release (IR/ER) content (37%/63%), unique among the available controlled-release MPH products, produces a clinically meaningful rapid initial (morning) postdose effect with a subsequent more prolonged effect across the day.

METHODS: A parallel, randomized, double-blind, fixed-dose, placebo-controlled study was conducted at 16 centers to evaluate the safety and efficacy of MPH-MLR (10, 15, 20, 40 mg/day) in the treatment of ADHD in patients aged 6-18 years. There were 4 study phases: 1) 4-week Screening/Baseline; 2) 1-week double-blind treatment; 3) 11-week, open-label, dose-optimization period; and 4) 30-day follow-up call. The primary endpoint was change from Baseline to the end of phase 2 in ADHD Rating Scale, version 4 (ADHD-RS-IV); secondary endpoints included the Clinical Global Impression-Improvement scale (CGI-I), adverse events (AEs), and quality of life (QoL) measures. Differences between treatment groups were analyzed by an analysis of covariance including terms for treatment, investigational site, and baseline ADHD-RS-IV total score as a covariate for the intent-to-treat population.

RESULTS: Children (N = 280; mean age, 10.8 ą 3.0 years) diagnosed with ADHD (by Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria) were screened and 230 entered the double-blind phase and were administered MPH-MLR 10 mg (n = 49), MPH-MLR 15 mg (n = 44), MPH-MLR 20 mg (n = 45), MPH-MLR 40 mg (n = 45), or placebo (n = 47) and 221 completed the 1-week double blind phase. MPH-MLR resulted in significantly greater improvement versus placebo in mean ADHD-RS-IV score ($P < 0.05$) and CGI-I score ($P < 0.05$). Clinical significance was seen at each of the 4 MPH-MLR fixed doses. 200 subjects completed the subsequent 11-week open label phase, during which their MPH-MLR dose was optimized. There was continuing improvement in efficacy over time.

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

QoL measures did not statistically improve during the one-week double-blind period but showed significant improvements by study end. The most common AEs were consistent with known MPH AEs. Most treatment-emergent AEs were mild or moderate in severity, and there were no serious drug-related AEs throughout the study.

CONCLUSIONS: Once-daily MPH-MLR significantly reduced mean baseline ADHD-RS-IV total score in this double-blind study compared with placebo in ADHD children aged 6-18 years. The novel drug release profile, unique immediate/extended drug release ratio, and 8 dose strengths provide more options for customized treatment of ADHD.

FUNDING: This study was funded by Rhodes Pharmaceuticals, L.P.

Time Course of Response to Methylphenidate Extended-Release Capsules in Children with ADHD: A Randomized, Placebo-Controlled, Double-Blind Study

Sharon Wigal, PhD[1]; Ann Childress, MD[2]; Laurence Greenhill, MD[3]; Annamarie Stehli, MPH[4]; Wei-wei Chang, PhD[5]; Akwete Adjei, PhD[6]; and Robert J. Kupper, PhD[6]

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ABSTRACT: Objective: To compare an extended-release multilayer bead formulation of methylphenidate (MPH-MLR) to placebo in children with ADHD in an analog classroom setting.

METHODS: Children 6-12 years with ADHD were evaluated in a laboratory classroom setting at a single site (CT identifier NCT01269463). After a screening period (up to 4 weeks) and a 2-day washout period, enrolled children were started on MPH-MLR 15 mg daily and entered an open-label, individualized dose optimization treatment period (2-4 weeks). The double-blind cross-over period (weeks 5 and 6) included 1 week each of placebo and the optimized MPH-MLR dose given daily. Laboratory time course evaluations were performed at the end of weeks 5 and 6. The primary efficacy endpoint was the mean of the on-treatment/post-dose Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) total scores over time points collected 1 to 12 hours after dosing. A mixed-effects analysis of covariance was used to evaluate the endpoints.

RESULTS: The evaluable population included 20 subjects. The least squares (LS) mean postdose SKAMP Total score was higher for placebo (2.18 vs. 1.32, $P = 0.0001$) indicating greater improvement with treatment. No difference in SKAMP Total score between subjects who initially received MPH-MLR or placebo in the double-blind phase was noted. From hours 1-12, the mean of all LS SKAMP Total Scores was significantly better for MPH-MLR than placebo ($P \leq 0.0261$). No new or unexpected safety findings were noted in the study.

CONCLUSION: MPH-MLR showed a significant decrease in SKAMP scores compared to placebo in ADHD children aged 6 to 12 years with an estimated onset within 1 hour of dosing and duration measured to 12 hours postdose.

FUNDING: This study was funded by Rhodes Pharmaceuticals, L.P.

Original Research: Effects of Quetiapine on Sleep Architecture and Parameters

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ABSTRACT: Objectives: To determine effects of Quetiapine on polysomnographic recorded sleep parameters and architecture to determine utility of this agent in management of various disorders. Introduction: Quetiapine is an atypical antipsychotic agent and it acts as an antagonist at Serotonin (5-HT 1A and 5-HT 2), Dopamine (D 1 and D 2), Histamine (H 1) and Adrenergic alpha 1 and 2 receptors; there is virtually no action on cholinergic, muscarinic and benzodiazepine receptors. This special receptor profile suggests a favorable effect on sleep, especially because of the combination of a 5 HT 2 receptor and an H 1 receptor blockade.

METHODS: A cross-sectional retrospective study of a convenience sample ($n = 42$) conducted at the sleep center in a community-based, tertiary care, hospital. Medical and polysomnographic sleep records were selected and reviewed from among patients who presented over 24-months for evaluation. 21 patients were selected and matched based on age, sex, body-mass index (BMI), and the presence/absence of obstructive sleep

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

apnea (OSA) to control without Quetiapine. Correlation analysis was performed to assess the association of Quetiapine with sleep efficiency, sleep and REM latency, wake time after sleep onset (WASO), and relative percentage of N1, N2, N3 and REM.

RESULTS: The study population was 57% female with a mean age of 44.8 years and mean BMI of 37.5. A higher proportion of patients with OSA were in the group without use of Quetiapine (81%, n = 17). Use of Quetiapine was not significantly associated with altered sleep efficiency, sleep latency, WASO, or the relative percentage of sleep stages. A notable, but not significant ($p = 0.08$), increase in the REM latency was observed.

CONCLUSIONS: Among the study population use of Quetiapine was not associated with a change in sleep efficiency, sleep and REM latency, WASO, or percentage of N1, N2, N3 and REM.

The Lack of a Team Model in Psychiatry: An Evaluation of Collaborative Nurse Practitioner and Physician Teams

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ABSTRACT: Background: The healthcare shortage benefits from the addition of nurse practitioners (NPs) that are able to meet the volume of need. Objective: The purpose of this review is to determine if there is any improvement in outcomes when a collaborative NP and physician team is used in providing healthcare.

METHODS: A literature search was conducted using the following databases: PUBMED, Academic Search Complete, Business Source Complete, CINAHL Plus, ERIC, the Legal Collection, and MEDLINE. Inclusion criteria were studies evaluating the NP and physician team in the United States between 2003 and 2013. Twelve articles met the criteria for this review.

RESULTS: In many cases, it was found that outcomes were improved when an NP was added to a physician's practice. In fact, none of the studies evaluated in this review reported any negative outcomes when NPs were used as adjunctive or collaborative members of a team with a physician. No studies reported any declines in satisfaction with the addition of NPs. There were no studies that evaluated NP and physician collaboration in psychiatry.

DISCUSSION: The NP and physician team benefits healthcare by improving outcomes, satisfaction, and communication. In all cases, the NP and physician team was comparable to physician-only practice and was often superior. While no conclusions or predictions can be made regarding the effectiveness of the NP and physician team in any one specialty, this review found no examples in which the collaborative team was less effective than physician-only practice. No studies have evaluated collaboration between NPs and psychiatrists. Further research should focus on identifying the best practice models for collaborative NP and physician teams in psychiatry.

Lurasidone Treatment for Bipolar I Depression: Effect on Core Depressive Symptoms

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ABSTRACT: Objective: Lurasidone has demonstrated efficacy in the treatment of bipolar I depression both as monotherapy and when used adjunctively with lithium or valproate, based on improvement in the Montgomery-Asberg Depression Rating Scale total score (MADRS). This post hoc analysis evaluated the antidepressant effect of lurasidone using the 6-item MADRS subscale which has been shown to be a unidimensional or "core" measure of depressive symptoms.

METHODS: Patients with bipolar I depression were randomized to 6 weeks of once-daily, double-blind treatment with lurasidone in a monotherapy study with fixed-flexible doses of 20–60 mg/d and 80-120 mg/d (N = 164 and N = 167, respectively) or placebo (N = 168); and in an adjunctive therapy study with flexible doses of 20-120 mg/d (N = 183) or placebo (N = 163), both adjunctive to either lithium or valproate. A subgroup with "more severe" depression, defined by a baseline MADRS total score ≥30, was also examined.

RESULTS: Lurasidone monotherapy resulted in significantly greater Week 6 improvement on the MADRS-6 score for the 20–60 mg and 80–120 dose groups vs placebo (−10.4 and −10.4 vs −6.9; $P < 0.001$ for both comparisons). Onset of significant improvement in the MADRS-6 was observed at Week 1 for the higher dose group and at Week 2 for the lower dose group. In the more severe depression subgroup, lurasidone therapy

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

(2 dosage groups combined vs placebo) was associated with significantly greater Week 6 improvement on the MADRS total score (−17.3 vs −11.8; P < 0.001) and on the MADRS-6 (−11.7 vs −7.5; P < 0.001). Week 6 effect size was greater for the severe (vs less severe) depression subgroup on the MADRS total score (0.56 vs 0.44), and the MADRS-6 score (0.62 vs 0.44). Treatment with adjunctive lurasidone, compared with placebo, was associated with significantly greater Week 6 improvement on the MADRS-6 score (−11.6 vs −9.1; P = 0.003). Onset of significant improvement in the MADRS-6, for lurasidone compared with placebo, was observed at Week 3. In the severe depression subgroup, numerically greater Week 6 improvement was observed on the MADRS total (−17.5 vs −14.6; P = 0.103) and MADRS-6 (−11.7 vs −9.7; P = 0.091). The Week 6 effect size was smaller for the severe vs moderate group on the MADRS total score (0.25 vs 0.40) and the MADRS-6 score (0.25 vs 0.49).

CONCLUSIONS: Treatment of bipolar I depression with lurasidone was associated with significant improvement in core depressive symptoms. In patients presenting with severe depression, monotherapy with lurasidone was associated with higher effect sizes, while effect sizes were smaller in severely depressed patients receiving lurasidone adjunctive with lithium or valproate. Lurasidone monotherapy at higher doses was associated with earlier improvement in the MADRS-6.

Clinicaltrials.gov identifier: NCT00868699, NCT00868452.

Sponsored by Sunovion Pharmaceuticals Inc.

Early Sustained Response with Lurasidone in the Treatment of Bipolar I Depression

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ABSTRACT: Objective: The goal of this secondary analysis was to evaluate the efficacy of lurasidone in achieving early sustained response during acute treatment of bipolar I depression.

METHODS: Patients with bipolar I depression, with a MADRS score ≤20, were randomized to 6 weeks of once-daily, double-blind, placebo-controlled treatment with lurasidone monotherapy with fixed-flexible doses of 20–60 mg/d or 80–120 mg/d; or with flexible doses of lurasidone (20–120 mg/d) adjunctive to either lithium or valproate (Li or VPA; adjunctive study). Treatment response was defined as a 50% reduction from baseline in MADRS score, with early sustained response defined by onset by Week 2 and maintained through Week 6 (completer analysis). Remission was defined by a MADRS score ≤12. Statistical significance was evaluated by logistic regression.

RESULTS: Monotherapy treatment with lurasidone was associated with significantly greater early sustained response (compared with placebo) for the 20-60 mg group (14.6% vs 3.9%; P = 0.007) and the 80-120 mg group (11.3% vs 3.9%; P = 0.036). Adjunctive lurasidone (with Li or VPA) was also associated with (non-significantly) greater early sustained response compared with placebo (18.9% vs 14.7%). In the monotherapy study, the majority of lurasidone responders at every week were also sustained responders; this was not the case for early placebo responders at Weeks 1, 2, and 3. The same study also saw a significantly greater proportion of remitters on lurasidone beginning at Week 4. In the adjunctive study, the majority of responders at each time point had sustained response to Week 6, regardless of treatment group; furthermore lurasidone + Li/VPA was associated with a significantly greater proportion of sustained responders (vs placebo + Li/VPA) from Week 3 onward. Adjunctive lurasidone treatment was also associated with a significantly greater proportion of remitters from Week 3.

CONCLUSIONS: Treatment of bipolar I depression with lurasidone was associated with significantly higher rates of early sustained response, which was significant for monotherapy, but non-significant for adjunctive therapy. Adjunctive lurasidone was, however, associated with achieving sustained response from Week 3 onward. Data from longer-term treatment studies are needed to confirm the clinical significance of early sustained response with lurasidone in patients with bipolar I depression.

