Abstract

Background. Pharmacogenomic testing has emerged to aid medication selection for patients with major depressive disorder (MDD) by identifying potential gene-drug interactions (GDI). Many pharmacogenomic tests are available with varying levels of supporting evidence, including direct-to-consumer and physician-ordered tests. We retrospectively evaluated the safety of using a physician-ordered combinatorial pharmacogenomic test (GeneSight) to guide medication selection for patients with MDD in a large, randomized, controlled trial (GUIDED).

Materials and Methods. Patients diagnosed with MDD who had an inadequate response to ≥1 psychotropic medication were randomized to treatment as usual (TAU) or combinatorial pharmacogenomic test-guided care (guided-care). All received combinatorial pharmacogenomic testing and medications were categorized by predicted GDI (no, moderate, or significant GDI). Patients and raters were blinded to study arm, and physicians were blinded to test results for patients in TAU, through week 8. Measures included adverse events (AEs, present/absent), worsening suicidal ideation (increase of ≥1 on the corresponding HAM-D17 question), or symptom worsening (HAM-D17 increase of ≥1). These measures were evaluated based on medication changes [add only, drop only, switch (add and drop), any, and none] and study arm, as well as baseline medication GDI.

Results. Most patients had a medication change between baseline and week 8 (938/1,166; 80.5%), including 269 (23.1%) who added only, 80 (6.9%) who dropped only, and 589 (50.5%) who switched medications. In the full cohort, changing medications resulted in an increased relative risk (RR) of experiencing AEs at both week 4 and 8 [RR 2.00 (95% CI 1.41–2.83) and RR 2.25 (95% CI 1.39–3.65), respectively]. This was true regardless of arm, with no significant difference observed between guided-care and TAU, though the RRs for guided-care were lower than for TAU. Medication change was not associated with increased suicidal ideation or symptom worsening, regardless of study arm or type of medication change. Special attention was focused on patients who entered the study taking medications identified by pharmacogenomic testing as likely having significant GDI; those who were only taking medications subject to no or moderate GDI at week 8 were significantly less likely to experience AEs than those who were still taking at least one medication subject to significant GDI (RR 0.39, 95% CI 0.15–0.99, p=0.048). No other significant differences in risk were observed at week 8.

Conclusion. These data indicate that patient safety in the combinatorial pharmacogenomic test-guided care arm was no worse than TAU in the GUIDED trial. Moreover, combinatorial pharmacogenomic-guided medication selection may reduce some safety concerns. Collectively, these data demonstrate that combinatorial pharmacogenomic testing can be adopted safely into clinical practice without risking symptom degradation among patients.

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A Combination of Olanzapine and Samidorphan in Adults with Schizophrenia and Bipolar I Disorder: Overview of Clinical Data

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Abstract

Objectives. Olanzapine effectively treats schizophrenia and bipolar I disorder (BD-I); however, its use is hindered by significant weight gain. A combination of olanzapine and samidorphan (OLZ/SAM) is in development to provide the efficacy of olanzapine while mitigating olanzapine-associated weight gain through opioid-receptor blockade. Here, we summarize OLZ/SAM clinical data.

Methods. The OLZ/SAM development program consists of 18 phase 1–3 clinical studies evaluating antipsychotic and weight mitigation efficacy of OLZ/SAM, along with pharmacokinetics, safety, and tolerability. Safety evaluation also included metabolic laboratory assessments.

Results. OLZ/SAM significantly improved psychotic symptoms (measured by Positive and Negative Syndrome Scale); improvements were similar to that observed with olanzapine vs placebo. OLZ/SAM resulted in significantly less weight gain than olanzapine. Additionally, 2 long-term phase 3 extension studies confirmed the durability of antipsychotic effect, as well as stabilization of weight and metabolic parameters in those continuing treatment. Supporting the potential use of OLZ/SAM in BD-I, OLZ/SAM or olanzapine resulted in bioequivalent olanzapine plasma concentrations, and OLZ/SAM did not affect lithium or valproate pharmacokinetics. OLZ/SAM treatment had no clinically relevant effects on ECG parameters (including QTc interval). OLZ/SAM and olanzapine safety were similar, except for reduced weight gain with OLZ/SAM; no additional safety risks were identified.

Conclusion. Data across 18 OLZ/SAM studies in >1600 subjects support an antipsychotic efficacy and safety profile for OLZ/SAM that is similar to olanzapine, with significantly less weight gain than olanzapine. OLZ/SAM is a potential new treatment for schizophrenia and BD-I patients needing efficacious long-term treatment with reduced risk of weight gain.

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