Personalized medicine for depression: searching for the most efficacious treatment for an individual patient

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Introduction:
Major depression is a common disorder that diminishes social functioning and quality of life and causes significant medical morbidity and mortality. (1-3) The World Health Organization (WHO) has ranked depression the 4th leading cause of disability worldwide (4) and projects that by 2020, it will be the second leading cause. (5)

DSM V: 5 (or more) of the following symptoms have been present during the same 2- week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure: Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others

• Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day• Significant weight loss when not dieting or weight gain or decrease in appetite nearly every day• Insomnia or hypersomnia nearly every day• Psychomotor agitation or retardation nearly every day• Fatigue or loss of energy nearly every day• Feelings of worthlessness or excessive or inappropriate guilt nearly every day• Diminished ability to think or concentrate, or indecisiveness, nearly every day• Recurrent thoughts of death, suicidal ideation(20)

Neurobiological mechanisms by which depression affects monoamine levels and consequently atypical features of major depression and how chronic stress affects both glucocorticoid and glutamate levels leading to altered neuroplasticity and consequently melancholic features of depression.(6)

Depression with Atypical and Melphalnchic Features:
Research shows that different faces of depression have different pathophysiology. Atypical depression may be associated with increased immune activity, reflected by increased proinflammation cytokine concentrations that affect the functioning of dopamine, norepinephrine and serotonin. (6) Therefore, it may be sensible to treat this specific group of patients with NSAIDs and anti-inflammatory drugs to counter this state of inflammation. Interestingly, there is evidence indicating that SRRs have an anti-inflammatory effect. (7) On the other hand, melancholic depression is associated with a hypofunctional CRF system and HPA axis, thereby glucocorticoid receptors are down-regulated and lead to feedback resistance, consequently, hypersecretion of glucocorticoids further increases and may decrease neuroplasticity in frontal cortex, PFC and hippocampus. (6, 8, 9) The decreased neuroplasticity may be a target for new drugs and is a promising area for further research.

Genetics and Personalized Psychopharmacology:
Genetic analysis shows that:
• Risk of depression was associated with allelic and/or haplotypic variations of CRNI and FAAH genes.

•TT homozygosity of CRNI at rs806368 and rs806371 was associated with increased risk of no remission following treatment. .

•HT genotype block of 1 of CRNI genotypes (rs806368-a1019535-c8360873, which is a combination C–G–G [minor-major-minor] allele), was associated with higher remission rates following treatment. .

•There is evidence of genotype-dependent variation in treatment response by gender.

•There is evidence that individuals considered clinical symptoms, personality traits, responses to environmental stimuli, risk and severity of depression are associated with SNPs and haplotype blocks of the CRNI gene. (11)

•There is also evidence of an association between the low expression 5- HTTLPR short allele and decreased response to psychological treatment. (12) However, another study found a lack of association between response to an SSRI and variation at the 5HTTLPR locus. (13) Future research is necessary to clarify the significance of this allele

The Relevance of Pharmacogenomic Testing in Depression Treatment:
A comprehensive review of CPY50 studies show that some studies indicate that the evidence of association with treatment outcomes was “mixed” (14); whereas others indicate that genetic profile was relevant for the dosage adjustments of nearly half of the antidepressants examined (15). The antidepressant response to newer antidepressants such as venlafaxine, paroxetine, citalopram, escitalopram, and sertraline was found to be dependent on genetic variation of the cytochrome P450 system. (16) Further research is necessary to clarify the usefulness of such genetic tests.

Predictors of Depression Therapy
Research shows that EGG findings may play a role in monitoring response to antidepressant treatments. Excess frontal theta and alpha activity was shown to be associated with being unresponsive to antidepressant treatments and it was suggested that this group might respond better to stimulant medications. (17)

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found that only one-third of patients went into remission using standard antidepressant medication after 3 months. After other medications were tried, only 50-60% were in remission after 1 year (18).

Having to carry out treatment for a long duration of time before the right medication is found is not an efficient approach and points out why predictors of remission are necessary. Several methods were tried to serve this purpose such as resting-state fMRI, immune markers, DNA and gene expression products, and dexamethasone/corticotropin-releasing hormone (DEX/CRH) testing and a comprehensive personality assessment. (19) Further research into this area may help clinicians find the most efficacious treatment for an individual and avoiding earlier response and remission.

Interpersonal Subgroups
Research shows that there are several distinct interpersonal subgroups of patients with depression. (21-23) Cain et al. identified six distinct interpersonal groups of patients with depression based on personality self-ratings. These subgroups were extraverted, dominant, arrogant, cold, submissive, and unassuming. The chronicity of depression and poorer functioning was found to be associated with submissive interpersonal style. (22) Therefore, literature analysis suggests that interpersonal heterogeneity may play an important role in treatment outcomes and should be considered as a component of personalized treatment strategies.

Conclusion:
Previous research points out that many individual factors such as genetic profile, metabolism and interpersonal subgroups make a difference in pathophysiology, prognosis, and treatment of depression. This is why it is important to consider the role of personalized treatment modalities. Current changes in resource allocation (25) is promising and the encouragement of such endeavors can make substantial improvements in the management of depression in the future.