Sex-Specific Treatment of Major Depressive Disorder using Transcriptomic Profiling and LINCS Analysis

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INTRODUCTION

Major depressive disorder (MDD) is considered the leading cause of disability worldwide, affecting 4.4% of the global population and causing an economic burden of $210.5 billion in the United States alone [1]. Sex differences are prevalent in MDD: the rate of MDD is two-threefold higher among females, symptom severity is greater in females, and emerging evidence suggests that distinct molecular mechanisms underlie sex-specific MDD phenotypes [2,3]. These findings support the rationale for gender-specific diagnostic approaches; however, the current therapeutic strategies do not consider these fundamental differences in male and female patients.

We hypothesize that sex-specific molecular and transcriptomic profiles in MDD extend to treatment responses, advocating for personalized therapeutic regimens tailored to each sex's distinct biology.

METHODS

To identify drugs that may be targeted to treat male and female MDD patients, we first analyzed a publicly available MDD postmortem tissue transcriptomic dataset (GEO ID: GSE102556) to identify female (female MDD vs. female control) and male (male MDD vs. male control) MDD disease signatures across six different brain regions implicated in the pathophysiology of MDD.

Principal component analysis was performed for dimensionality reduction and identification of outliers. Raw data was aligned to the appropriate reference genome using HISAT2. Differential expression analysis of all count data was performed using EdgeR. The Library of Integrated Network-Based Cellular Signatures (LINCS) database was interrogated to identify chemical perturbagen (drug) signatures that are discordant (score<-0.50) with female and male MDD disease signatures independently.

The top and bottom 5% (p<0.05) of the L1000 "hub" genes were extracted and utilized to generate sex-specific drug signatures.

RESULTS

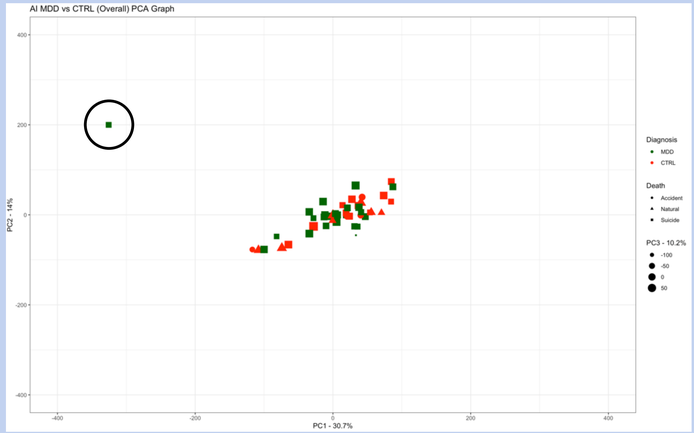

Figure 1: Principal Component Analysis (PCA). PCA performed for dimensionality reduction and identification of outliers. One outlier found in the MDD vs. CTL comparison in the anterior insula (AI) brain region: a male MDD subject who died by suicide. This subject was removed from further analysis. *Total subjects after removal = 47 (26 MDD, 21 CTRL; 22 females, 25 males).*

	Chemical Perturbagens from LINCS based on Top 5% L1000 Input Signature (MDD AI)	Chemical Perturbagens from LINCS based on Top 5% L1000 Input Signature (MDD AI) | Post-Filtering
Comparison: MDD vs CTL | All	6,035	1,358
Comparison: MDD vs CTL | Females	5,222	1,430
Comparison: MDD vs CTL | Males	6,675	1,459

Table 1: Summary of Chemical Perturbagens (CP) from LINCS. Number of CP based on the top 5% L1000 signature for MDD in the anterior insula (AI) brain region. Right most column shows CP after non-FDA approved drugs were removed and top cell lines were filtered. These CP were further filtered based on mechanism of action to decipher a final list of CP (drugs).

Chemical Perturbagen (Females) (n=31)	Mechanism of Action	Average Discordant Score
Tetrahydrozoline	Adrenergic receptor agonist	-0.62
Dipyrone	Cyclooxygese inhibitor | Opioid receptor agonist	-0.61
Clomipramine	**Serotonin transporter inhibitor**	-0.52
Fluphezine	Dopamine D2 receptor antagonist	-0.52
Formoterol	Adrenergic receptor agonist	-0.51
Dextromethorphan	Glutamate receptor antagonist|Sigma receptor agonist	-0.49
Iodophenpropit	Histamine receptor antagonist	-0.49
Candesartan	Angiotensin receptor antagonist	-0.48
Methysergide	**Serotonin receptor antagonist**	-0.48
Trimipramine	Histamine H1 receptor antagonist | Dopamine D2 receptor antagonist|**Serotonin 2a (5-HT2a) receptor antagonist (Serotonin 2a|Serotonin 2c (5-HT2c) receptor antagonist (Serotonin 2c|Norepinephrine transporter inhibitor** | Adrenergic receptor alpha-1 antagonist	-0.48
Dibenzepin	**Norepinephrine reuptake inhibitor**	-0.47
alizapride	Dopamine receptor antagonist	-0.47
(+)-Tranylcypromine	**Monoamine oxidase inhibitor**	-0.46
Nicergoline	Adrenergic receptor antagonist	-0.46
Oligomycin A	ATPase inhibitor|ATP synthase inhibitor	-0.45
Niguldipine	Adrenergic receptor antagonist|Calcium channel blocker	-0.45
Volasertib (BI 6727)	Serine/threonine-protein kise PLK1 inhibitor	-0.45
Prothiaden Spofa	**Norepinephrine reuptake inhibitor | Serotonin reuptake inhibitor | Tricyclic antidepressant**	-0.44
Riluzole	Glutamate inhibitor	-0.43
Dexfenfluramine	**Serotonin receptor agonist**	-0.43
Propranolol	Adrenergic receptor antagonist	-0.42
Nortriptyline	**Serotonin transporter inhibitor**|Norepinephrine transporter inhibitor	-0.42
Oxedrine	Adrenergic receptor agonist	-0.42
Vanoxerine	Dopamine uptake inhibitor	-0.42
Perphezine	Dopamine D2 receptor antagonist	-0.42
Suprofen	Cyclooxygese inhibitor	-0.41
Salvinorin A	Opioid receptor agonist	-0.41
Fexofedine	Histamine receptor antagonist	-0.40
Terfedine	Histamine receptor antagonist	-0.40
Cetirizine	Histamine receptor antagonist	-0.38
N-Methyl-quipazine	**Serotonin receptor agonist**	-0.37