FUNDING: Sponsored by Sunovion Pharmaceuticals Inc.

Clinicaltrials.gov identifier: NCT00868699, NCT00868452

Exposure-Response Model of Lurasidone in Patients with Bipolar Depression

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https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

ABSTRACT: Objective: Characterization of dose- response relationships for psychotropic agents may be difficult to determine based on results of individual clinical trials, due to various confounds such as variability in attrition, background medications, flexible dosing designs, and placebo-response rates. The goal of this exposure-efficacy response analysis was to characterize dose-response effects for lurasidone and to simulate lurasidone responses at Week 6 in a fixed dose study design, based on the results of two recently completed placebo-controlled flexible-dose studies in patients with bipolar depression (Loebel *et al.* Am J Psychiatry 2014;171:160-8; Loebel *et al.* Am J Psychiatry 2014;171:169-77).

METHODS: The exposure-efficacy response analyses were derived from two randomized, 6-week, double-blind, placebo-controlled, flexible-dose (20-120 mg/day in adjunctive Study D1050235; 20-60 or 80-120 mg/day in monotherapy Study D1050236) studies in subjects with bipolar depression. A total of 5245 Montgomery-Asberg Depression Rating Scale (MADRS) assessments from 825 patients (who had received lurasidone or placebo treatments, with or without lithium or valproic acid background medication) were included in the analysis. The MADRS data were fitted with nonlinear mixed effects modeling methodology implemented using NONMEM software. The exposure-efficacy response model characterized the time course of the placebo effect. Effect of background medications and effect of lurasidone were added to the time course of the placebo effect. This model allows prediction of the treatment effect contributed by placebo, background medication, and lurasidone. The exposure-efficacy response model was then used to predict exposure-response results from a simulated fixed-dose, placebo-controlled study design.

RESULTS: MADRS vs time profiles for lurasidone and placebo were adequately described using a linear dose-response relationship, built on an exponential asymptotic placebo model. A net improvement in MADRS due to lurasidone treatment (the drug effect) was significant ($P < 0.001$) and a positive dose-response was detected. Age and use of concomitant medication had statistically significant covariate effects on placebo change. Overall, the dose-dependent effect of lurasidone indicates that higher doses are likely to produce greater improvement. The dose-response was consistent for both monotherapy and adjunctive therapy studies.

CONCLUSIONS: The effect of lurasidone was described using a linear dose-response model for drug effect, with increased treatment response in patients with bipolar depression observed at higher doses of lurasidone.

Sponsored by Sunovion Pharmaceuticals Inc.

Clinicaltrials.gov identifier: NCT00868699, NCT00868452.

Short- and Longer-term Treatment with Lurasidone in Patients with Bipolar I Depression: Effect on Metabolic Syndrome

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ABSTRACT: Objectives: Patients with bipolar disorder are at a higher risk of cardiovascular disease and mortality. A recent meta-analysis found that individuals with bipolar disorder treated with an antipsychotic medication had a significantly higher risk of developing metabolic syndrome compared with untreated subjects (Vancampfort *et al.*, Am J Psychiatry 2013;170:265-74). The aim of the current analysis was to evaluate the effect of lurasidone on the prevalence of metabolic syndrome in bipolar I depression.

METHODS: Data were pooled from 3 short-term studies in patients with bipolar I depression who were randomized to 6 weeks of once-daily, double-blind, placebo-controlled treatment with lurasidone (20-120 mg/d), either as monotherapy (one study, N = 499), or adjunctive therapy with lithium (Li) or valproate (VPA; two studies, combined N = 694). Patients completing these three 6-week studies continued to receive 6 months of additional treatment with lurasidone 20-120 mg/d in an open-label extension study (N = 494). National Cholesterol Education Program (NCEP) criteria (JAMA 2001;285:2486-97) for metabolic syndrome were used. Change at 6 months (for completers) was calculated from double-blind baseline of the 6-week acute study.

RESULTS: At baseline, the prevalence of metabolic syndrome was similar in the adjunctive studies (lurasidone, 14.8%; placebo, 13.5%) and in the monotherapy study (lurasidone, 14.3%; placebo, 15.5%). After 6 weeks of adjunctive therapy, the prevalence of metabolic syndrome in the lurasidone vs. placebo groups was 17.0% vs. 12.4% (last observation carried forward; LOCF); after 6 weeks of monotherapy, the prevalence was 15.8% vs. 17.7% (LOCF). For patients who completed 6 months of extension phase treatment, the prevalence of metabolic syndrome was 23.8% (adjunctive therapy) and 17.9% (monotherapy). For the subgroup with metabolic

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

syndrome at baseline in the adjunctive therapy studies (n = 31), the following median changes were observed (completer analysis): weight (0.0 kg), cholesterol (−6.0 mg/dL), triglycerides (+11.0 mg/dL), and glucose (+2.0 mg/dL). For the subgroup with metabolic syndrome at baseline in the monotherapy study (n = 30), the following median changes were observed: weight (−0.3 kg), cholesterol (−4.0 mg/dL), triglycerides (−22.0 mg/dL), and glucose (−2.0 mg/dL).

CONCLUSIONS: In patients with bipolar depression, 7 months of treatment with lurasidone was associated with minimal metabolic changes. In at-risk patients with metabolic syndrome at baseline, treatment with lurasidone was not associated with worsening of metabolic parameters.

Sponsored by Sunovion Pharmaceuticals Inc.

Clinicaltrials.gov identifiers: NCT00868452; NCT00868699; NCT01284517.

Efficacy and Safety of Treatment with Lurasidone Adjunctive with Lithium or Valproate in Bipolar I Depression: Results of Two 6-Week Studies

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ABSTRACT: Objective: Few studies have been reported that demonstrate the efficacy of adjunctive therapy for patients with bipolar I depression who have had an insufficient response to monotherapy with mood stabilizing agents. Currently, lurasidone is the only atypical antipsychotic approved by the FDA for adjunctive therapy of bipolar I depression with lithium (Li) or valproate (VPA). The aim of the current analysis was to evaluate the efficacy and safety of adjunctive therapy with lurasidone in bipolar I depression utilizing pooled data from 2 studies.

METHODS: Data were pooled from 2 studies in which patients meeting Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM IV-TR) criteria for bipolar I depression received 6 weeks of double-blind treatment with lurasidone 20-120 mg/d (N = 355) or placebo (N = 327), adjunctive with Li or VPA. The primary and key secondary efficacy measures were; respectively, the Montgomery-Asberg Depression Rating Scale (MADRS) and the Clinical Global Impression, Bipolar - Severity of Illness Scale (CGI-BP-S), assessed using a mixed model for repeated-measures (MMRM) analysis. Secondary efficacy outcomes included the Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR16), Hamilton Anxiety Rating Scale (HAM-A), and Quality of Life; Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF), and were assessed at last observation carried forward (LOCF) endpoint by an analysis of covariance (ANCOVA).

RESULTS: At Week 6 endpoint, treatment with lurasidone (vs placebo) was associated with improvement vs placebo in the mean MADRS (−14.4 vs −11.9; P = 0.003), CGI-BP-S (−1.7 vs −1.3; P = 0.001), QIDS-SR16 (−7.4 vs −5.7; P < 0.001), HAM-A score (−7.0 vs −5.0; P < 0.001 [LOCF]), and Q-LES-Q (+18.5 vs +13.2; P < 0.001). Responder rates (MADRS reduction ≥50%) were significantly higher with lurasidone vs placebo (48% vs 37%; P = 0.002; LOCF-endpoint). Minimal LOCF-endpoint changes were observed for adjunctive lurasidone vs placebo in mean weight (+0.1 vs +0.2 kg), median total cholesterol (−4.0 vs −1.0 mg/dL), LDL (−3.0 vs −1.0 mg/dL), triglycerides (+4.0 vs −2.0 mg/dL), and glucose (0.0 vs 0.0 mg/dL). Discontinuation rates due to adverse events were similar for lurasidone vs placebo (5.8% vs 4.8%); adverse events (≥5% incidence) were nausea (13.9% vs 10.2%), Parkinsonism (12.8% vs 8.1%), somnolence (11.4% vs 5.1%), and akathisia (10.8% vs 4.8%).

CONCLUSIONS: Results of this pooled analysis demonstrated that adjunctive therapy with lurasidone and Li or VPA was effective in treatment of patients with bipolar depression, with a low rate of discontinuation due to adverse events and minimal effect on weight or metabolic parameters.

Sponsored by Sunovion Pharmaceuticals Inc.

Clinicaltrials.gov identifiers: NCT00868452, NCT01284517.

Lurasidone in Bipolar I Depression: A 24 Week, Open-label Extension Study

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ABSTRACT: Objectives: Bipolar I disorder is a chronic, recurrent illness, and long-term treatment is complicated by recurrent depressive episodes that predominate over manic episodes in the majority of patients. Few agents (quetiapine, lamotrigine) have demonstrated maintenance efficacy in the prevention of depression relapse. Lurasidone has demonstrated efficacy in the acute treatment of bipolar depression. The aim of the current study was to evaluate the longer term safety, tolerability, and effectiveness of lurasidone in bipolar I depression.

METHODS: Patients completing 6 weeks of double-blind, placebo-controlled treatment with either lurasidone monotherapy (1 study) or lurasidone adjunctive therapy with lithium or valproate (2 studies), were treated for 6 months with flexible doses of lurasidone; 20-120 mg/d in this open-label extension study (N = 813; monotherapy, 39%; adjunctive therapy, 61%). Safety endpoints were analyzed as change from double-blind baseline to Month 6 (observed case [OC] analysis). Efficacy endpoints were secondary, and included the Montgomery-Asberg Depression Rating Scale (MADRS).

RESULTS: A total of 68% of patients completed the extension study. Adverse events (AEs; incidence ≥5%) for the monotherapy and adjunctive therapy groups, respectively, were 6.0% and 9.5% for akathisia, 11.1% and 5.6% for headache, 7.3% and 7.8% for nausea, 6.3% and 6.4% for insomnia, and 4.4% and 6.6% for anxiety; and 7.0% and 8.7% discontinued due to an AE. Mean changes in weight at Month 6, for the monotherapy and adjunctive therapy groups, respectively, were +0.45 kg and +0.90 kg; and median changes were 0.0 mg/dL and −1.5 mg/dL for total cholesterol, +6.0 mg/dL and +8.0 mg/dL for triglycerides, 0.0 mg/dL and +1.0 mg/dL for glucose, and +1.3 mg/dL and +1.3 mg/dL for prolactin. The incidence of treatment-emergent mania was 1.3% in the monotherapy treatment subgroup and 3.8% in the adjunctive subgroup. Mean changes in MADRS, from open-label baseline to month 6, was −6.9 in the monotherapy group and −6.5 in the adjunctive therapy group (OC analysis).

CONCLUSIONS: Six months of treatment with lurasidone 20-120 mg/d was safe and well tolerated with minimal effect on weight and metabolic parameters. There were minimal differences in tolerability or safety outcomes in patients who received lurasidone monotherapy or adjunctive therapy with lithium or valproate. Treatment with lurasidone was associated with sustained improvement in MADRS.

Sponsored by Sunovion Pharmaceuticals Inc.

Clinicaltrials.gov identifier: NCT00868959.

Early Improvement Predicts Endpoint Response to Lurasidone in Schizophrenia: Pooled Analysis of Five Double-Blind Trials

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ABSTRACT: Objectives: Early improvement following initiation of treatment is a potentially important predictor of subsequent response that has clinical implications for the successful management of schizophrenia. The goal of this pooled completer analysis was to evaluate the clinical value of early improvement in the Positive and Negative Syndrome Scale (PANSS) total score and the Clinical Global Impression-Severity (CGI-S) score as predictors of response to 6 weeks of treatment with lurasidone in patients with an acute exacerbation of schizophrenia.

METHODS: Data were pooled from 5 similarly designed, 6-week, double-blind, placebo-controlled trials of patients hospitalized with an acute exacerbation of schizophrenia who were randomly assigned to fixed, once-daily doses of lurasidone 40-80 mg (n = 404) or 120–160 mg (n = 264), or placebo (n = 280). Endpoint responder rates were calculated using the ≥40% reduction from Baseline in PANSS total score criteria. Early improvement was separately assessed at Weeks 1, 2, and 3 using two criteria (CGI-S ≥1-point improvement; PANSS improvement ≥20%). Calculations were made of sensitivity and specificity. Receiver operating characteristic (ROC) curves were used to determine the optimal cut-scores for prediction of endpoint response, based on the highest area under the curve (AUC).

