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ABSTRACT: Introduction: Improvement in hypergeusia in response to alpha lipoic acid treatment has not heretofore been described. Such a case is presented.

METHODS: Case Study: A 64 year old right handed nasute female noted the sudden onset of salty hypergeusia, about 200% saltier than foods should be. Concurrently she experienced a constant phantogeusia of salt involving the front half of her tongue, lips, and inside her mouth. She denied any smell problems, cacogeusia, or palinageusia. This persisted for five months until treatment with 1800 mg/day of alpha lipoic acid, whereupon, over a one month duration, the salty hypergeusia gradually resolved. Suppression of the salty hypergeusia continued until she developed an upper respiratory infection, whereupon, despite the continuation of alpha lipoic acid, the salty hypergeusia returned to 250% of normal. During the cold, her ability to taste dropped down from 100% to 80%, and ability to smell dropped from 100% to 50% and upon resolution of the cold, the senses returned to normal and the salty hypergeusia remitted.

RESULTS: Abnormalities in Neurologic Examination: Reflexes: 3 + bilateral quadriceps femoris and pendular. Chemosensory testing: Olfaction: Alcohol Sniff Test: 12 (hyposmia), Phenylethyl Alcohol Threshold: greater than –2 (anosmia). Suprathreshold Amyl Acetate Odor Intensity Testing: parallel pattern (normosmia). Pocket Smell Test: 4(normosmia). Retronasal Olfactory Testing: Retronasal Smell Index: 8(normosmia). Gustatory testing: Propylthiouracil Disc Taste Test: 5(normogeusia). Taste Super threshold Testing: normogeusia to sodium chloride, sucrose, and phenylthiocarbamol: hypogeusia(10–30%) to urea; ageusia(0%) to hydrochloric acid. Taste Quadrant Testing: taste weakness to sodium chloride for the entire mouth.

DISCUSSION: The alpha lipoic acid may have acted to improve smell and associated enhanced retro nasal smell, inhibiting savory gustatory discharge, and thus, effectively reducing salt perception. Such a mechanism would also explain the recurrence of hypergeusia with the upper respiratory infection; the infection presumably transiently reducing the olfactory ability, overcoming any olfactory enhancing effects of alpha lipoic acid. On the other hand, this agent could have acted to improve smell as well as taste. With such enhanced chemosensory capacity, the normal olfactory and gustatory components of food would have inhibited competing pathologically discharging gustatory receptors for salt, reducing dysgeusia and hypergeusia. Moreover, the alpha lipoic acidmay have acted to focus the patient's attention on the gustatory stimulation which may have caused her to perceive not just the predominant salt sensation but enhanced perception of the other gustatory sensations which acted to competitively inhibit the perception of salt. Further investigation of alpha lipoic acid in the management of dysgeusia and hypergeusia is warranted.

75
Formulation Properties of Long-acting Injectable Antipsychotics and the Impact on Administration: Focus on Aripiprazole Lauroxil

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ABSTRACT: Clinicians using long-acting injectable (LAI) antipsychotics may assume that there is uniformity in the injection technique for all LAIs. However, because LAIs have significant differences in their formulation, each requires a specific administration procedure. Here, we focus on how the formulation properties of the atypical LAI aripiprazole lauroxil impact its administration.

The history of LAI formulations is presented as a background to recent advances in formulation technology. A shared challenge for new LAIs is to adapt the formulation of insoluble drugs to aqueous-based suspensions.

The early LAIs kept the drug product dissolved as oil-based solutions, which were stable and did not require mixing prior to injection. However, oil-based solutions tend to be viscous and cause injection-site reactions (ISRs).

New LAI formulations tend to be aqueous-based suspensions and need to be resuspended or reconstituted before injection. Beyond this common element, formulation properties lead to differences in administration for each of the available LAIs.

We reviewed the formulations of LAIs indicated for the treatment of schizophrenia and how they impact instructions for use, with a focus on aripiprazole lauroxil.

