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ABSTRACT: Background: Major depressive disorder (MDD) is a leading cause of disease burden worldwide, with lifetime prevalence in the United States of 17%. Here we present the results of the first prospective, large-scale, patient- and rater-blind, randomized controlled trial evaluating the clinical importance of achieving congruence between combinatorial pharmacogenomic (PGx) testing and medication selection for MDD.

METHODS: 1,167 outpatients diagnosed with MDD and an inadequate response to ≥1 psychotropic medications were enrolled and randomized 1:1 to a Treatment as Usual (TAU) arm or PGx-guided care arm. Combinatorial PGx testing categorized medications in three groups based on the level of gene-drug interactions: use as directed, use with caution, or use with increased caution and more frequent monitoring. Patient assessments were performed at weeks 0 (baseline), 4, 8, 12 and 24. Patients, site raters, and central raters were blinded in both arms until after week 8. In the guided-care arm, physicians had access to the combinatorial PGx test result to guide medication selection. Primary outcomes utilized the Hamilton Depression Rating Scale (HAM-D17) and included symptom improvement (percent change in HAM-D17 from baseline), response (50% decrease in HAM-D17 from baseline), and remission (HAM-D17 <7) at the fully blinded week 8 time point. The durability of patient outcomes was assessed at week 24. Medications were considered congruent with PGx test results if they were in the 'use as directed' or 'use with caution' report categories while medications in the 'use with increased caution and more frequent monitoring' were considered incongruent. Patients who started on incongruent medications were analyzed separately according to whether they changed to congruent medications by week 8.

RESULTS: At week 8, symptom improvement for individuals in the guided-care arm was not significantly different than TAU (27.2% versus 24.4%, $p = 0.11$). However, individuals in the guided-care arm were more likely than those in TAU to achieve remission (15% versus 10%; $p < 0.01$) and response (26% versus 20%; $p = 0.01$). Remission rates, response rates, and symptom reductions continued to improve in the guided-treatment arm until the 24 week time point. Congruent prescribing increased to 91% in the guided-care arm by week 8. Among patients who were taking one or more incongruent medication at baseline, those who changed to congruent medications by week 8 demonstrated significantly greater symptom improvement ($p < 0.01$), response ($p = 0.04$), and remission rates ($p < 0.01$) compared to those who persisted on incongruent medications.

CONCLUSIONS: Combinatorial PGx testing improves short- and long-term response and remission rates for MDD compared to standard of care. In addition, prescribing congruency with PGx-guided medication recommendations is important for achieving symptom improvement, response, and remission for MDD patients.
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Adjunctive Buprenorphine/Samidorphan Combination in Patients with Major Depressive Disorder: Phase 3 Long-term Extension Study Results

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ABSTRACT: Introduction: Buprenorphine/samidorphan (BUP/SAM), a combination of BUP (a μ-opioid receptor

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partial agonist and κ-antagonist) and SAM (a sublingually bioavailable μ-opioid antagonist), is an investigational opioid system modulator for depression. BUP/SAM has shown efficacy versus placebo as an adjunctive treatment for major depressive disorder (MDD) and a consistent safety profile in previously reported, placebo-controlled clinical studies.[1,2]

STUDY OBJECTIVE(S):

1. To characterize the safety profile following long-term treatment with BUP/SAM
2. To explore depression symptoms and remission rates in patients with MDD following long-term treatment with BUP/SAM

METHODS: FORWARD-2 (Clinicaltrials.gov ID: NCT02141399) enrolled patients who had participated in 1 of 4 controlled studies as well as de novo patients. All patients had a confirmed diagnosis of MDD, had a history of inadequate response to standard antidepressant therapies (ADTs), and had been treated with an adequate dose of an established ADT for ≥8 weeks before BUP/SAM initiation. ADT dosage could be titrated, but the ADT could not be changed. During the study, patients received open-label, sublingual BUP/SAM 2 mg/2 mg as adjunctive treatment for up to 52 weeks. Safety (primary objective) was assessed via adverse events (AEs), vital signs, laboratory analytes, and electrocardiography. Suicidal ideation or behavior (SIB) was evaluated by the Columbia Suicide Severity Rating Scale. Abuse potential, dependence, and withdrawal were assessed by AEs and the Clinical Opiate Withdrawal Scale. Exploratory efficacy endpoints included mean Montgomery–Åsberg Depression Rating Scale (MADRS) scores and remission rate (MADRS ≤ 10).

RESULTS: Of 1454 total patients, 49% completed the 52-week study, 11% discontinued due to an AE, and 40% discontinued because of other reasons as of the interim data cutoff date (April 30, 2017). Most AEs were of mild/moderate severity. Serious AEs were reported in 3.2% of patients. AEs occurring in ≥10% of patients were nausea, headache, constipation, dizziness, and somnolence. There was no evidence of increased risk of SIB with BUP/SAM. Incidence of euphoria-related events was low (1.2%). After abrupt discontinuation of BUP/SAM, there was little evidence of withdrawal. BUP/SAM was not associated with meaningful changes in laboratory or metabolic parameters or in bodyweight. The mean MADRS score decreased from 22.9 (±9.7) at baseline to 9.8 (±8.8) after 52 weeks. The remission rate at 52 weeks was 52.5%.

CONCLUSIONS: Long-term treatment with BUP/SAM did not reveal any new safety findings and confirmed that the risk of abuse and dependence with BUP/SAM was low. BUP/SAM maintained an antidepressant effect for up to 52 weeks of treatment in patients with MDD.

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Computer Vision, Facial Expressivity and Schizophrenia: A Review

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ABSTRACT: Introduction: Facial expressivity in schizophrenia has been a topic of clinical interest for the past century. Besides the schizophrenia sufferers difficulty decoding the facial expressions of others, they often have difficulty encoding facial expressions. Traditionally, evaluations of facial expressions have been conducted by trained human observers using the facial action coding system. The process was slow and subject to intra and inter-observer variability. In the past decade the traditional facial action coding system developed by Ekman has been adapted for use in affective computing. Here we assess the applications of this adaptation for schizophrenia, the findings of current groups, and the future role of this technology.

MATERIALS AND METHODS: We review the applications of computer vision technology in schizophrenia using pubmed and google scholar search criteria of "computer vision" AND "Schizophrenia" from January of 2010 to June of 2018.

RESULTS: Five articles were selected for inclusion representing 1 case series and 4 case-control analysis. Authors assessed variations in facial action unit presence, intensity, various measures of length of activation, action unit clustering, congruence, and appropriateness. Findings point to variations in each of these areas, except action unit appropriateness, between control and schizophrenia patients. Computer vision techniques were also demonstrated to have high accuracy in classifying schizophrenia from control patients, reaching an AUC just under 0.9 in one study, and to predict psychometric scores, reaching pearson's correlation values of under 0.7.

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