RESULTS: In the combined lurasidone dose groups, the proportion of patients showing early improvement was similar for the PANSS ≥20% criterion and the CGI-S ≥1 criterion, respectively, at Week 1 (32.5% and 36.1%) and Week 2 (53.8% and 59.8%); but was lower at Week 3 for the PANSS ≥20% criterion (70.7% and 88.0%). Endpoint response in the lurasidone group was 50.2% using PANSS ≥40% responder criteria. For prediction of endpoint response (using the PANSS ≥40% criterion), PANSS ≥20% improvement at Week 1 had 46.6% sensitivity, 81.6% specificity, and AUCROC = 0.660. CGI-S improvement ≥1 at Week 1 had 46.2% sensitivity, 74.0% specificity, and AUCROC = 0.621. At Week 2, PANSS ≥20% improvement had 75.2% sensitivity, 67.8% specificity, and AUCROC = 0.733. CGI-S improvement

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

≥1 at Week 2 had 74.4% sensitivity, 54.8% specificity, and AUCROC = 0.650. At Week 3, PANSS ≥20% improvement had 91.9% sensitivity, 50.5% specificity, and AUCROC = 0.730. At Week 3, CGI-S improvement ≥1 had 87.3% sensitivity, 43.7% specificity, and AUCROC = 0.656.

CONCLUSIONS: Lack of PANSS improvement at Week 3 was highly predictive of non-response at Week 6. These data are consistent with prior studies with other antipsychotics where lack of early improvement predicted endpoint nonresponse. Since these results are based on group means, individual response trajectories require further study and should be considered in the clinical decision making and individualization of care in patients with chronic schizophrenia.

Sponsored by Sunovion Pharmaceuticals Inc.

Randomized Controlled Safety and Efficacy Trials of Lisdexamfetamine Dimesylate for Adults with Moderate to Severe Binge Eating Disorder

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ABSTRACT: Study Objectives: Lisdexamfetamine dimesylate (LDX), a d-amphetamine prodrug, may reduce binge eating (BE) frequency in adults with binge eating disorder (BED). The current studies evaluated the efficacy of LDX for treatment of BED in adults with protocol-defined moderate to severe binge eating, as measured by the number of binge eating days per week, as well as to assess safety and tolerability.

METHODS: Two multicenter, randomized, double-blind, placebo-controlled trials enrolled adults (study 1, n = 383; study 2, n = 390) meeting DSM-IV-TR BED criteria. Participants were randomized (1:1) to dose titration with placebo or LDX (50 or 70 mg/d), with the optimized dose maintained to the end of double-blind treatment (week 12 or early termination). The primary efficacy endpoint, change in BE days/week from baseline to weeks 11-12, was assessed with mixed-effects models for repeated measures. Safety and tolerability endpoints included treatment-emergent adverse events (TEAEs) and vital signs assessment.

RESULTS: The LS mean (95% CI) treatment difference for change in BE days/week from baseline to week 11-12 significantly favored LDX (study 1: −1.35 [−1.70, −1.01]; study 2: −1.66 [−2.04, −1.28]; both $P < 0.001$). Statistically significant improvements favoring LDX were seen for all key secondary endpoints (all $P \leq 0.002$) in both studies. In both studies, TEAEs reported by ≥10% of LDX participants were dry mouth, insomnia, and headache; mean pulse and blood pressure changes were consistent with known LDX effects.

CONCLUSIONS: Optimized LDX doses significantly reduced BE days/week versus placebo in adults with BED. The safety and tolerability profile of LDX is generally consistent with known profile of LDX in adults with ADHD.

FUNDING: This clinical research was funded by Shire Development LLC.
Previous presentations: These findings have been presented at the 167th annual meeting of the American Psychiatric Association (New York, New York; May 3-7, 2014) and are scheduled for presentation at the 54th annual meeting of the American Society for Clinical Psychopharmacology (Hollywood, FL; June 16-19, 2014).

Lurasidone for the Treatment of Bipolar Depression: Current State of the Evidence

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ABSTRACT: Objective: Evidence-based treatment options remain limited for the management of bipolar I depression. Lurasidone is an atypical antipsychotic that has recently been approved, both as adjunctive therapy and monotherapy for the treatment of bipolar depression. We summarize here key aspects of the lurasidone bipolar development program.

METHODS: The efficacy and safety of lurasidone was evaluated for the treatment of patients with major depressive episodes associated with bipolar disorder, based on results from 3 double-blind, placebo-controlled, 6-week trials (lurasidone, N = 691; placebo, N = 502). In a 6-week monotherapy trial, patients were assigned to one of two fixed-flexible dose ranges of lurasidone (20-60 mg/d or 80-120 mg/d); in the two 6-week adjunctive trials, patients received flexible doses of lurasidone (20-120 mg/d) or placebo, adjunctive with lithium or valproate. Patients (N = 813) completing the three 6-week trials continued in a 6 month open-label extension study.

RESULTS: In the monotherapy study, treatment with lurasidone, in both daily dose ranges, was associated

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

with significantly greater improvement in the MADRS (primary outcome) starting at week 2 through the week 6 endpoint. Significantly greater efficacy was also observed on secondary efficacy measures, including the Clinical Global Impression, Bipolar - Severity of Illness scale (CGI-BP-S), MADRS-6 (core items), Hamilton Anxiety Rating scale (HAM-A), and patient-rated measures of quality of life and functioning. In the first 6-week adjunctive therapy trial, treatment with lurasidone was associated with significantly greater improvement in the MADRS at week 3 through week 6 endpoint. Significantly greater efficacy was also observed on secondary efficacy measures, including the CGI-BP-S depression severity, and patient-rated measures of quality of life and functioning. In the second 6-week adjunctive trial, lurasidone was associated with significantly greater improvement in the MADRS starting at week 2 and continuing through week 5; significance was not maintained at week 6. In this study, significant improvement at endpoint was observed on the HAM-A, and on a patient-rated measure of quality of life. The most frequently reported adverse events in the three short-term studies were nausea, somnolence and akathisia. Low rates of weight gain and few effects on lipid and glucose parameters were observed. Treatment with lurasidone for 6 months was safe and well-tolerated with minimal effect on weight and metabolic parameters. Sustained improvement in depressive symptoms was observed during longer-term treatment.

CONCLUSIONS: Lurasidone, both as monotherapy and as adjunctive therapy with lithium or valproate, appears to be an effective treatment for bipolar depression with a favorable benefit-risk profile in short and longer-term treatment.

Sponsored by Sunovion Pharmaceuticals Inc.

Clinicaltrials.gov identifiers: NCT00868452; NCT00868699; NCT01284517; NCT00868959

Dual Arm Randomized Pilot Study of Maintenance NeuroStar Transcranial Magnetic Stimulation (TMS) in Patients with Major Depression - Interim Analysis

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ABSTRACT: Study Objective: Transcranial magnetic stimulation (TMS) is an effective acute treatment for patients with major depressive disorder (MDD), however the ideal long-term TMS maintenance strategy is unknown. The purpose of this study is to compare two different TMS maintenance treatment regimens in a medication-free population.

METHODS: Patients with a diagnosis of unipolar, non-psychotic MDD, who had failed to receive benefit from prior antidepressant treatment, participated in a randomized, open-label, multisite trial. Patients were randomized to either: once monthly maintenance TMS treatments (arm A) or monthly observation (arm B). Patients in either arm could receive a TMS reintroduction course for protocol defined symptomatic worsening. The primary outcome was the proportion of patients without symptomatic worsening throughout the 3 months of the maintenance treatment phase

RESULTS: 67 medication-free patients were enrolled, 49 patients were randomized (23 arm A, 26 arm B); 32 patients (16 A, 16 B) met evaluable criteria at 21 weeks. 41 of 67 enrolled patients met remission criteria at end of acute treatment (61.2%). At the 3-months, 10/16 patients (62.5%) (A) vs. 7/16 patients (43.8%) (B) did not experience symptomatic worsening. At the six-months, 15/16 patients (A) vs. 8/16 patients (B) remained in the study.

CONCLUSIONS: A fixed acute 6-week course of NeuroStar TMS treatment induced remission in 61.2% of all enrolled patients. A trend towards improved outcome was shown with once monthly maintenance TMS regimen. Overall there was a good durability of effect of TMS therapy over 3 months in a medication free population regardless of maintenance regimen. Clinical trial posted on www.clinicaltrials.gov, listing numbers NCT 01415154

FUNDING: Supported by funding from Neuronetics, Inc.

Efficacy of Lurasidone in the Treatment of Schizophrenia with Prominent Negative Symptoms: A Post-Hoc Analysis of Short-Term Trials

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https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

ABSTRACT: Objective: Negative symptoms in schizophrenia are associated with impairment in quality of life and functioning. The aim of this post hoc analysis was to evaluate the efficacy of lurasidone in patients with prominent negative symptoms hospitalized for an acute exacerbation of schizophrenia.

METHODS: This post-hoc analysis utilized pooled data from five 6-week, double-blind, placebo-controlled trials of patients (N = 1532) with an acute exacerbation of schizophrenia who were randomized to fixed, once-daily oral doses of lurasidone in the range of 40-160 mg. Patients with prominent negative symptoms at baseline were identified based on the following criteria: a PANSS negative subscale score ≥25 (median score); and a PANSS positive score <25 (median score). MMRM analyses were performed for change in PANSS total, negative subscale and CGI-S scores. Responder status was evaluated for the PANSS total, defined as reduction from baseline of ≥20%, ≥30%, or ≥40% (LOCF-endpoint); number needed to treat (NNT) was calculated.

RESULTS: A total of 256/1532 (16.7%) patients met criteria for prominent negative symptoms. Treatment of the prominent negative symptom group with lurasidone (vs. placebo) was associated with significantly greater week 6 improvement in the PANSS total score (−23.2 vs. −13.5; $p < 0.001$), PANSS-negative subscale score (−6.3 vs. −4.5; $p < 0.01$), and CGI-S (−1.3 vs. −0.8; $p < 0.001$). Treatment of the prominent negative symptom group with lurasidone (vs. placebo) was associated with significantly greater endpoint response using the PANSS total 20% improvement criterion (69.2% vs. 51.5%; $p < 0.01$; NNT = 6), 30% criterion (54.1% vs. 34.0%; $p < 0.01$; NNT = 5), and 40% criterion (42.1% vs. 26.8%; $p < 0.05$; NNT = 7). In the group without prominent negative symptoms, treatment with lurasidone (vs. placebo) was associated with significantly greater endpoint responder rates using the PANSS 20% improvement criterion (62.3% vs. 43.4%; $p < 0.0001$; NNT = 6), 30% criterion (49.5% vs. 31.3%; $p < 0.0001$; NNT = 6), and 40% criterion (35.7% vs. 22.8%; $p < 0.0001$; NNT = 8). Discontinuation due to adverse events, for lurasidone vs. placebo, respectively, was low in both the prominent negative symptom group (6.3% vs. 2.1%) and the group without prominent negative symptoms (6.5% vs. 3.7%). In the prominent negative symptom group, the 3 most common adverse events reported for lurasidone (and greater than placebo) were headache (22.0% vs. 14.4%), somnolence (22.0% vs. 4.1%), and insomnia (18.2% vs. 16.5%).

CONCLUSIONS: Patients who presented with prominent negative symptoms responded to treatment with lurasidone with significantly improved PANSS total and negative subscale scores. Treatment with lurasidone was well-tolerated in the prominent negative symptom group.

Sponsored by Sunovion Pharmaceuticals, Inc.

Efficacy Comparison of TMS and Antidepressant Drugs in the Treatment of Major Depression

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ABSTRACT: Study Objective: A recent, large multisite study of acute TMS treatment in clinical practice showed a significant reduction in depression scores at the conclusion of acute treatment (Carpenter, *et al.*, 2012). Here, we used propensity score matching to compare TMS outcomes in real world practice settings to patients enrolled in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.

METHODS: Three hundred and six patients were matched using a propensity score greedy algorithm in both a forward and reverse matching manners. A logistic regression model was used for constructing propensity scores. Acute treatment clinical outcomes were classified using a decision analysis model into four depression health states based on QIDS-SR score.

RESULTS: Mean (SD) 6 week QIDS-SR scores were 10.36 (6.18) and 12.97 (6.94) for the TMS and STAR*D populations, respectively ($p < 0.0001$). Categorical outcomes at 6 weeks using the QIDS-SR definitions for none (0-5), mild (6-10), moderate (11-15) or moderate to severe (16-27) depression demonstrated that patients treated with TMS reported significantly greater clinical improvement compared to the STAR*D population (QIDS-SR total score <10: TMS, 53% vs STAR*D, 38%, $P = 0.0023$, reverse matching method).

CONCLUSION: Among a propensity-score matched population of patients who had failed to benefit from initial antidepressant medication, TMS results in a greater proportion of patients achieving clinically and statistically meaningful levels of improvement at the end of 6 weeks compared to patients treated with conventional medication therapy. Clinical trial posted on www.clinicaltrials.gov, listing number NCT 01114477

FUNDING: Supported by funding from Neuronetics, Inc.