Aripiprazole monohydrate and olanzapine pamoate are lyophilized powders that require reconstitution before administration and should be injected slowly. Risperidone is formulated as microspheres in powder form that require reconstitution before injection, although the injection speed is not specified. Paliperidone palmitate is a ready-to-use aqueous suspension of crystalline particles and should be injected slowly. Aripiprazole lauroxil is an aqueous-based, ready-to-use suspension of crystalline particles. Unlike other LAIs, the formulation of

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aripiprazole lauroxil contains particles that are loosely associated to facilitate resuspension. Because loosely associated suspensions are shear-thinning, meaning the viscosity of the formulation decreases with higher injection force, the injection must be given rapidly. Vigorous shaking and rapid injection are key aspects of administration and have been accepted by patients and investigators in clinical trials. In a pivotal phase 3 study of aripiprazole lauroxil, the incidence of ISRs was low (3.9% and 5.8% for aripiprazole lauroxil 441 mg and 882 mg , respectively) and mostly associated with the first injection.

Advances in formulation technology have increased LAI options for patients with schizophrenia. The aripiprazole lauroxil formulation differs from other LAIs in that the particles are loosely associated to support use as a ready-to-use pre-filled syringe. Because the suspension is shear-thinning, aripiprazole lauroxil requires rapid injection, which is not required when using other LAIs. An understanding of the differences in formulation design and how they impact the specific techniques associated with an LAI is essential for successful administration.

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77
Long-term Valbenazine Treatment in Patients with Schizophrenia/Schizoaffective Disorder or Mood Disorder and Tardive Dyskinesia

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ABSTRACT: Background: Patients treated with antipsychotics, regardless of psychiatric diagnosis, are at risk for developing tardive dyskinesia (TD), a potentially debilitating drug-induced movement disorder. Valbenazine (INGREZZA; VBZ) is a novel vesicular monoamine transporter 2 (VMAT2) inhibitor approved to treat TD in adults. Data from KINECT 4 (NCT02405091) were analyzed to evaluate the long-term effects of VBZ in adults with schizophrenia/schizoaffective disorder (SZD) or mood disorder (MD) and moderate or severe TD.

METHODS: KINECT 4 included open-label treatment (48 weeks) followed by washout (4 weeks). Entry requirements included: moderate or severe TD, qualitatively assessed at screening by a blinded, external reviewer; DSM diagnosis of SZD or MD; psychiatric stability (Brief Psychiatric Rating Scale score <50). Stable concomitant psychiatric medications were allowed. Dosing was initiated at 40 mg, with escalation to 80 mg at Wk4 if participants had a Clinical Global Impression of Change-TD score of ≥3 (minimally improved to very much worse) and tolerated 40 mg. A reduction to 40 mg was allowed if 80 mg was not tolerated (80/40 mg); participants unable to tolerate 40 mg were discontinued. Safety was the primary focus, but the Abnormal Involuntary Movement Scale (AIMS) total score (sum of items 1–7) was used to evaluate changes in TD. Mean changes from baseline (BL) in AIMS total score (rated by on-site investigators) were analyzed descriptively. Safety assessments included treatment-emergent adverse events (TEAEs) and psychiatric scales (Positive and Negative Syndrome Scale [PANSS], Calgary Depression Scale for Schizophrenia [CDSS], Montgomery-Åsberg Depression Rating Scale [MADRS], Young Mania Rating Scale [YMRS], and Columbia-Suicide Severity Rating Scale [C SSRS]).

RESULTS: Of 163 participants in the analyses, 103 completed the study. Adverse events (n = 26) was the most common reason for discontinuation. Analyses included 119 participants with SZD (40 mg = 37; 80 mg = 76; 80/40 mg = 6) and 44 with MD (40 mg = 8; 80 mg = 31; 80/40 mg = 5). At Wk48, mean improvements from BL in AIMS total score were: SZD (40 mg, –10.1; 80 mg,–10.7); MD (40 mg, 10.2; 80 mg: –11.6). AIMS total scores at Wk52 (end of washout) indicated a return toward BL levels. Compared to SZD, the MD subgroup had a higher incidence of any TEAE (84% vs 61% [all doses]) but fewer TEAEs leading to discontinuation (7% vs 18%). Urinary tract infection was the most common TEAE in the MD subgroup (18%); somnolence and headache were most common in the SZD subgroup (7% each). Psychiatric status remained stable from BL to Wk48: SZD (PANSS positive, –0.7, PANSS negative, –0.6; CDSS, –0.7); MD (MADRS, –0.3; YMRS, –0.3). Most participants (95%) had no change in C-SSRS score during the study.

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