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ABSTRACT: Study objectives: Symptoms of anxiety are prevalent in Major Depressive Disorder (MDD) and are associated with greater illness severity, suicidality, impaired functioning and poor response to antidepressant treatment (ADT). In MDD, anxiety symptoms can be assessed as 'anxious distress' (new DSM-5 specifier) or 'anxious depression' (score ≥7 on the HAM-D anxiety/somatization factor). Brexpiprazole is a serotonin–dopamine activity modulator that is a partial agonist at 5-HT1A and dopamine D2 receptors, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors – all at similar potency. Brexpiprazole is approved in the US for treatment ofschizophrenia, and as adjunctive treatment in MDD. The objective of this post-hoc analysis was to assess the efficacy of brexpiprazole as adjunct to ADT in patients with MDDand anxiety symptoms, using these two definitions of anxiety.

METHODS: Data were pooled from three randomized, double-blind, placebo-controlled studies with similar designs (Pyxis – NCT01360645; Polaris – NCT01360632; Sirius – NCT02196506). In each study, patients with MDD and an inadequate response to 1–3 ADTs received single-blind ADT for 8 weeks. Patients with inadequate response throughout this prospective phase were randomized to receive either ADT+brexpiprazole (2mg in Pyxis and Sirius; 1mg or 3 mg in Polaris) or ADT+placebo for 6 weeks. Proxies used to categorize patients as having 'anxious distress' included a score of ≥2 on the following symptoms at randomization: tension (MADRS item 3 score ≥3); restlessness (IDS item 24 score ≥2); concentration (MADRS item 6 score ≥3); or apprehension (HAM-D item 10 score ≥3). Scores on the items of the HAM-D anxiety/somatization factor at randomization (baseline) were used to identify patients with 'anxious depression'. Efficacy was assessed as the change in MADRS total score from baseline to Week 6. Statistical analysis used a Mixed Model Repeated Measure approach using pooled brexpiprazole doses.

RESULTS: After 8 weeks of prospective ADT monotherapy, 57.6% (n = 797/1,383) of patients met the criteria for anxious distress, and 48.5% (n = 671/1,383) for anxious depression. The mean MADRS total score was 29.0 for patients with anxious distress in the adjunctive brexpiprazole (n = 462) group and 29.1 in the placebo (n = 327) group; while those with anxious depression were 28.9 (brexpiprazole; n = 384) and 28.6 (placebo; n = 282). Compared to those receiving placebo, patients with both anxious distress and anxious depression who received adjunctive brexpiprazole showed a greater improvement in MADRS total score (LS mean difference -2.38, $p = 0.0001$ and -1.68, $p = 0.012$, respectively). These improvements, compared to placebo, were similar to those in patients who had not met the criteria for anxious distress (-1.40, $p = 0.023$) or anxious depression (-2.17, $p < 0.001$).

CONCLUSION: Adjunctive brexpiprazole may be efficacious in reducing depressive symptoms both in patients with or without symptoms of anxiety.

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Epochs of Anosmia and Ageusia in Multiple Sclerosis: Chemosensory Uhthoff's Phenomenon

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ABSTRACT: Study Objective: To reveal that while long duration of anosmia and ageusia has been seen with Multiple Sclerosis (MS) [Doty 1997], repetitive shorter epochs ofanosmia and ageusia has not heretofore been presented.

METHODS: Case Study: A 39 year old right-handed male, with a history of MS, presents with six years MS concurrent with epochs of anosmia and ageusia. The anosmia andageusia present concurrently, preventing him from smelling and tasting his meal. At baseline, he is able to smell and taste coffee, peppermint, gum, sweet and salty foods, rating his smell and taste at 70% normal. However, during the epochal events, he reports the inability to smell and taste white rice, shrimp, meat, butter, carrots, onions, spinach, and sour foods. He states that these episodes occur approximately ten times a week, last for two hours, and rates his smell and taste from 0-10% during these events.