Health Economics Comparison of TMS and Antidepressant Drugs in the Treatment of Major Depression

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ABSTRACT: Study Objective: A recent, large multisite study of acute TMS treatment in clinical practice showed a significant reduction in depression scores at the conclusion of acute treatment (Carpenter, *et al.*, 2012). In this report we examined the comparative health economic value of TMS in real world practice settings to patients enrolled in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.

METHODS: Three hundred and six patients were matched using a propensity score greedy algorithm in both a forward and reverse matching manners. Acute treatment clinical outcomes were classified using a decision analysis model into four depression health states based on QIDS-SR score. Cost of medical care, drug utilization and clinical outcomes were quantified for each health state. A Markov model was used to estimate total cost and quality-adjusted life years (QALY) for each treatment, over a two year time horizon.

RESULTS: TMS shows an incremental cost-effectiveness ratio (ICER) of $36,383/QALY. Mean annual costs were $11,886 and $10,888 for TMS and STAR*D patients, respectively. The estimated payment per member per month (PMPM) cost to provide TMS as a covered benefit for a moderate-sized payor comprised of 6,000,000 covered lives and assuming a 2% incidence of patients failing to benefit from initial medication, and a utilization of TMS of 15% among these patients was $0.25 over two years of treatment and follow up.

CONCLUSION: TMS is cost-effective for patients who fail to benefit from initial antidepressant treatment. Clinical trial posted on www.clinicaltrials.gov, listing number NCT 01114477

FUNDING: Supported by funding from Neuronetics, Inc.

Aripiprazole Once-Monthly for Long-Term Maintenance Treatment of Schizophrenia: A 52-Week Open-Label Study

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ABSTRACT: Objective: The objective of this 52-week, open-label extension study was to evaluate the overall long-term effectiveness of aripiprazole once-monthly 400 mg as maintenance treatment in subjects with schizophrenia. This was accomplished by assessing the long-term safety and tolerability and evaluating the long-term maintenance of the therapeutic effect of aripiprazole once-monthly.

METHOD: This study (NCT00731549) enrolled subjects who participated in one of the lead-in randomized, double-blind, placebo- or active-controlled registration studies (Study 246 [NCT00705783] [1]; or Study 247 [NCT00706654] [2]), or enrolled new (i.e. de novo) subjects. This multicenter, open-label trial comprised a screening phase (if applicable), a conversion phase to oral aripiprazole (Phase 1, if applicable), an oral stabilization phase (Phase 2), and an aripiprazole once-monthly maintenance phase (Phase 3). De novo subjects entered this study at screening, and then proceeded to Phase 1 or Phase 2, depending on their current antipsychotic treatment. Subjects who completed one of the lead-in studies bypassed screening and Phase 1, but were re-stabilized on oral aripiprazole in Phase 2. Only subjects meeting stability criteria entered Phase 3, where they received open-label aripiprazole once-monthly administered every 4 weeks for a maximum of 52 weeks. Study visits were scheduled weekly in Phase 1 and every second week in Phase 2. In Phase 3, visits were scheduled weekly for the first 4 weeks, every second week for 8 weeks, and then every 4 weeks through Week 52.

RESULTS: A total of 1081 subjects entered the open-label aripiprazole once-monthly maintenance phase (464 from Study 246 [1], 474 from Study 247 [1] and 143 de novo subjects). Of these, 79.4% (858/1081) completed 52 weeks of treatment. The most frequent primary reasons for discontinuation were withdrawal of consent (8.2%), impending relapse (4%) [3.4% with adverse events plus 0.6% without adverse events], and adverse events (2.9%). Adverse events reported by? 5% of patients in the extension study were headache (7.6%), nasopharyngitis (7%), anxiety (6.8%), and insomnia (6.6%). The proportion of subjects in Phase 3 meeting impending relapse criteria (previously defined [1;2]) was 8.25% (89/1079).

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

CONCLUSIONS: Over a 52-week period, subjects participating in an open-label trial of aripiprazole once-monthly had a high completion rate and a low rate of discontinuation due to impending relapse. The safety and tolerability profile was similar to that observed in the lead-in studies, with no new safety signals arising during long-term treatment. The results suggest that aripiprazole once-monthly 400 mg maintains effectiveness throughout long-term treatment.

FUNDING: The current research is supported by H. Lundbeck A/S and Otsuka Pharmaceutical Development & Commercialization, Inc

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2 Fleischhacker *et al.* (in press). Br Journal of Psychiatry.

Hospitalization Rates in Patients Switched From Oral Antipsychotics to Aripiprazole Once-Monthly: a Mirror Study

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ABSTRACT: Objective: This study assessed psychiatric hospitalization rates in patients with schizophrenia switched to prospective treatment with aripiprazole once-monthly 400 mg (an extended-release injectable suspension with efficacy in the treatment of schizophrenia [Kane *et al.* J Clin Psych. 2012;73:617–624]) compared with the same patients previously treated with oral antipsychotics.

METHOD: This was a Phase IIIb multicenter, open-label study in patients with schizophrenia treated prospectively (6 months) with aripiprazole once-monthly 400 mg compared with a retrospective treatment (6 months) with oral antipsychotics in a naturalistic community setting. Eligible patients were aged 18 to 65 years with a current diagnosis of schizophrenia (DSM-IV-TR criteria), a history of illness (>1 year), and 7 months of hospitalization data. The prospective treatment arm had two phases: an oral conversion phase (Phase A; 4 weeks), where patients were cross-titrated to oral aripiprazole (ARI) monotherapy; and a 24-week, open-label treatment phase (Phase B), where patients received 400 mg aripiprazole once-monthly (option to decrease to 300 mg for tolerability) while receiving concomitant ARI for the first 14 days from the start of Phase B. The primary endpoint was to compare psychiatric hospitalization rates (proportion of patients with ?1 inpatient psychiatric hospitalization) between oral antipsychotic treatment (retrospective analysis, months ?4 to ?1 prior to oral conversion) and after switching to aripiprazole once-monthly 400 mg (prospective analysis, last 3 months [ie, month 4 to 6 after aripiprazole once-monthly 400 mg initiation]). Safety and tolerability were also assessed.

RESULTS: Of 433 patients in the efficacy analysis, 336 entered the 4th month of Phase B and were part of the primary efficacy outcome comparison. Hospitalization rates for patients receiving aripiprazole once-monthly 400 mg (2.7% [n = 9/336]) were significantly lower than for the same patients previously treated with oral antipsychotics (27.1% [n = 91/336]; $P < 0.0001$). All-cause discontinuations during the entire prospective phase B were 32.3% (n = 140/433). The most common reasons for discontinuation were patient withdrew consent (9.5% [n = 41/433]), adverse events (8.5% [n = 37/433]), and patient lost to follow-up (7.6% [n = 33/433]). Adverse events with?5% incidence were insomnia (6.7% [n = 29/431]) and akathisia (6.5% [n = 28/431]).

CONCLUSIONS: Switching to aripiprazole once-monthly from oral antipsychotics produced a significant and marked improvement in rates of psychiatric hospitalizations, confirming results from a preliminary analysis in a subset of patients (Kane *et al.* J Med Econ. 2013; 16:917–25).

FUNDING: The current research is supported by H. Lundbeck A/S and Otsuka Pharmaceutical Development & Commercialization, Inc

Hyperammonemia Caused by Valproate; This Common Side Effect Needs More Attention

Jiping Xiao, Pankaj Lamba, Clarice Chan, William Cardasis, and Anil Jain

ABSTRACT: Introduction: The elevations in ammonia concentrations with normal hepatic function has been described in 16%-52% of patients receiving valproate (VPA) therapy. Unfortunately, to our knowledge, this has attracted little clinical and scientific interest. This is despite the fact that it is common, has potential to cause

encephalopathy, known as Valproate-induced hyperammonemic encephalopathy (VHE) and further, animal models of chronic hyperammonemia shows impairment in motor and cognitive functions. However, hyperammonemia is not routinely monitored and there are no guidelines on testing or managing it. Over the course of last two years, we have encountered several patients on our inpatient unit with hyperammonemia and VHE. Here, we present one of the selected case to raise the awareness regarding the risks in psychiatric patient.

CASE REPORT: A 59-year-old female was admitted to the mental health unit for depression. She was receiving benzodiazepines and had a history of opiate dependence and COPD prior to admission. On admission, the following medication were started, duloxetine and quetiapine for mood disorder, phenobarbital in tapering dosage for benzodiazepine detoxification and buprenorphine/naloxone for chronic pain. VPA 500 mg QHS was added for mood stabilization on hospital day four. On day six, she became confused and disoriented. The relevant laboratory test results included therapeutic VPA level, 45.7 mcg/ml; normal level of ALT; elevated ammonia level, 61 (normal range 11-32 μmol/L). EEG showed waveforms suggestive of metabolic encephalopathy. VPA was discontinued and lactulose was added to lower absorption of ammonia from the gut. Over the next 4 days the serum ammonia level decreased to normal range and she improved clinically.

DISCUSSION: Thus, physician should have a high threshold in measuring serum ammonia when a patient receiving VPA develops vomiting, increased seizure frequency, and impaired consciousness. Finally, it is important to remember that VPA concentrations may be in the therapeutic range, with normal liver function tests. Treatment for VHE consists of ceasing VPA and providing supportive care.

Why certain patients develop VHE and others do not, is not clear. Though, as VHE typically presents acutely, the magnitude of the increase in ammonia concentration could be causal factor. We hypothesize that in this case the combined use of VPA and phenobarbital might have led to rapid increase in serum ammonia. The combination of VPA with other antiepileptic drug (AED), especially phenobarbital and phenytoin, has been reported as a risk factors.

The presentation underscores the importance of geting a baseline and routine monitoring of ammonia especially when initiating VPA, it's even more important when combining VPA with other AED. Also, routine monitoring would encourage studies on the deleterious effects of chronic hyperammonemia, as demonstrated in the animal models.

Innovative Psychopharmacology Teaching Strategies in Development of a Strong Psychiatric Nurse Practitioner Workforce

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ABSTRACT: Purpose: With constant and complex advances in pharmacological management of the spectrum of psychiatric conditions, how are medical and nursing educators able to prepare the future psychiatric workforce to competently and effectively prescribe psychotropic medications? This "moving target" of current psychopharmacology knowledge must be taught from the beginning as a continual, interactive learning process.

CONTENT: Rather than a traditional didactic or strictly case-based course, Psychiatric Mental Health Nurse Practitioner (PMHNP) students are trained using contemporary, cutting edge resources. Pairing emphasis on the evolutionary science of psychopharmacology with applied learning strategies, training includes:. Integration of Stahl's psychopharmacology texts, the most comprehensive, up-to-date sources. Neuroscience Education Institute's (NEI) Master Psychopharmacology Program (MPP) o Self-Paced online modules on per psychotropic class o MPP study guides outline readings from Stahl's texts and embed NEI conference videos o Module and final examinations yield Master Psychopharmacology certificate. Live class sessions promote group discussions contrasting psychotropic choices o Teams analyze case studies with formal supervision o Integration of progressively complex cases from Stahl's case book. Video-recorded, simulated (classmate actor as patient) initial psychiatric evaluation and treatment sessions o Self-critiqued for skills of rapport, interviewing, and collection of data o Faculty-critiqued for diagnostic formulation and treatment plan, psychotropic prescription initiation, and plan for clinical monitoring

METHODOLOGY: This pilot program at the University of Texas School of Nursing began in September 2013.

POPULATION: All PMHNP students enroll in the Psychopharmacology course, which follows in sequence a general Advanced Pharmacology course and precedes the final series of courses focused on psychiatric diagnosis and management.

RESULTS: Preliminary outcomes are qualitative, finding more confidence in breadth of prescribing among novice PMHNPs, increased employer satisfaction with initial prescriptive skills, marketability of new PMHNP graduates, and plans for ongoing use of NEI membership as

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

lifelong psychopharmacology learners. We anticipate enduring, improved learning outcomes and will evaluate trends in course grades, post-licensure board certification first-time pass rates, prescriber efficiency, as well as employer and patient satisfaction.

IMPLICATIONS: As prescribers of psychotropic medications, PMHNPs have the immense responsibility to their patients of not only knowledge acquisition but also embracing a culture of continuing psychopharmacology education. Cultivation of this mindset must begin at the outset of their graduate training, and this innovative program will equip the burgeoning PMHNP workforce with the soundest scientific knowledge of psychopharmacology.

Effect of Long-Term Treatment with Lurasidone or Risperidone on Metabolic Syndrome Status in Patients with Schizophrenia

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ABSTRACT: Study Objective: To evaluate the effect of long-term treatment with lurasidone or risperidone on metabolic syndrome status.

METHOD: In a 12-month, multiregional, double-blind study, outpatients with clinically stable schizophrenia were randomized 2:1 to flexibly dosed, once-daily lurasidone (40-120 mg/d) or risperidone (2-6 mg/d). In the subsequent open-label extension, all patients received flexibly dosed lurasidone (40-120 mg/d) for up to 6 months. The determination of metabolic syndrome status was based on the NCEP/ATP-III criteria, which required the presence of ≥3 of the following: waist circumference >102 cm in men or >88 cm in women, triglycerides ≥150 mg/dL, HDL cholesterol <40 mg/dL in men or <50 mg/dL in women, blood pressure ≥130/85 mmHg, or glucose ≥110 mg/dL. Chi-square tests and logistic regression analysis were used to compare lurasidone and risperidone groups.

