**A possible role for sarcosine in the management of schizophrenia - supplementary material**

David Curtis MA MD PhD FRCPsych

Honorary Professor

Centre for Psychiatry, Queen Mary University of London

UCL Genetics Institute, University College London

UCL Genetics Institute, Darwin Building, Gower Street, London WC1E 6BT.

d.curtis@ucl.ac.uk

Summary of published reports of sarcosine in the treatment of schizophrenia. Doses given are per day. Abbreviations: PANSS - Positive and Negative Syndrome Scale (Kay et al. 1987); SANS - Scale for the Assessment of Negative Symptoms (Andreasen 1989); CGI-S - Clinical Global Impression - Severity scale (Guy 1976); CDSS - Calgary Depression Scale for Schizophrenia (Addington et al. 1990); PULSAR - PoLish SARcosine study in schizophrenia (Strzelecki et al. 2018).

|  |  |
| --- | --- |
| **Study design** | **Outcome** |
| Double blind randomised control trial of schizophrenia patients on stable medication treated for 6 weeks with additional placebo (N=21) or sarcosine 2 g (N=17) (Tsai et al. 2004) | Sarcosine group improved more than placebo group with respect to positive, negative, cognitive and general psychiatric symptoms. Well-tolerated with no significant side effects. |
| Double-blind randomised control trial. Patients admitted with acute exacerbation of schizophrenia treated for 6 weeks with risperidone plus placebo (N=23), D-serine 2 g (N=21) or sarcosine 2 g (N=21). (Lane et al. 2005)  | Sarcosine group improved more than placebo and D-serine groups on PANSS and SANS and more likely to show a marked response (>30% reduction in PANSS score) than placebo group. Mild adverse effects did not differ between groups. |
| Double-blind randomised control trial of patients on clozapine treated for 6 weeks with additional placebo (N=10) or sarcosine 2 g (N=10). (Lane et al. 2006) | No difference in response between placebo and sarcosine groups. Side effects mild and short-lived. |
| Double-blind randomised control trial of patients hospitalised with exacerbation of schizophrenia treated for 6 weeks with sarcosine 1 g (N=9) or 2 g (N=11) but no other antipsychotic medication. (Lane et al. 2008) | Two patients from 1 g group dropped out due to unsatisfactory response. Overall no significant effect of dose although 5/11 of the 2 g group versus 0/9 of the 1 g group were responders (>20% reduction in PANSS score). Well-tolerated with minimal side effects. |
| Double-blind randomised control trial of patients with schizophrenia stabilised on optimal antipsychotic treatment to which was added placebo (N=20), D-serine 2 g (N=20) or sarcosine 2 g (N=20). (Lane et al. 2010) | Sarcosine superior to placebo on measures of positive and negative symptoms, quality of life and global functioning, with larger effect sizes than D-serine for all measures. Well tolerated with only mild side effects. |
| Case report of patient in PULSAR study with schizophrenia on quetiapine 500 mg and citalopram 10 mg to which was added sarcosine 2 g. (Strzelecki et al. 2014) | Initially improved but developed hypomania which resolved after reducing dose of sarcosine to 1 g, after which patient described subjectively better mental state compared to before starting treatment. |
| Case report of patient in PULSAR study with schizophrenia on olanzapine 25 mg and venlafaxine 75 mg to which was added sarcosine 2 g. (Strzelecki et al. 2015) | Patient developed hypomania which resolved after decreasing dose of venlafaxine to 37.5 mg and patient subjectively felt better after starting sarcosine. |
| Double-blind randomised control trial of patients with chronic schizophrenia on stable antipsychotic medication to which was added placebo (N=21), sarcosine 2 g (N=21) or sarcosine 2 g plus benzoate 1 g (N=21). (Lin et al. 2017) | The sarcosine plus benzoate group improved significantly more than placebo on global and cognitive functioning but not PANSS or CGI-S. The improvement of the sarcosine group did not differ from that of the placebo group. Well tolerated with only mild and brief side effects. |
| PULSAR - double-blind randomised control trial of patients with paranoid schizophrenia and residual symptoms on stable medication treated for six months with additional placebo (N=30) or sarcosine 2 g (N=30). (Strzelecki et al. 2018) | Sarcosine group improved more than placebo group on PANSS and CDSS with more responders: 16/30 versus 1/30. Two subjects with transient hypomania (as in case reports above) but otherwise well tolerated with frequency of side effects similar in both groups.  |

**References**

Addington, D., Addington, J. & Schissel, B., 1990. A depression rating scale for schizophrenics. *Schizophrenia Research*, 3(4), pp.247–251.

Andreasen, N.C., 1989. The Scale for the Assessment of Negative Symptoms (SANS): Conceptual and Theoretical Foundations. *British Journal of Psychiatry*, 155(S7), pp.49–52.

Guy, W., 1976. *ECDEU assessment manual for psychopharmacology* Rev., Rockville Md.: U.S. Dept. of Health Education and Welfare Public Health Service Alcohol Drug Abuse and Mental Health Administration National Institute of Mental Health Psychopharmacology Research Branch.

Kay, S.R., Fiszbein, A. & Opler, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophrenia Bulletin*, 13(2), pp.261–276.

Lane, H.-Y. et al., 2010. A randomized, double-blind, placebo-controlled comparison study of sarcosine ( N-methylglycine) and d-serine add-on treatment for schizophrenia. *The International Journal of Neuropsychopharmacology*, 13(04), p.451.

Lane, H.-Y. et al., 2006. Glycine Transporter I Inhibitor, N-methylglycine (Sarcosine), Added to Clozapine for the Treatment of Schizophrenia. *Biological Psychiatry*, 60(6), pp.645–649.

Lane, H.-Y. et al., 2008. Sarcosine (N-Methylglycine) Treatment for Acute Schizophrenia: A Randomized, Double-Blind Study. *Biological Psychiatry*, 63(1), pp.9–12.

Lane, H.-Y. et al., 2005. Sarcosine or D-Serine Add-on Treatment for Acute Exacerbation of Schizophrenia. *Archives of General Psychiatry*, 62(11), p.1196.

Lin, C.-Y. et al., 2017. Adjunctive sarcosine plus benzoate improved cognitive function in chronic schizophrenia patients with constant clinical symptoms: A randomised, double-blind, placebo-controlled trial. *The World Journal of Biological Psychiatry*, 18(5), pp.357–368.

Strzelecki, D. et al., 2015. Hypomania after augmenting venlafaxine and olanzapine with sarcosine in a patient with schizophrenia: a case study. *Neuropsychiatric Disease and Treatment*, 11, p.533.

Strzelecki, D., Szyburska, J. & Rabe-Jabłońska, J., 2014. Two grams of sarcosine in schizophrenia &amp;ndash; is it too much? A potential role of glutamate- serotonin interaction. *Neuropsychiatric Disease and Treatment*, 10, p.263.

Strzelecki, D., Urban-Kowalczyk, M. & Wysokiński, A., 2018. Serum levels of TNF-alpha in patients with chronic schizophrenia during treatment augmentation with sarcosine (results of the PULSAR study). *Psychiatry Research*, 268, pp.447–453.

Tsai, G. et al., 2004. Glycine transporter I inhibitor, N-Methylglycine (sarcosine), added to antipsychotics for the treatment of schizophrenia. *Biological Psychiatry*, 55(5), pp.452–456.