Tradeoffs between life extension and quality of life:
A psychiatric perspective on practical pharmacological interventions

Jon Berner MD PhD; Woodinville Psychiatric Associates

Abstract:

Aim: General human use of FDA approved medications known to increase lifespan (rapamycin and lithium) is potentially limited by tolerability in terms of mood disturbance and maximal cognitive output.

Objective: Identification of objective biochemical pathways in the CSF and associated behavioral phenotypes may allow for medication selection and dose finding for acute stabilization, primary prevention, and secondary prophylaxis of progression of age-related mood and cognitive disorders.

Methods: Patients, N=29, with depression refractory to current medications provided AM fasting CSF samples with subsequent z-score estimation of approximately 151 metabolites. Chart review provided subsequent response to medication treatment, contemporaneous clinical status with self-reported checklists, and basic demographic information. Hypothesis free multivariate analysis compressed the resultant 5000 item data array into 2 dimensions which collectively accounted for approximately 34% of the variance.

Results: Dimension 1 accounted for 17.5% of the variance. One end of the line loaded heavily on self-reported autism scores, male gender, and cognitive fatigue checklists. The other end loaded heavily with bipolar diagnosis, mood stabilizer use, rapamycin response, and ethylmalonate disturbance. Dimension 2 accounts for 15.7% of the variance. One end of the line loads heavily with age and the Frobenius norm of the metabolome matrix. The other end of the line loads heavily with TMHF concentration, homocarnosine elevation, and self-reported checklists of depression (PHQ9) and anxiety (GAD21). Incidental findings are age correlating most highly with GABA metabolites (homocarnosine and 4-acetamidobutanoate) and ketamine response correlating with 2-hydroyxbutyrate elevation.

Discussion: The caloric restriction literature in Drosophila subspecies strongly cautions against using metabolic manipulation uniformly across populations, given a decrease in longevity observed in 10% of species variants. Multivariate estimates of CSF metabolic gradients can allow for nearest neighbor patient identification independent of genetic kinship or alternative phenotypic expression. Immediate clinical utility is illustrated with examples of PPAR gamma modulation.