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

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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).

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| **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. |

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