RESULTS: At double-blind baseline, the prevalence of metabolic syndrome was similar in the lurasidone group (22.8%; 95/416) and risperidone group (23.4%; 47/201). After 12 months of treatment, metabolic syndrome prevalence (observed cases [OC]) was 20.8% (31/149) with lurasidone and 32.6% (30/92) with risperidone ($p < 0.05$). In patients without metabolic syndrome at baseline, 14.0% (16/114) of lurasidone-treated patients and 21.4% (15/70) of risperidone-treated patients met criteria for metabolic syndrome after 12 months (OC); risk of developing metabolic syndrome was reduced by 40% with lurasidone relative to risperidone (odds ratio = 0.60; 95% CI, 0.27-1.30). Among patients with metabolic syndrome at baseline, 55.9% (19/34) in the lurasidone group and 28.6% (6/21) in the risperidone group no longer met criteria for metabolic syndrome after 12 months (OC, $p < 0.05$). The incidence of metabolic-related adverse events during the double-blind phase was 11.7% in the lurasidone group and 20.8% in the risperidone group. For patients who took lurasidone in both the double-blind and open-label phases (n = 109, completers), metabolic syndrome prevalence was 20.2% at both open-label baseline and at open-label month 6. The prevalence of metabolic syndrome in patients switched to open-label lurasidone after 12 months of double-blind risperidone treatment (n = 65, completers) was 33.8% at open-label baseline and decreased to 29.2% after 6 months of open-label lurasidone.

CONCLUSIONS: Twelve months of treatment with lurasidone was associated with a lower risk of metabolic syndrome compared with risperidone. The prevalence of metabolic syndrome increased during 12 months of risperidone treatment and remained stable over 18 months of continuous treatment with lurasidone. In patients who completed 12 months of risperidone, metabolic syndrome prevalence decreased after a switch to lurasidone for 6 months.

FUNDING: Sunovion Pharmaceuticals Inc.

ClinicalTrials.gov identifier: NCT00641745

An Open-Label Extension Study of Lurasidone in Patients with Schizophrenia Previously Randomized to Lurasidone or Risperidone

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ABSTRACT: Objective: To evaluate the long-term safety and efficacy of lurasidone in patients with schizophrenia who continued on lurasidone or switched from risperidone treatment.

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

METHOD: Clinically stable outpatients with schizophrenia who completed 12 months of treatment with flexibly dosed lurasidone (40-120 mg/d) or risperidone (2-6 mg/d) in a randomized, double-blind, active-controlled safety study were eligible for a 6-month open-label extension (OLE) study with flexibly dosed lurasidone (40-120 mg/d). Descriptive statistics were used to summarize changes on measures of safety and efficacy.

RESULTS: The OLE study enrolled 136 patients continued on lurasidone (LUR-LUR) and 87 patients switched from risperidone (RIS-LUR). Mean lurasidone dose during the OLE was 81.1 mg/d. The OLE completion rate was 80.1% for LUR-LUR and 74.7% for RIS-LUR. During the double-blind study, mean weight increased (2.3 kg) in risperidone-treated patients who subsequently continued into the OLE but decreased in lurasidone-treated patients (−1.0 kg). During the OLE, mean (SD) change in weight was −0.6 kg (3.3 kg) for LUR-LUR and −2.9 kg (5.4 kg) for RIS-LUR patients (observed cases [OC]). For LUR-LUR patients, median changes in metabolic parameters from OLE baseline to endpoint (OC) were −4.0 mg/dL for total cholesterol, −4.5 mg/dL for triglycerides, and 0.0 mg/dL for glucose. For RIS-LUR patients, median changes in metabolic parameters from OLE baseline to endpoint (OC) were 4.5 mg/dL for total cholesterol, −5.5 mg/dL for triglycerides, and −3.0 mg/dL for glucose. During the double-blind study, median prolactin level increased in risperidone-treated patients who subsequently continued into the OLE (men, 12.8 ng/mL; women, 35.2 ng/mL), but levels decreased in lurasidone-treated patients (men, −0.6 ng/mL; women, −0.8 ng/mL). During the OLE, prolactin levels showed little change in LUR-LUR patients (median change from OLE baseline to endpoint [OC]: men, 0.2 ng/mL; women, 1.3 ng/mL) and decreased in RIS-LUR patients (men, −11.2 ng/mL; women, −30.8 ng/mL). During the OLE, 5.1% of LUR-LUR patients and 6.9% of RIS-LUR patients discontinued due to an adverse event (AE). Extrapyramidal symptom-related AEs were noted in 8.1% of LUR-LUR patients and 6.9% of RIS-LUR patients during the OLE. Akathisia and somnolence each occurred in 3.7% of LUR-LUR patients and 2.3% of RIS-LUR patients during the OLE. Mean (SD) Positive and Negative Syndrome Scale total score was 55.5 (12.7) at OLE baseline, and mean change at month 6 of the OLE was 0.6 in both the LUR-LUR and RIS-LUR groups (OC).

CONCLUSIONS: In this 6-month OLE study, switching to lurasidone after 12 months of double-blind treatment with risperidone was associated with decreased weight and prolactin levels. Lurasidone effectively maintained clinical stability both in patients who transitioned from risperidone and those who continued on lurasidone.

FUNDING: Sunovion Pharmaceuticals Inc.

ClinicalTrials.gov identifier: NCT00641745

Lurasidone for Maintenance of Efficacy in Patients with Schizophrenia: a Double-Blind, Placebo-Controlled, Randomized Withdrawal Study

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ABSTRACT: Study Objective: To evaluate the efficacy and safety of lurasidone as a long-term maintenance treatment for patients with schizophrenia.

METHOD: Patients aged 18 to 75 years diagnosed with schizophrenia and experiencing an acute exacerbation were enrolled into a 12- to 24-week open-label stabilization phase in which they received flexibly dosed lurasidone (40–80 mg/d). Patients who responded to treatment with open-label lurasidone and achieved ≥12 weeks of clinical stability entered the 28-week, double-blind withdrawal phase and were randomized to either continue on lurasidone (initially at the final stabilization dose, then flexibly dosed [40-80 mg/d]) or were switched to placebo. Kaplan-Meier survival curves of time to relapse were generated and the primary efficacy endpoint (time to relapse) was analyzed using log-rank test and Cox proportional hazards model. Secondary outcomes included change from baseline in Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression-Severity (CGI-S) scores, incidence of treatment-emergent adverse events (TEAEs), and change in weight and metabolic parameters.

RESULTS: Of the 676 patients enrolled in the open-label stabilization phase, 285 met stabilization criteria and were randomized to lurasidone (N = 144) or placebo (N = 141). Among randomized patients, mean PANSS total score decreased from 90.1 at open-label baseline to 54.4 at double-blind baseline, indicating substantial symptom improvement during the open-label phase. Time to relapse was significantly delayed (log-rank test, p = 0.039), and the risk for relapse was reduced by 33.7% in lurasidone-treated patients versus patients in the placebo group (Cox model hazard ratio [95% CI], 0.663 [0.447–0.983]; p = 0.041). Patients receiving placebo experienced significantly greater clinical worsening based on mean change in PANSS and CGI-S scores

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

over the double-blind period compared with lurasidone-treated patients (PANSS, +12.4 vs +8.3 [p = 0.029]; CGI-S, +0.7 vs +0.4 [p = 0.015]; LOCF). The most common AEs reported in patients treated with lurasidone (open-label baseline through double-blind endpoint) were akathisia (16.7%), insomnia (12.5%), headache (11.8%), nausea (11.1%), and anxiety (11.1%). Discontinuation rates due to TEAEs in the double-blind phase were 13.9% for lurasidone and 15.6% for placebo. Lurasidone-treated patients experienced minimal changes in weight and prolactin, lipid, and glucose parameters throughout the study.

CONCLUSIONS: This placebo-controlled, randomized withdrawal study demonstrated the efficacy and safety of lurasidone for the maintenance treatment of patients with schizophrenia. Long-term treatment with lurasidone was generally well tolerated and produced minimal effects on weight and other metabolic parameters.

FUNDING: Sunovion Pharmaceuticals Inc.

ClinicalTrials.gov identifier: NCT01435928

Pharmacological Profile of Brexpiprazole

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ABSTRACT: Purpose: Brexpiprazole [7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}quinolin-2(1H)-one] (brex) is in development for psychiatric disorders. Brex is a rationally designed molecule that is a partial agonist at 5-HT1A and D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors. The in vitro and in vivo pharmacological profile of brex was evaluated.

METHODS: In vitro receptor binding affinities of brex were measured in cell membranes expressing cloned human receptors, including serotonin 5-HT1A/1B/1D/1E/1F/2A/2B/2C/3/5A/6/7, dopamine D1/2L/3/4/5, adrenergic alpha1A/1B/1D/2A/2B/2C and beta1/2/3, histamine H1, and muscarinic M1receptors. Functional activity was measured in cells expressing cloned human 5-HT1A/2A/2B/2C/6/7, D2L/3, alpha1A/1B/1D/2A/2B/2C, beta1/2/3, and H1 receptors using appropriate functional read-outs. Receptor occupancies were measured by in vivo binding (D2, 5-HT2A, 5-HT6 receptors) or ex vivo receptor autoradiography (5-HT1A, 5-HT7, 5-HT transporter) 2 h after oral administration in mice or rats. Plasma levels were determined by liquid chromatography/mass spectrometry. Effects of brex on brain levels of serotonin, norepinephrine, dopamine, acetylcholine and histamine were measured by in vivo microdialysis in rats.

RESULTS: Brex demonstrated subnanomolar binding affinities for 5-HT1A (Ki = 0.12 nM), 5-HT2A (0.47), D2L (0.30), alpha1B (0.17), and alpha2C (0.59) receptors, with affinity of <5 nM at 5HT2B/7, D3 and alpha1A/1D receptors. In functional assays, brex acted as: a potent partial agonist at 5-HT1A and D2L/3; a moderate partial agonist at 5-HT2C; a potent antagonist at 5-HT2A/2B, alpha1A/1B/1D, and H1 and; a moderate antagonist at alpha2C. Consistent with in vitro binding affinities, receptor occupancy was in the following order of potency: D2 > 5-HT2A > 5-HT1A > 5-HT6 > 5-HT transporter > 5-HT7. Oral brex (1-30 mg/kg) in rats increased brain levels of histamine in the medial prefrontal cortex and decreased dopamine levels in the nucleus accumbens but exerted no effect on the other neurotransmitters.

CONCLUSION: Brexpiprazole shows a unique pharmacology with serotonin, dopamine, and noradrenaline receptor activity modulation. In vivo occupancy at relevant monoamine receptors can be achieved in whole animals at relevant plasma levels that would predict efficacy and safety/tolerability in psychiatric disorders.
Encore Presentation: Presented at the 2014 Society of Biological Psychiatry meeting in New York, NY May 8th - 10th in two separate abstracts that will be published in a supplement to Biological Psychiatry following the meeting. Studies were sponsored by Otsuka Pharmaceutical Co. Ltd. and H. Lundbeck A/S.

Traumatic Brain Injury Due to Blast Exposure in Women Deployed to a Combat Theater

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ABSTRACT: Background: Traumatic brain injury (TBI) has been described as the signature injury in the war on terror. The small amount of available data suggest that women have a worse outcome as compared to men after sustaining a TBI. (1,2). In 2013 the Pentagon began

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

allowing women to serve in combat, so clearly there is a need for more study of TBI in women.

METHODS: We present two cases of female Marines who sustained concussions due to blast exposure in combat. The first Marine was exposed to numerous blasts during a 2007 deployment to Iraq. At her presentation in our clinic in 2009 she complained of headaches, disturbed sleep and memory problems. Her physical exam and laboratory studies were unremarkable. The second Marine was seen in 2012. Her chief complaints were headaches, sleep disturbance, short term memory loss and decreased hearing. Her physical exam was normal. Her laboratory studies were remarkable for vitamin D deficiency.

RESULTS: Both service members underwent treatment. The first Marine was medically discharged and the second completed her enlistment and left active duty, but remains in the Reserves.

CONCLUSION: Camp Lejeune is home to tens of thousands of Marines, and thousands of these Marines are deployed every year to a combat theater. In spite of this fact, we saw only two women over several years with the diagnosis of TBI after a blast exposure. If the number of women with TBI blast is truly as small as it would appear to be, then data on women with TBI due to blast will need to be collected from multiple military bases to ascertain the true incidence of TBI in women service members and its effect on women's health, including reproductive health.

