Table 1.

Item (mean CFB at Week 3 [standard deviation])	Psilocybin 25mg	Psilocybin 10mg	Psilocybin 1mg
MADRS - Inability to Feel	-1.8 [1.81]	-0.9 [1.54]	-0.8 [1.61]
MADRS - Apparent Sadness	-1.7 [1.94]	-1.1 [1.60]	-0.9 [1.62]
MADRS - Lassitude	-1.6 [1.81]	-1.2 [1.83]	-0.8 [1.58]
MADRS - Reported Sadness	-1.6 [1.95]	-1.0 [1.52]	-0.6 [1.53]
QIDS-SR$_{16}$ - Feeling Sad	-1.1 [1.08]	-0.8 [1.07]	-0.4 [0.91]

Conclusions: A single administration of COMP360 psilocybin therapy rapidly and dose-relatedly improved symptoms of depressed mood and anhedonia – the two key symptoms of depression. As anhedonia is predictive of poorer treatment response, and improvements in anhedonia correlate with improvements in functioning, it is important to understand the impact of treatments on this symptom.

Disclosure of Interest: G. Goodwin Shareolder of: COMPASS Pathways, P1Vital, and P1Vital products , Employee of: COMPASS Pathways, L. Marwood Shareolder of: COMPASS Pathways, Employee of: COMPASS Pathways, S. Mistry Employee of: COMPASS Pathways, A. Nowakowska Employee of: COMPASS Pathways, H. Simmons Employee of: COMPASS Pathways, J. Tsai Employee of: COMPASS Pathways, S. Williams Employee of: COMPASS Pathways, M. Young Shareolder of: COMPASS Pathways, Employee of: COMPASS Pathways, E. Malievskaia Employee of: COMPASS Pathways

O0069

Patient iPSC-derived neurons reveal mechanisms underlying antidepressant response: a potential diagnostic tool

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Introduction: Depression is a leading cause of disability worldwide despite dozens of approved antidepressants. There are currently no clear guidelines to assist the physician in their choice of drug, with existing tools limited to pharmacogenetics that have shown suboptimal response prediction outcomes resulting in a subscription process that is largely a trial and error one. Consequently, the majority of depressed patients do not respond to their first prescribed antidepressant, with >30% not responding to subsequent drugs. We report here on molecular readouts from an in vitro-based platform that provides patient-specific information on antidepressant mechanisms using cortical neurons derived individually from each patient.

Objectives: To assess gene expression differences in prefrontal cortex neurons derived from responders and non-responders to two commonly used antidepressants, the selective serotonin reuptake inhibitor Citalopram and the atypical antidepressant Bupropion.

Methods: Patient-derived lymphoblastoid cell lines from the Sequenced Treatment Alternatives to Relieve Depression (STARD) study with known response to Citalopram or Bupropion were reprogrammed and then differentiated to cortical neurons. Differential gene expression analysis was preformed to identify genes that are differentially expressed between drug responders and non-responders.

Results: Significant differential expression was shown in 359 genes between Bupropion responders and non-responders (Fig1A) and 12 genes between Citalopram responders and non-responders (Fig1B). Clustering on the differentially expressed genes showed high agreement with the known response to both drugs (Fig1). Functional enrichment analysis revealed biologically relevant pathways that differ between responders and non-responders in Bupropion versus Citalopram.
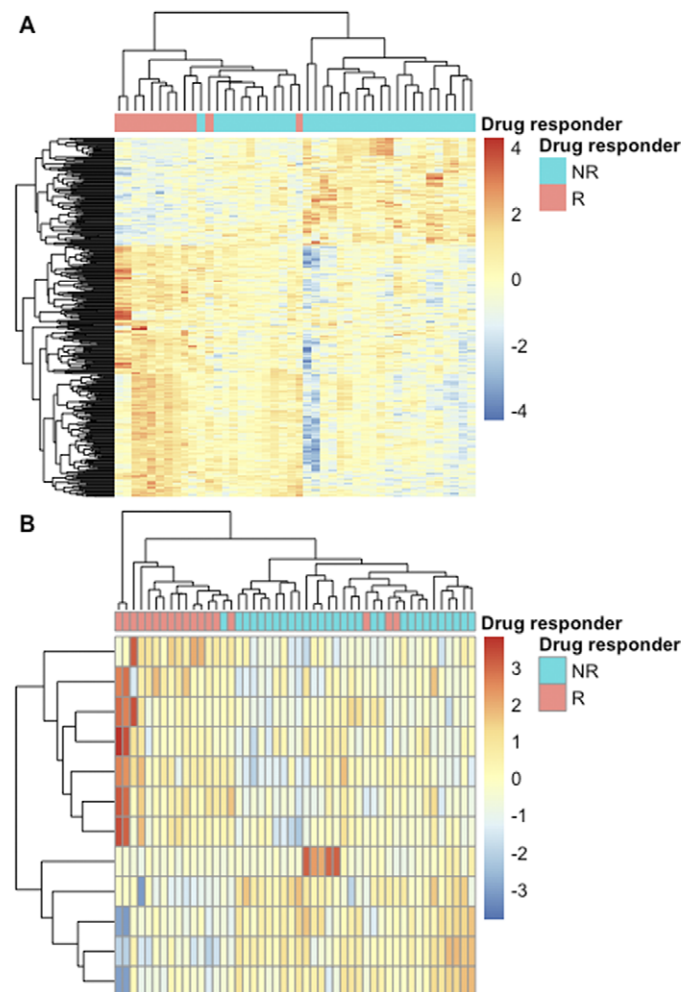
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Figure 1. Heatmap of the expression of genes that show significant differential expression between neurons derived from Bupropion (A) and Citalopram (B) responders and non-responders. Color is the scaled gene expression; lines are genes and columns are samples. Column side colors represent the known response of the patient. Colum and line dendrograms are unsupervised hierarchical clustering.

