2021 Best Research Poster Award

Barwon Health

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The potential role of metabolic profiles in predicting treatment response after adjunctive N-acetylcysteine therapy in bipolar depression

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INTRODUCTION

▲Neurogenesis ▲Mitochondrial function

NAC

▼Inflammation ▼Oxidative stress

NAC has shown effects on multiple aspects which have been implicated in the pathophysiology of psychiatric disorders[1,2]. The prediction of treatment response in individuals with bipolar depression has been a major focus in the field.

OBJECTIVES

To assess **A)** if NAC could have a positive impact on social functioning and **B)** if metabolic profiles at baseline could predict treatment responses.

METHOD

60 participants (NAC n=31; placebo n= 29) with bipolar disorder and current depressive symptoms were enrolled in a 16-week, double-blinded, randomised controlled trial where participants were randomised to 2,000mg/day NAC in addition to treatment as usual or placebo[3].

The primary outcome was change in MADRS total score from baseline to endpoint (ie. week 16). SOFAS and LIFE-RIFT were used to quantify level of social functioning. NAC responders are defined as participants with >50% reduction in MADRS score from baseline to endpoint. Metabolites were measured in plasma samples collected at baseline using semi-quantitative gas chromatography.

RESULTS

1) **Higher** MADRS was associated with **worse** functioning

2) Baseline SOFAS and LIFE-RIFT did **not** predict NAC's effects between NAC vs. Placebo and NAC responders vs. non-responders

3) Within NAC group, **higher** baseline metabolite levels were associated with **worse** functioning at endpoint

Metabolites @BL associated with SOFAS @EP

Metabolite	R	P	Holm P
Glycine	-0.38	0.047	1
β-alanine	-0.39	0.039	1

After adjusting for baseline score, age, sex & BMI in a multi-variate linear regression model

Overall P	Adj. R^2
0.004 **	0.42

Glycine was statistically significant **

Metabolites @BL associated with LIFE-RIFT @EP

Metabolite	R	P	Holm P
L-alanine	0.50	0.0069	1
Glycine	0.43	0.022	1
Oxalic acid	0.48	0.011	1
L-proline	0.49	0.0088	1
Nor leucine	0.41	0.031	1
Pyroglu B	0.39	0.042	1
16ABD	0.41	0.029	1
L-hist	0.43	0.024	1
L-cystine	0.38	0.044	1

Overall P	Adj. R^2
0.27 ns	0.14

4) Within NAC group, **higher** baseline metabolite levels were associated with **reduced** functioning from baseline to endpoint

Metabolites @BL associated with ΔSOFAS (EP - BL)

Metabolite	R	P	Holm P
Valine	-0.44	0.019	1
Glycine	-0.42	0.028	1
Nor leucine	-0.39	0.043	1

Overall P	Adj. R^2
0.20 ns	0.12

Metabolites @BL associated with ΔLIFE-RIFT (EP - BL)

Metabolite	R	P	Holm P
Glycine	0.54	0.0032	1
Nor leucine	0.55	0.0027	1
16ABD	0.51	0.0058	1
Ribitol	0.41	0.028	1
L-cystine	0.42	0.028	1

Overall P	Adj. R^2
0.10 ns	0.23

DISCUSSION

Within the NAC group, higher levels of some metabolites at baseline tend to be associated with worse functioning at endpoint, and also with greater reductions in functioning from baseline to endpoint. The role of significant metabolites in social functioning needs to be explored. Other biomarkers (eg. C-reactive protein) could also be examined for their potential associations with treatment responses.

CONCLUSION

In participants treated with adjunctive NAC, specific metabolites could predict treatment responses in social functioning. The role of these metabolites requires further investigations.

REFERENCES & ACKNOWLEDGEMENTS

1. Deepmala, Slattery, J., Kumar, N., Delhey, L., Berk, M., Dean, O., Spielholz, C., & Frye, R. (2015). Clinical trials of N-acetylcysteine in psychiatry and neurology: A systematic review. *Neuroscience and biobehavioral reviews*, *55*, 294–321.
2. Dean, O., Giorlando, F., & Berk, M. (2011). N-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action. *Journal of psychiatry & neuroscience : JPN*, *36*(2), 78–86.
3. Berk, M., Turner, A., Malhi, G. S., Ng, C. H., Cotton, S. M., Dodd, S., Samuni, Y., Tanious, M., McAulay, C., Dowling, N., Sarris, J., Owen, L., Waterdrinker, A., Smith, D., & Dean, O. M. (2019). A randomised controlled trial of a mitochondrial therapeutic target for bipolar depression: mitochondrial agents, N-acetylcysteine, and placebo. *BMC medicine*, *17*(1), 18.