The Selective α7 Nicotinic Acetylcholine Receptor Partial Agonist Encenicline (EVP-6124) Does Not Engender Cross Generalization to Nicotine in Rats

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ABSTRACT: Encenicline (EVP-6124) is a novel selective α7 nicotinic acetylcholine receptor (nAChR) partial agonist, which has shown activity in nonclinical cognition impairment models and in clinical trials for the treatment of cognition impairment in schizophrenia and Alzheimer's disease. CNS active compounds, such as nicotine, can also engender reward and addictive properties leading to abuse potential (α4b2 Ki = 16.1 nM). Of the nAChRs, the α7 receptors have a low affinity for nicotine (α7 Ki = 2.11 uM) and are generally regarded as having a low potential for abuse. Several global regulatory health agencies (EMA, FDA, and ICH) recommend tiered in vitro and in vivo approaches to identify early indicators of human abuse potential. Although encenicline has low affinity for known receptors associated with addiction or dependency (i.e., α4b2 nAChR, GABA, opiate, etc.), the psychoactive properties and novel mechanism of action warranted further in vivo abuse potential evaluation. In this study, male Sprague Dawley rats were evaluated in a cross-generalization study to investigate any interoceptive or subjective effects of encenicline compared to those engendered by nicotine. Rats were initially trained to differentiate between subcutaneous (s.c.) administration of nicotine (0.32 mg/kg) and saline based on drug-appropriate lever responses. Once the training criteria were met, rats were administered s.c. saline (nicotine vehicle; 0 mg/kg), nicotine positive control (0.032 to 0.56 mg/kg), 50 mM sodium acetate (encenicline vehicle; 0 mg/kg), or encenicline (0.03 to 3.0 mg/kg). Abuse liability potential was assessed through drug discrimination lever press responses. The % drug-appropriate lever response increased with the escalating nicotine dose (75% at ~0.18 mg/kg) producing the anticipated sigmoidal dose-response. Whereas the encenicline % lever response did not exceed 14% and produced no dose-response relationship. The rate of lever responses was not negatively affected by nicotine or encenicline at any dose level. Therefore, encenicline did not engender cross-generalization to the nicotine training/reference stimulus up to the highest dose of encenicline administered (3.0 mg/kg), which resulted in a mean plasma concentration of 148 ng/mL. These results suggest that encenicline does not share the discriminative stimulus properties of nicotine, and thus may have a reduced potential for abuse or as a substitute for nicotine. No external funding was secured for this study.

Orthostatic Hypotension After First Dose of Quetiapine Extended Release: A Case Report and Clinical Pearls

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ABSTRACT: Introduction: Here we present a case report on orthostatic hypotension after the first dose of quetiapine extended-release (XR). We discuss the case in an attempt to raise awareness of this serious adverse effect. We also describe a few clinical pearls on the pathophysiology, recognizing the risk factors and management.

CASE REPORT: Ms. A, a 40-year-old female was admitted with complaints of depressed and anxious mood, sleep difficulty, poor appetite and suicidal thoughts. However, she was not taking prescription medications or over the counter medications at the time of admission. The last use of psychotropic medication was a decade ago.

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

No substance abuse or medical problems were identified during admission and vitals were recorded as within the normal range. She was prescribed quetiapine XR 50 mg and gabapentin 300 mg. Both drugs were used off- label to treat insomnia, anxiety while being further evaluated for bipolar depressive episode. The patient had an episode of near syncope next morning. Orthostatic hypotension secondary to a quetiapine XR was diagnosed. Quetiapine XR was discontinued.

DISCUSSION: Adequate autonomic response, mediated by postsynaptic alpha 1-adrenoceptors on vascular smooth muscle cells, and acceleration of heart rate, which is mediated by postsynaptic myocardial beta 1- adrenoceptors are required for maintenance of blood pressure after postural changes. The increase in systemic vascular resistance is attenuated by the alpha 1-adrenoceptor-blocking properties of antipsychotics leading to symptoms of orthostatic hypotension and tachycardia. Among atypical antipsychotics, clozapine and quetiapine have been implicated to have a higher incidence because of a high affinity for the alpha 1-adrenoceptor.
Literature review suggest that prospective monitoring for changes in postural blood pressure is important because patients with psychiatric disorders often do not articulate symptoms of orthostasis and the subjective report of dizziness does not correlate well with orthostatic blood pressure changes.
We did not come across a report comparing the IR to XR. Traditional wisdom is that incidence may be lower with XR. Given the median time to Cmax (tmax) values are 5 and 2 hours for quetiapine XR and IR respectively. It's important to recognize that orthostatic changes due to XR preparation could be delayed by several hours, as seen in this case.

CONCLUSION: Orthostatic hypotension is a very serious side effect and it's advisable to start patients on the smallest dose, slowly titrate the medication, and advise monitoring for orthostatic vitals when changing the dosage. Further, patients should be counselled about this phenomenon and advised to avoid sudden changes in posture from the supine position. The report also begs the question if we should promote the off-label use of quetiapine.

Vortioxetine, a Novel Antidepressant with Multimodal Mechanism of Action, Lacks Sexual Side Effects in a Male Rat Model for Sexual Function

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ABSTRACT: Purpose: Antidepressants acting via inhibition of the serotonin (5-HT) transporter (SERT) inhibit sexual behavior. Vortioxetine, an antidepressant with a multimodal mechanism of action, is an inhibitor of the SERT, a 5-HT3A, 5-HT7 and 5-HT1D receptor antagonist, a 5-HT1A receptor agonist and a 5-HT1B receptor partial agonist. Since modulating 5-HT receptor subtypes (e.g., 5-HT1A, 5-HT1B receptors) and the transporter may affect sexual function differently, we compared the effects of vortioxetine and a selective serotonin reuptake inhibitor (SSRI), paroxetine, on the sexual behavior of male rats. In an effort to dissect vortioxetine pharmacology, the effects of modulation of several serotonin receptors (5-HT1A, 5-HT1B and 5-HT3) were also studied in the same behavior paradigm.

METHOD: Young adult male Wistar rats received 5 weekly trainings on copulation with a estrus female. Low performers were excluded from the study. Mating sessions were video taped and manually scored on measures of sexual behavior: latency and number of ejaculations, mounts and intromissions. The effects of vortioxetine (1 and 10 mg/kg/day), paroxetine (10 mg/kg/day), flesinoxan (5-HT1A agonist, 2.5 mg/kg twice daily), CP-94253 (5-HT1B agonist, 5 mg/kg daily), ondansetron (5-HT3 antagonist, 1 mg/kg twice daily) and vehicle were compared immediately after the first dosing and after 1 and 2 weeks of repetitive dosing. As the affinity of vortioxetine for the rat 5-HT1A receptor is approximately10-fold lower than for the human 5-HT1A receptor, vortioxetine was also tested in the presence of flesinoxan (2.5 mg/kg twice daily) to mimic the human level of 5-HT1A receptor activation. Antidepressant exposures were determined as SERT occupancy using ex vivo autoradiography.

RESULTS: Neither vortioxetine nor vortioxetine plus flesinoxan affected sexual behavior in male rats, whereas 2 weeks of paroxetine impaired sexual behavior significantly in several measures. Vortioxetine, 1 and 10 mg/kg, corresponded to 50 and 87% SERT occupancy, which matched occupancies seen at clinical doses (5-20 mg/day), as shown in human PET studies. Paroxetine produced approximately 90% SERT occupancy. Flesinoxan enhanced sexual function in male rats after acute and 1-week dosing, but not after 2 weeks' treatment. Acute, 1-week and 2-week CP-94235 treatment significantly impaired sexual behavior. Ondansetron impaired ejaculation frequency only after 2 weeks of treatment.

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

CONCLUSION: Vortioxetine at clinically relevant levels of SERT occupancy did not affect male rat sexual performance. Studies of selective compounds acting on the 5-HT receptor subtypes targeted by vortioxetine showed either improvement or deterioration of sexual performance in male rats. Therefore, the apparent neutral effect on sex performance of vortioxetine in this animal model is likely to be the result of a summation of simultaneous modulation of multiple 5-HT receptors plus SERT inhibition.

The Effect of Vortioxetine on Sexual Dysfunction

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ABSTRACT: Objective Vortioxetine (VOR) is an approved antidepressant with a multimodal mechanism of action that combines direct modulation of serotonin (5-HT) receptor activity and inhibition of the 5-HT transporter. The receptor profile of vortioxetine and available preclinical data suggest limited impact on sexual functioning. Our goal was to assess the impact of vortioxetine on sexual function.

METHODS: The incidence of treatment-emergent sexual dysfunction (TESD) for VOR was evaluated using the Arizona Sexual Experience Scale (ASEX) across 7 short-term studies in MDD and GAD, with comparisons to placebo (PBO). Five studies included duloxetine (DUL) 60mg as an active reference. In a pooled analysis of over 1100 patients, non-inferiority to PBO in rates of TESD was evaluated, with a clinically meaningful margin of 10%. In addition, a head-to-head clinical trial comparing VOR and escitalopram (ESC) on sexual functioning was conducted in well-treated MDD patients experiencing SSRI-induced TESD.

RESULTS: The risk of developing TESD for MDD or GAD patients without sexual dysfunction at baseline was not statistically significantly different between VOR (5-20 mg/day) and PBO, with non-inferiority demonstrated for 5 mg. The risk of developing TESD was higher with DUL compared to placebo or VOR 5 and 10 mg. In the head-to-head comparison with ESC (NCT01364649), VOR 10-20 mg was statistically significantly superior to ESC 10-20 mg in improving TESD as measured by change from baseline in Changes in Sexual Functioning Questionnaire (CSFQ) total score. Of 447 patients enrolled, 348 completed the 8-week study (VOR, n = 169/225 [75.1%]; ESC, n = 179/222 [80.6%]). In the primary MMRM analysis, LS mean change from Baseline in CSFQ-14 total score was 6.6 in the ESC group and 8.8 in the VOR groups at Week 8. The LS mean difference of 2.2 (95% CI: 0.48-4.02) was statistically significant (p = 0.013), demonstrating the improvement in sexual functioning for the VOR group was superior to the improvement in the ESC group. Numerically more VOR-treated patients demonstrated clinically meaningful improvements in sexual functioning (change from Baseline CSFQ-14 total score ≥3; OR = 1.50; P = 0.06) and shifted to normal sexual functioning during the study (OR = 1.37; P = 0.112), compared with ESC. MDD treatment response achieved with earlier antidepressants (citalopram, paroxetine and sertraline) was maintained in both groups. The AE profile for vortioxetine was similar to that seen in previous trials, with nausea, headache, and dizziness the most common AEs.

CONCLUSIONS: Assessments of TESD by ASEX in the VOR clinical development program showed TESD rates similar to that of PBO at lower doses and lower than with DUL 60mg across VOR doses. Assessment of sexual functioning using the CSFQ-14 in MDD patients with SSRI-induced TESD switched to VOR (10-20mg) or ESC (10-20mg) demonstrated that switching to VOR was statistically significantly superior to ESC in improving TESD.

Vortioxetine, a Novel Antidepressant with Multimodal Activity: A Review of its Preclinical Mechanism of Action and Clinical Profile

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ABSTRACT: Study objectives: An overview of vortioxetine's preclinical profile and the potential contribution of its combined action on serotonin (5-HT) receptors and the 5-HT transporter (SERT) to its clinical profile.

METHODS: Preclinical in vitro and in vivo studies used cellular systems expressing vortioxetine's primary biological targets and rodent models assessing its antidepressant and pro-cognitive potential, impact on sexual behavior and sleep architecture. Clinical efficacy in reduction of depressive symptoms and improvement in cognitive function was assessed in adults with major depressive disorder (MDD). Tolerability was based on the incidence of adverse events (AEs) in short-term clinical trials.

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

RESULTS: In preclinical studies vortioxetine led to changes in the function of several neurotransmitter systems including 5-HT, norepinephrine, dopamine, acetylcholine, histamine, gamma butyric acid (GABA) and glutamate in the rat brain. These effects likely derive from its interaction with serotonin receptor-mediated negative feedback mechanisms controlling neuronal activity of these brain areas, which is differentfrom the mechanism of action of current antidepressants, such as SSRIs. Studies in rodents revealed a differentiated profile in models predictive of antidepressant activity, increased synaptic plasticity and improved cognitive function compared to SSRIs and SNRIs. Furthermore, vortioxetine showed reduced interference with sexual function and sleep architecture compared to SSRIs in rats.
In placebo-controlled clinical trials of adults with MDD, vortioxetine (VOR) was efficacious in reducing depressive symptoms vs placebo (and vs agomelatine in a trial of patients with an inadequate response to SSRI/SNRI treatment) and was significantly superior to placebo in pre-defined cognitive outcomes. In a pooled analysis of patients treated with placebo (n = 1621) or VOR (5-20mg/day) (n = 2616), the incidence of insomnia-related AEs was 2.0–5.1% for VOR vs placebo (4.4%) and sexual dysfunction-related AEs was 1.6-2.6% for VOR vs placebo (1.1%). In a sleep EEG study with healthy subjects, VOR at a given SERT occupancy seemed to affect REM sleep less than paroxetine. In a pooled analysis of 7 clinical trials, the risk of developing treatment-emergent sexual dysfunction was not significantly different between VOR (5-20 mg/day) and placebo using the Arizona Sexual Experience Scale (ASEX). MDD patients treated with VOR experienced a significantly greater improvement in the Changes in Sexual Functioning Questionnaire (CSFQ-14) total score compared to escitalopram in a head-to-head study.