Conclusions: Gene expression patterns of neurons derived from patients with depression differ according to their response to two common antidepressants from different groups. The identification of distinct drug response dependent expression patterns in derived neurons can help elucidate mechanisms underlying antidepressant activity, supporting new drug development and response prediction.

Disclosure of Interest: None Declared

O0070

Pharmacogenetics to Personalize Dosing of Tricyclic Antidepressants in Major Depressive Disorder: A Randomized Clinical Trial (PITA study)

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Introduction: Tricyclic antidepressants (TCAs) have an important role in pharmacotherapy of Major Depressive Disorder (MDD). TCA dosing is aimed at achieving a concentration in the therapeutic window. Due to inter-individual differences in activity of Cytochrome P450 (CYP) 2D6 and 2C19, (enzymes involved in TCA metabolism) patients require an individualized dose. Currently, finding of a suitable dosage is a process of trial-and-error, including multiple drug concentration measurements and dose adjustments. A starting dose based on a patient CYP2D6 and CYP2C19 metabolizer phenotype may contribute to achieving a therapeutic concentration more quickly, possibly resulting in higher treatment efficacy and the occurrence of fewer adverse effects.

Objectives: We aimed to study whether genotype-informed dosing in TCAs leads to faster attainment of therapeutic plasma concentrations, a higher reduction of depression severity symptoms and less adverse effects.

Methods: We conducted a double-blind randomized clinical trial, in which patients (18-65 years) diagnosed with severe MDD and eligible for treatment with a TCA were randomized in two treatment arms: The intervention arm (Pharmacogenetics Informed Treatment; PIT) and standard treatment (Treatment As Usual; TAU). Patients were treated with nortriptyline, clomipramine or imipramine for seven weeks and depressive symptom severity and adverse effects were monitored weekly. The primary outcome measure, time needed to attain a therapeutic drug concentration, was analyzed using Kaplan-Meier analyses. The secondary outcome measures, reduction in depressive symptoms and adverse effects, were analyzed with mixed model linear regression.

Results: In total, we randomized 111 patients. The PIT group (n=56) reached a therapeutic plasma concentration significantly faster (Kaplan Meier, X^2 (1) = 4.3, p=0.039) compared to TAU (n=55), especially for patients treated with nortriptyline. On average depressive symptoms decreased relatively more in PIT than in TAU, although this was not significantly different: $F(6) = 0.45$, p = 0.84. The severity of adverse events during the study period differed significantly between PIT and TAU ($F(6)=3.10$, p=0.008). PIT experienced fewer adverse effects than TAU, especially in the last two weeks of the study.

Conclusions: Genotype-informed dosing leads to faster attainment of therapeutic TCA concentrations and does not lead to more adverse effects. Although we were not able to demonstrate that genotype-informed dosing leads to a significantly better response, we conclude that pharmacogenetics can contribute to the optimization of pharmacological treatment. Future research may focus on subgroups for which pharmacogenetics may be of great value, such as specific antidepressants or patients with an abnormal pharmacogenetic profile.

Disclosure of Interest: None Declared

O0071

Rapid improvements in MADRS with zuranolone in major depressive disorder and postpartum depression: results from the LANDSCAPE/NEST clinical development programmes

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Introduction: Rapid-acting therapies remain an unmet need in the treatment of major depressive disorder (MDD) and postpartum depression (PPD). Zuranolone (ZRN) is being evaluated as a once-daily, oral, 14-day treatment for adult patients with MDD and PPD.

Objectives: To evaluate the efficacy (assessed by Montgomery–Åsberg Depression Rating Scale [MADRS]) and safety of ZRN versus placebo across clinical studies with MDD and PPD.

Methods: In 5 completed Phase 2/3 placebo-controlled randomised studies of once-daily ZRN 30 or 50 mg in adults with MDD or PPD, improvement in depressive symptoms was assessed at Day 15 (end of 14-day treatment) by change from baseline in MADRS total score and the percentage of patients achieving MADRS response (≥ 50% improvement from baseline in total score) and remission (total score ≤ 10). Safety was assessed throughout.

Results: Patients in the ZRN arm achieved improvements in depressive symptoms, as assessed by MADRS. Improvements in MADRS total score at Day 15 were observed in all 5 studies and were nominally significant (p < 0.05) versus placebo in 4 studies (**Fig. 1**). Percentage of patients achieving response and/or remission in the ZRN arm was numerically greater than placebo in all MDD studies and significantly greater than placebo in the PPD studies (**Fig. 2 and 3**). ZRN was generally well tolerated with consistent safety and tolerability profiles across studies. The most common treatment-emergent adverse events (≥5 % in ZRN treatment arm) were headache, somnolence, dizziness, nausea, sedation, diarrhea, upper respiratory tract infection, fatigue, and COVID-19.