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RESULTS: Abnormalities Neurological Examination: Cranial Nerve (CN) Examination: CN II: bilateral pale discs. CN III, IV, VI: bilateral ptosis. CN IX, X: decreased gag reflex bilaterally. Motor Examination: Drift Test: positive left pronator drift, with right adductor digiti minimi sign and right cerebellar spooning. Sensory Examination: Ipswich Touch Test: decreased in left lower extremity. Temperature: decreased in left lower extremity. Rydel-Seiffer Vibratory Test: bilateral upper extremities 5 and bilateral lower extremities 3. Tandem Gait: unstable. Cerebellar Examination: Holmes Rebound Phenomena: positive with left greater than right. Reflexes: 1+ bilateral upper extremities, absent bilateral lower extremities. Neuropsychiatric Examination: Animal Fluency Test: 15 (abnormal). Clock Drawing Test: 3 (abnormal). Center for Neurologic Study Lability Scale: 16 (pseudobulbar affect).

CONCLUSION: Primary olfactory dysfunction with secondary inhibition of retronasal smell and perceived taste [Gruss 2015] can be an etiology. Such an olfactory dysfunction may reflect variation in nasal mucosal engorgement due to normal variability of the olfactory cycle [Eccles 1978]. This phenomenon is an unlikely due to the short duration ofepochs.

The cause of anosmia and ageusia in this patient suggests a central lesion involved in the processing of both smell and taste. Transient rapid symptoms associated with temperature change, as in Uhthoff's phenomenon seen in MS, can manifest with deficiency in special senses including visual field loss [Davis 2010]. Such also may be the origin for the chemosensory loss seen here. While this phenomenon may be induced by hot baths, more subtle temperature changes may also induce such symptoms [Romani 2000]. Given that olfactory threshold changes have been demonstrated in acute inflammatory changes in MS, such a temperature related etiology is more likely to manifest [Lutterotti 2011]. MS patients should be screened for chemosensory dysfunction, and those with chemosensory dysfunction should be assessed for demyelinating disease.

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Short Duration Monoballismus

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ABSTRACT: Study Objective: While monoballismus has been reported to be associated with hemorrhagic lesions in the subthalamic nucleus (Ohnishi, 2009) and multiple sclerosis (MS) (Rosa, 2011), the duration has been reported to be at least six days (Soysal, 2012). A patient with epochs of monoballismus lasting for 45 minutes is presented.

METHODS: Case Study: A 57 year old right handed female with attention deficit hereditary disorder predominantly inattentive on amphetamine sulphate, presented with two years of memory loss. For instance, after ordering food in restaurants, by the time the food arrives, she could not recall what she ordered. At the onset of this symptom, she noted three epochs of her left arm jerking for 45 minutes. The jerking would begin with low amplitude and low frequency and rapidly progress to the forearm and arm of greater magnitude and low frequency. With her right hand she would try to hold down her left arm without success. There was no associated paresis, sensory phenomena, headaches, dizziness, presyncope, loss of consciousness, or strong emotions. She admitted to frequent jamais vu.

RESULTS: Abnormalities: Neurological Examination: Mental Status Examination: Memory: Immediate Recall: 5 digits forward and 2 digits backwards. Cranial Nerve (CN) Examination: CN I: Alcohol Sniff Test 8 (hyposmia). CN XII: tongue tremor on protrusion. Motor Examination: Drift Test: positive right pronator drift. Gait Examination: Tandem Gait: unstable. Reflexes: 0-1 throughout. Neuropsychiatric Examination: Go-No-Go Test: 6/6 (normal). Animal Fluency Test: 15 (normal). Clock Drawing Test: 3 (abnormal). Center for Neurologic Study Lability Scale: 16 (pseudobulbar affect). Other: MRI with and without infusion: normal.

CONCLUSION: Transient tonic-clonic movements of one limb have been described with focal epilepsy associated with diabetic non-ketotic hyperglycemia (Grant, 1985). A metabolic abnormality such as transient hypoglycemia or hyperkalemia can cause a focal dystonia (Soysal, 2012), which theoretically could manifest with monoballismus. This could be a somatic manifestation of underlying conflict, conversion disorder, or as a result of a physical manifestation of panic attack with hyperventilation and tetany (Mihai, 2008). This may be the first manifestation of a generalized cerebral disorder associated with chorea or ballismus such as Wilson's disease, or Huntington's Chorea (Mihai, 2008). It is possible that this is a variant of Alien Hand Syndrome with parietal lobe involvement (Shrestha, 2015). But this is unlikely given the absence of hemineglect or hemiagnosia. It is possible that amphetamines may have induced a monochorea. Chronic amphetamine use has been demonstrated to cause chorea (Klawans, 1974) and it theoretically could have

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