CONCLUSIONS: The preclinical studies in rodents indicate a markedly different mechanism of action of vortioxetine compared to SSRIs and SNRIs. The unique pharmacological profile of vortioxetine suggests the potential for a differentiated clinical profile that differs from that of SSRIs and SNRIs, with a low incidence of sexual dysfunction and sleep disruption.

Clinical Outcomes in Schizophrenia Patients During First Years of Diagnosis, a Cohort Study

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ABSTRACT: Observational study of a cohort of 50 patients with a recent diagnosis of schizophrenia (within five years of baseline visit), followed up during at least three years and up to five years, with periodic evaluations every three months. No changes were made in therapeutic schemes. This registry has the objective to describe the clinical outcomes in this particular group of patients.
The diagnosis of schizophrenia was confirmed with M.I. N.I. and evaluations include Clinical Global Impression - CGI, Global Assessment of Functioning - GAF, and Personal and Social Performance Scale - PSP, and the Schedule of Assessment of Insight Scale - SAI-E.

RESULTS: We present here the first year findings. Most patients were men, single with secondary school grades. Regarding schizophrenia symptoms, 80% of patients experienced prodromal symptoms with a median duration of 426 days (IR 90-914), before the schizophrenia diagnosis were made the patients experimented a median of 423 days of psychotic symptoms (IR 77-823).
Before entering to the cohort the patients were experienced a median of 2 psychotic episodes (IR 2-4), and 2 psychiatric hospitalizations (IR 2-4). The rate of substance use observed in patients was 36%, and the main substance of abuse was cannabis.
The treatment in the patients were as follow: most patients were with atypical antipsychotic (96%), 16% were in treatment with depot medication. 64% of patients were receiving concomitant medications. And just 8% of patients were receiving any kind of non pharmacological treatment. Satisfaction with medication was negative in 14%, neutral in 20% and positive in most patients (66%). Adherence to treatment was described by patient and relatives as high (average 88%).
Most patients were described as mild to without clinical compromise according to CGI-S, patients exhibit mild to moderate compromise in functioning as median values of PSP were 55 (IR 45-60) and GAF 55 (IR 50-65). During the first year of follow up one third of patients experienced at least one relapse of psychotic symptoms and they expended an average of 24 days with psychotic symptoms. 3 patients attempted against their lives and 2 committed suicide.

DISCUSSION: The findings so far in our cohort are similar to those reported previously in other studies. It is noticeable the long period of time the patient spends with prodromal and psychotic symptoms before the diagnosis is made, especially regarding the known impact of the duration of untreated psychosis in the final outcome of patients. The relationship between schizophrenia and cannabis use it is not fully elucidated, however there is a strong association in those entities. Most patients with schizophrenia will have at least one

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

relapse within the first five years, in our sample almost half relapsed within the first year.
We didn't explore so far factors associated to relapses in patients as we are showing initial results.

MRS Findings Before and After Treatment in Adults with BPD

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ABSTRACT: Introduction: Borderline Personality Disorder (BPD) is a mental illness characterized by psychological and social dysregulation. Symptoms of BPD include impulsivity, unstable relationships and emotions, and low self-esteem. Patients with BPD engage in greater impulsive and risk-taking behaviors. The anterior cingulate cortex (ACC) is a frontal cortical region that has been implicated in BPD features such as cognitive and affective processes. The authors examined the correlations between BPD symptom severity measures in adults and metabolites found in the ACC as acquired through Proton Magnetic Resonance Spectroscopy (1H-MRS).

METHODS: Twenty-one BPD participants and 10 healthy control subjects (HCS) were enrolled in this study. BPD participants completed a comprehensive battery of clinical assessments to ascertain a BPD diagnosis and to fully characterize their psychopathology. 1H-MRS scans were acquired from each participant to measure brain metabolites using a 3.0 Tesla Siemens scanner. A 1.5 x 1.5 x 1.5 cm^3 voxel was positioned in the central ACC. BPD patients completed a second MRI following eight weeks of placebo or quetiapine 150mg or 300mg. To test for differences between the groups, ANCOVA measures were used to covary for gray and white matter. In addition, paired t-tests were completed to determine if metabolite levels changed due to the administration of quetiapine.

RESULTS: At baseline, BPD participants exhibited significantly higher levels of myo-inositol (Ins) than HCS when co-varying for gray and white matter ($p = 0.042$). Eight BPD participants received placebo treatment for eight weeks and seven received quetiapine. No significant differences were found between the baseline and exit metabolite levels in the placebo group. Following treatment with Quetiapine, creatine (Cr; $t(6) = 2.560$; $p = 0.043$) and glutamate/glutamine (Glx; $t(6) = 2.721$, $p = 0.035$) levels decreased.

CONCLUSIONS: The ACC is a central region of the frontolimbic network that has been previously implicated in adults with BPD. Our findings suggest that a connection exists between the Ins in the ACC and BPD. This finding has not been previously described in BPD, but increased levels of Ins have been shown in adults with dementia. In addition, our findings showed that treatment with quetiapine may lead to neurochemical changes over time in the ACC. Further analysis will be completed to examine if correlations exist between the neurochemicals and clinical features of BPD before and after treatment.

The Effect of Encenicline, an α7 Potentiator, on Memory Performance and Neurotransmitter Release in Rodent Models

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STUDY OBJECTIVE(S): Numerous psychiatric and neurological conditions are characterized by cognitive impairment, with deficits in, among other functions, attention, memory, problem solving, language, and goal-directed behavior. These and related cognitive deficits are associated with poor functional outcomes and quality of life across diverse patient populations, underscoring the need for improved treatment strategies. Clinical and preclinical studies have validated the rationale for α7 receptor agonists as a treatment strategy for improving functionally impairing cognitive deficits in patients with schizophrenia, Alzheimer's disease (AD), and other disorders. Encenicline, an α7 agonist that primes the α7 receptor at low concentrations by potentiating the effect of the natural ligand acetylcholine (ACh), is in clinical development for schizophrenia and AD. In this study, the effects of encenicline on neurotransmitter systems and cognition in rats were examined.

METHODS: Encenicline was evaluated in α7 receptor binding assays in vitro using rat cortical preparations. To characterize receptor physiology, human α7 receptors were expressed in Xenopus laevis oocytes and used to record inward currents in the absence or presence of ACh. Microdialysis and liquid chromatography studies were used to estimate the levels of encenicline-induced neurotransmitter release in the rat brain. Cognitive performance of rats was evaluated in an object recognition task.

RESULTS: In oocytes from Xenopus laevis, encenicline significantly increased ion currents through α7 receptors. Further, encenicline promoted the release of ACh and glutamate (Glu) in the medial prefrontal cortex (mPFC), whereas dopamine (DA) release was enhanced in both

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

the mPFC and the nucleus accumbens. An α7 receptor antagonist blocked encenicline-induced release of DA and Glu, and partially blocked the release of ACh. Cognitive testing in the rat demonstrated that encenicline improved memory performance in an object recognition task. Encenicline elicited the effects on cognition and neurotransmitter efflux in vivo at sub-nanomolar doses. Interestingly, administration of encenicline followed an inverted U-shaped dose-response curve for both measures of cognition and neurotransmitter efflux, such that higher doses resulted in diminished cognitive improvements and neurotransmitter release.

CONCLUSIONS: These data indicate that encenicline potentiates ACh-induced currents in vitro and enhances neurotransmitter release and memory in rats. Taken together, the data suggest that encenicline may potentiate α7 receptor-mediated release of DA, Glu, and ACh in prefrontal systems governing cognition. The effects of encenicline on neurotransmitter release and cognition occur within a sub-nanomolar dose range, suggesting that low doses may be sufficient to stimulate procognitive effects while maintaining a favorable tolerability profile. These data may have important implications for encenicline in the therapeutic management of such higher cognitive disorders as schizophrenia and AD, investigations of which are underway in international Phase III clinical programs (NCT01969123, NCT01969136, NCT01714661, NCT01716975, NCT01714713).

FUNDING: FORUM Pharmaceuticals Inc.

Encenicline, a Potentiator of α7 Receptor Signaling: Effects on Cognition & Clinical Function in Schizophrenia Patients on Chronic Stable SGA Therapy

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STUDY OBJECTIVE(S): Despite treatment with antipsychotics, patients with schizophrenia have persistent cognitive deficits that adversely affect everyday functioning and quality of life. Numerous studies have demonstrated that cognitive impairment is the best predictor of patient function in the community, underlining the importance of direct interventions to improve cognitive performance. Recent advances in cognitive neurosciences have identified signaling through the α7 receptor as essential for the functional integrity of such cognitive domains as learning and memory, attention, processing speed, and executive function. Diminished α7 receptor signaling may be causally related to the cognitive dysfunction aspect of the complex clinical presentation of schizophrenia. Agents capable of potentiating α7 receptor signaling may therefore enhance cognition and potentially improve patient functioning and quality of life. Encenicline is a novel, potent α7 receptor potentiator that has exhibited a pharmacokinetic profile suitable for once-daily oral dosing. The objective of this Phase IIb study was to assess the effects of two doses of encenicline (0.3 mg and 1 mg) versus placebo on cognitive and clinical function in stable patients with chronic schizophrenia.

METHODS: Subjects (N = 317) receiving stable atypical antipsychotics were treated with placebo (n = 105), or 0.3 mg (n = 107) or 1 mg (n = 105) of encenicline for 84 days. Efficacy was evaluated using the Overall Cognition Index (OCI) from the CogState testing battery and Trails 2 and 4 of the Neuropsychological Test Battery, the MATRICS Consensus Cognitive Battery (MCCB), the Schizophrenia Cognition Rating Scale (SCoRS), and the Positive and Negative Syndrome Scale (PANSS). Results were considered significant at $P < 0.10$ (one-sided tests).

RESULTS: The OCI plus Trails 2 and 4 suggested that versus placebo, 0.3 mg encenicline was associated with significant improvement in general cognitive function ($P = 0.009$) due mainly to the improvements in visual learning, visual attention, and social cognition. The positive effect on the OCI was supported by a trend for improved cognition on the MCCB ($P = 0.069$) in the 1 mg dose group. For the 1 mg group, the mean change from baseline at day 84 in the overall Composite T-score and the associated percentile change were higher than for the 0.3 mg and placebo groups. There were no clinically significant safety findings. A total of 192 treatment-emergent adverse events were reported in 101 (31.9%) subjects. The incidence of serious adverse events was similar among all treatment groups; none was judged related to drug. Significant improvements in clinical function were observed with encenicline as measured by the SCoRS at all visits for the 1 mg group versus placebo ($P = 0.011$), and a significant effect on Negative Symptoms in the 1 mg group ($P = 0.028$) was observed versus placebo on Day 77.

DISCUSSION: Compared with placebo, the encenicline-treated group showed significant improvements in cognitive function in this Phase IIb study. These results may have important implications for the clinical management of schizophrenia since cognitive symptoms predict functional outcomes including employment, independent living status, and social functioning. Larger Phase III trials are ongoing to further evaluate the safety and efficacy of encenicline on cognitive impairment in patients with schizophrenia.

FUNDING: FORUM Pharmaceuticals Inc.

Psychosis in the Elderly: Did You Consider Injectable Steroid?

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ABSTRACT: Introduction: Here we illustrate 2 cases of new-onset psychotic symptoms late in their life. The differential diagnoses of late-onset psychosis include dementia-related syndromes with psychosis, delirium due to generalized medical condition or drugs, late-onset primary psychiatric disorder (including depression with psychotic features, delusional disorder, schizophrenia or schizoaffective disorder), substance use and drug-induced psychosis.

CASES: Ms. A, a 68-year-old woman was brought to hospital by husband for suicidal intention with plan. For the last 3 days, she demonstrated bizarre behaviors and verbalized delusional thoughts. She believed that, "St. Michael, the archangel, cared for her and she had to join him in heaven." Patient had no significant psychiatric history and was only taking psychotropic medication amitriptyline for fibromyalgia. She was admitted to the psychiatric unit and later developed multiple hypotensive episodes which required a transfer to the medical unit. We ruled out delirium, dementia, and our working diagnosis was major depressive disorder with psychotic feature. Later, during the medical evaluation for repeated hypotensive episodes and hyponatremia, it became evident that she had been receiving corticosteroids, intramuscular injections of 80mg depot methylprednisolone acetate every 3 months, for the past 4 years as a treatment for fibromyalgia.