Chemical Perturbagen (Males) (n=35)	Mechanism of Action	Average Discordant Score
Morin	Cytochrome P450 inhibitor	-0.58
Nefazodone	Adrenergic inhibitor | **Norepinephrine reuptake inhibitor |Serotonin receptor antagonist | Serotonin reuptake inhibitor**	-0.54
Clotrimazole	Cytochrome P450 51 inhibitor	-0.48
Bepotastine Besilate	Histamine H1 receptor antagonist	-0.46
Sulcozole	Cytochrome P450 51 inhibitor	-0.46
Butocozole	Cytochrome P450 51 inhibitor	-0.45
Thioproperazine	Dopamine receptor antagonist	-0.44
Eliprodil	Glutamate receptor antagonist	-0.44
Sulpiride	Dopamine receptor antagonist	-0.43
Itracozole Hydrochloride	Cytochrome P450 51 inhibitor	-0.43
Flurbiprofen	Cyclooxygese inhibitor	-0.43
Dihydroergotamine	**Serotonin 1d (5-HT1d) receptor agonist (Serotonin 1d**	-0.43
Triflupromazine	Dopamine receptor antagonist	-0.42
Mianserin	**Serotonin receptor antagonist**	-0.42
Mefloquine	Adenosine receptor antagonist|Hemoglobin antagonist	-0.42
fronyl	Adrenergic receptor antagonist	-0.41
Nepafec	Cyclooxygese inhibitor	-0.41
Amperozide	Dopamine receptor antagonist	-0.41
Apigetrin	Cytochrome P450 inhibitor	-0.41
Darifecin	Acetylcholine receptor antagonist	-0.40
Phenelzine	**Monoamine oxidase inhibitor**	-0.40
Zolantidine	Histamine receptor antagonist	-0.40
Thiocolchicoside	GABA receptor antagonist	-0.40
Solifecin succite	Muscarinic acetylcholine receptor M2 antagonist|Muscarinic acetylcholine receptor M3 antagonist	-0.40
Piperine	**Monoamine oxidase inhibitor**	-0.40
Olopatadine	Histamine receptor antagonist	-0.39
Risperidone	Dopamine receptor antagonist|Serotonin receptor antagonist	-0.39
Ifenprodil	Adrenergic receptor antagonist|Glutamate receptor antagonist	-0.39
Epinephrine HCl	Adrenergic receptor agonist	-0.39
Andamide	**Cannabinoid receptor agonist**	-0.39
Fenoterol	Adrenergic receptor agonist	-0.38
Tenoxicam	Cyclooxygese inhibitor	-0.38
Ethylbeta-carboline-3-carboxylate	GABA benzodiazepine site receptor inverse agonist	-0.38
Binospirone	**Serotonin receptor antagonist**	-0.37
Allopurinol	Xanthine oxidase inhibitor	-0.34

DISCUSSION & FUTURE WORK

- Unsurprisingly, several established **antidepressant medications** (**SSRIs, SNRIs, MAOIs, TCAs**) were discordant across brain regions in female and male groups, suggesting the robustness of this method in identifying known therapies that reverse associated pathology (only anterior insula (AI) brain region results shown, based on sex).
- Interestingly, **antipsychotics (e.g., perphezine, amperozide, olanzapine)** were significantly discordant with MDD AI signature in females and males, lending support for **off-label use of antipsychotics** for the treatment of MDD.
- Distinct transcriptomic signatures and drug signatures were found for females and males based on brain region. A greater number of **purinergic system modulators** were found in **females**. A greater number of **MAOIs** were found in **males**. **Cannabinoid receptor agonists** and **cytochrome P450 modulator**s were found only in **males**.
- **Future work**: Analysis to decipher and cluster the mechanism of actions of drugs within each profile, which will give broader insight into sex-specific treatments for this challenging illness.

REFERENCES

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CONTACT INFORMATION

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