Another case came to our attention several months later, Ms. B, a 58-year-old woman presented with paranoid ideation and delusions of persecution worsening for the last 8 months. Her medical problems included multiple sclerosis and Parkinson-plus syndrome. Neurologist reported that she had been receiving intravenous (IV) methylprednisolone injections on a monthly basis for multiple sclerosis. This duration corresponded to the time frame of worsening of symptoms.

DISCUSSION: Both these cases developed drug (steroid)-induced psychosis. The neuropsychiatric adverse effects of corticosteroids are complex, unpredictable and often severe, ranging across most categories of psychopathology from subtle mood changes to full-blown affective syndromes and frank psychosis. Unfortunately, these patients suffer protracted hospital course. The reasons include 1) psychiatric team does not enquire about steroids; 2) patients' families are not aware of the psychiatric adverse effects of injectable steroid and thus forget to mention it when providing the current medication list.

CONCLUSION: We report these cases together to stress upon the following points: 1) steroid usage in elderly, including injectable (intra-articular, intramuscular or intravenous), should be considered as a differential when evaluating psychosis; 2) the use of corticosteroids is increasing, and while the physical complications of their use are well-known, the neuropsychiatric consequences are not well-known; 3) finally, these cases demonstrate the importance of collecting a thorough medical history.

Categorical Improvements in Disease Severity in Schizophrenia Patients Treated with Cariprazine

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ABSTRACT: Background: Schizophrenia is a severe mental illness characterized by a diverse set of symptoms that can lead to patient distress, functional impairment, and poor quality of life. Reducing the overall severity of illness and improving global functioning is an important treatment goal. While symptom specific scales, such as the Positive and Negative Syndrome Scale (PANSS), evaluate symptom severity more broad assessments like the Clinical Global Impression-Severity (CGI-S) scale allows for evaluation of overall disease severity including symptom intensity, patient functioning, and quality of life. Cariprazine is an orally active and potent dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors. Cariprazine was effective and generally well tolerated in 3 phase II/III studies in patients with schizophrenia. In this pooled analysis, the effect of cariprazine on overall disease severity was evaluated by measuring clinically relevant shifts in CGI-S scores.

METHODS: Data were pooled from 3 positive, Phase II/III, double-blind, placebo-controlled trials in patients with acute exacerbation of schizophrenia (NCT00694707, NCT01104766, NCT01104779). All cariprazine dose groups were combined for analyses (cariprazine dose range, 1.5 to 9 mg/day). The secondary efficacy parameter in all 3 studies was change from baseline in the CGI-S. In this post hoc analysis, improvements in global disease severity at Week 6 were assessed by analyzing the proportion of patients shifting from a baseline CGI-S score of ≥6 (severely ill or worse) to

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

endpoint score of ≤3 (mildly ill or better). Additional analyses included CGI-S score shifts from ≥5 (markedly ill or worse) to ≤2 (borderline ill/normal). Data were analyzed using a logistic regression model and odds ratios (OR) were determined.

RESULTS: In the individual studies, all cariprazine dose groups showed superiority to placebo ($P < .05$) on mean change from baseline to Week 6 in CGI-S scores. Least square mean differences (LSMD) ranged from −0.3 to −0.6. The pooled population comprised 161 patients (placebo, n = 50; cariprazine, n = 111) that were classified as severely or extremely ill and 1033 patients (placebo, n = 311; cariprazine, n = 722) that were at least markedly ill. A significantly greater proportion of severely ill patients at baseline improved to mildly ill or better in the cariprazine group compared with placebo (42% vs 18%; OR = 3.43 [95% CI: 1.5, 7.9]; P = .004). In patients who were markedly ill or worse at baseline, 7% of cariprazine vs 3% of placebo patients improved to borderline ill/normal at Week 6 (OR = 2.33 [95% CI: 1.1, 4.8]; P = .022).

CONCLUSIONS: Cariprazine treatment compared with placebo resulted in a significantly greater proportion of patients achieving clinically relevant improvements in global disease severity as measured by CGI-S category shifts.

Global Improvement in Bipolar Mania Patients Treated with Cariprazine

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ABSTRACT: Background: Bipolar I disorder is associated with morbidity, mortality, and disability. The Clinical Global Impression-Severity (CGI-S) scale measures the patient's global severity of illness. Unlike scales designed to measure specific symptom severity such as the Young Mania Rating Scale, the CGI-S can capture additional dimensions that contribute to disease severity such as comorbidity, patient distress, and functional impairment.

Cariprazine is a potent dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors. Cariprazine was effective and well-tolerated in 3 double-blind, placebo-controlled trials in patients with bipolar mania (NCT00488618, NCT01058096, NCT01058668). Pooled data from these studies were used to evaluate the efficacy of cariprazine on overall severity of illness by measuring the percentage of patients that showed categorical improvement in CGI-S scores.

METHODS: All cariprazine doses were pooled for this analysis (2 studies: flexibly dosed 3-12 mg/d; 1 study: fixed/flexibly dosed 3-6 mg/d or 6-12 mg/d). The mean change in CGI-S score was the secondary efficacy measure in all 3 studies. This pooled analysis evaluated the proportion of patients who improved from a more severe CGI-S category at baseline to a less severe category at Week 3. The 3 different shift criteria analyzed were: 1) shifting from a baseline CGI-S score of ≥4 (moderately ill or worse) to ≤2 (borderline ill/normal) at Week 3; 2) ≥5 (markedly ill or worse) to ≤2 (borderline ill/normal); 3) ≥6 (severely ill or extremely ill) to ≤3 (mildly ill or better). For each of these categorical shifts, comparisons for cariprazine vs placebo were performed using a logistic regression model and odds ratios (OR) were determined.

RESULTS: At baseline, 97 patients (placebo, n = 42; cariprazine, n = 55) were severely or extremely ill, 637 patients (placebo, n = 254; cariprazine, n = 383) were at least markedly ill, and 1033 (placebo, n = 428; cariprazine, n = 605) were at least moderately ill. A significantly greater percentage of cariprazine vs placebo patients improved from moderately ill or worse at baseline to borderline ill/normal at Week 3 (32% vs 22%; OR = 1.71; $P < .001$). Similarly, a greater percentage of cariprazine vs placebo patients shifted from markedly ill or worse to borderline ill/normal (markedly ill: 32% vs 18%; OR = 2.10; $P < .001$). A greater proportion of cariprazine vs placebo patients shifted from severely or extremely ill to mildly ill or better (55% vs 36%; odds ratio [OR] = 2.12; P = .09) but differences did not reach statistical significance, probably due to small sample size.

CONCLUSIONS: In patients with manic or mixed bipolar I episodes, cariprazine was associated with clinically relevant improvements in global disease severity, as shown by the greater proportion of cariprazine vs placebo patients that shifted to less severe categories on the CGI-S after treatment.

CNS Pharmacology of Dextromethorphan (DM): New Insights on Potential Mechanism of Action and Therapeutic Applications

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https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

ABSTRACT: Dextromethorphan (DM) has been in use for over 50 years. Originally classified as a nonopioid antitussive, it was later discovered to act at multiple CNS targets relevant to neurological and behavioral disorders. DM has been evaluated in preclinical models of neuroprotection, neuropathic pain, depression and seizure control, among others. The promise of utility in CNS therapeutics was only met after DM was combined with the CYP2D6 inhibitor quinidine (Q). The combination (NUEDEXTA®, DM/Q), was recently approved in the US and EU for treatment of pseudobulbar affect (PBA), a disorder of emotional expression occurring secondary to brain injury or other neurological conditions. Q blocks the metabolism of DM to its major metabolite dextrorphan (DX), increasing DM and reducing DX exposure. We review the pharmacological targets of DM in the CNS and discuss potential clinical applications.

METHODS: Pharmacology of DM from published literature and sponsored studies from DM/Q development are reviewed and assessed in comparison to clinical plasma concentrations achieved.

RESULTS: DM, the non-opioid d-isomer of levorphanol, is a low affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist with IC50 and Kd values ranging from 0.6 μM to 11 μM for blocking sustained NMDA-induced calcium or barium currents. DM has relatively rapid NMDA receptor dissociation kinetics which may be significant for tolerability. DM also inhibited ligand binding to SERT with a Ki = 40 nM, has been shown to be relatively potent inhibitor of serotonin reuptake into rat brain synaptosomes in vitro (Ki = 0.023 μM), and appears to inhibit serotonin reuptake in other animal models. It is a potent sigma-1 receptor agonist (Ki = 200 nM), which has been indicated to be at least partly responsible for antidepressant-like activity of DM in the mouse forced swim test. DM weakly inhibits binding at the norepinephrine transporter (Ki = 6-13 μM), but effectively inhibits the reuptake of norepinephrine (Ki = 240 nM). Potential actions at other receptors, such as presynaptic antagonism of nicotinic acetylcholine receptors, are considered. Clinical efficacy appears driven by DM despite higher total DX exposure even in presence of Q. This may be due to the rapid conjugation and renal elimination of DX (lower CNS bioavailability) and differential activity at some key receptors. DM administration without Q metabolic inhibition is largely ineffective.

CONCLUSIONS: DM exhibits multifaceted interactions which may be involved in the mechanism of action in treating PBA. The multimodal pharmacology of DM may lead to therapeutic improvements not achievable with agents acting at a single site. Based on preliminary clinical and nonclinical evidence of effect, clinical studies evaluating DMQ in depression, agitation secondary to Alzheimer's disease, and levodopa-induced dyskinesia are ongoing.

FUNDING: Supported by Avanir Pharmaceuticals, Inc.

Treatment Considerations for Fibromyalgia and PTSD

James P. Figueroa, MD

OBJECTIVE: Typically fibromyalgia requires combination therapy for successful treatment. This is accomplished by identifying and treating causes of fibromyalgia such as pain, infection, hormonal imbalance, connective tissue disease. This combined with sleep augmentation can result in clinical benefit. Fibromyalgia can be difficult to treat depending on its origins and the patient being treated. Patients with PTSD have profound sleep disturbances with severe tender point pain (tpp) that aggravates their underlying anxiety and depression. Problematic concentration and memory contribute to confounding their efforts to create a favorable life situation and not untypically exhibit difficulty in their ability to respond to various types of psychiatric therapy. Over recent years there has been developed a first of its kind analgesic with dual receptors, tapentadol. This compound has a receptor site both as a mu agonist as well as a norepinephrine reuptake inhibitor. This latter site is seen in two FDA approved compounds for fibromyalgia, duloxetine and milnacipran. Tapentadol when provided with minimal mu stimulation appears clinically to augment its capacity to benefit fibromyalgia. Subsequently both tpp is reduced and sleep is improved. This can benefit patients with PTSD.

METHODS: Initially patients are screened for causes of fibromyalgia i.e. bloodwork consisting of ESR, CBC, chemprofile, uric acid, TSH, rheumatoid factor, ANA and any other relevant testing ie. Lyme testing, thyroid autoantibodies etc. After identifying and treating any of these factors, additional medication would be prescribed to modulate tender point pain and augment restorative sleep ie. the combination of tramadol and tizanidine capsules. Consideration to the addition of pregabalin, duloxetine or milnacipran can be given. If fibrocystic symptoms such as sleep and tpp remain unimproved the addition of tapentadol, initially at 50 mg PO Q HS and then increasing to 100 mg PO Q HS and then clinically monitor. The use of tapentadol alone without mu receptor augmentation (can be low-dose tramadol, hydroxycodone or oxycodone) typically was unsuccessful.

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press

RESULTS: In >40 patients thus treated over 3 years, all experienced an increased duration of sleep, less awakenings, and less fatigue. Subsequently tpp was reduced, as was fatigue, headache and stiffness. The FIQR significantly improved. Also both concentration/memory are improved and gradually so is the y to focus on a goal and accomplish it. Their response to various concomitant psychiatric therapies was improved - as demonstrated by a lessening of their anxiety/depression.

CONCLUSIONS: This treatment method for fibromyalgia, as seen in PTSD, benefits sleep, fatigue, concentration/memory and the ability to accomplish a goal. The response to various types of adjunctive psychiatric therapies was significantly improved. These observations suggest that fibromyalgia should be assessed at every psychiatric visit.

Family Discordance and Paranoid Psychosis

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ABSTRACT: One of the issues in psychiatry which is often debated is whether the stress from having discordant family in childhood can contribute to/precipitate the development of psychosis in adulthood.

We present the case/example of a young female patient whose early life experiences of perceived abuse by parents have culminated into a paranoid disorder/personality and the a possible correlation between these. The patient developed symptoms of paranoid psychosis in early adulthood on the background of significantly unstable/discordant family dynamics and now has started waging a internet warfare against her parents. Psychobiosocial treatments have been making little inroads into her recovery.

This case supports/illustrates the possibility of a relationship between familial discord, with its inherent adverse impact on an individual's sense of security; and the subsequent vulnerability of the individual to develop psychosis in the face of external stressors/challenges.

https://doi.org/10.1017/S1092852914000765 Published online by Cambridge University Press