A possible role for sarcosine in the management of schizophrenia

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Summary

Sarcosine, which is freely sold as a dietary supplement, has pharmacological activity to boost functioning of the glutamatergic N-methyl-D-aspartate receptor (NMDAR) and hence represents a biologically rational treatment for schizophrenia. The small number of studies carried out to date provide some evidence for its efficacy and psychiatrists could consider suggesting its use to their patients.

As summarised recently (Balu 2016; Tsavou & Curtis 2019), there is convergent and compelling evidence from pharmacological, autoimmune and genetic studies that impaired functioning of the glutamatergic N-methyl-D-aspartate receptor (NMDAR) can produce psychotic symptoms and is sometimes involved in the pathogenesis of schizophrenia. As well as binding glutamate, NMDAR also possesses a modulatory site at which glycine acts as a co-agonist. Thus, this site represents a rational therapeutic target for the treatment of schizophrenia.

One method whereby NMDAR activity could be enhanced is through increasing the availability of synaptic glycine by the attenuation of glycine reuptake through glycine transporter 1 (GlyT-1). Bitopertin is a glycine reuptake inhibitor and in the recent CandleLyte phase II/III trial it was compared against placebo and olanzapine as monotherapy for patients with an exacerbation of schizophrenia (Bugarski-Kirola et al. 2014). This study failed to achieve separation from placebo for the main outcome measures by either olanzapine or bitopertin, reflecting that patients in all groups improved following admission. However it was noted that more patients in both the bitopertin 30 mg group (51%) and the olanzapine 15 mg group (53%) than the placebo group (33%) were ready for hospital discharge at week 4. Bitopertin was safe and well tolerated.

Another inhibitor of GlyT-1 is N-methylglycine (sarcosine) (Herdon et al. 2001). This has been the subject of a number of small trials in the treatment of schizophrenia which are detailed in the supplementary material. The standard dose used is 2 g per day, though it is sometimes suggested to work up to this gradually. In some studies sarcosine on its own or as adjunctive therapy is superior to

placebo and in others there are no significant differences. In particular, there is some suggestion that sarcosine may produce improvement in negative as well as positive symptoms. The most recent and largest (though still with only 30 patients per arm) is the PULSAR study, and this also had a longer follow up period than the others, of 6 months (Strzelecki et al. 2018). In this study, patients with paranoid schizophrenia treated with additional sarcosine as compared with placebo had improved outcomes and higher a response rate. In the PULSAR study two out of 30 patients developed hypomania following addition of sarcosine to their usual treatment. The first was also receiving quetiapine 500 mg and citalopram 10 mg and the second was also receiving olanzapine 25 mg and venlafaxine 75 mg. Both episodes resolved satisfactorily following adjustment of dosage, consisting of reducing the sarcosine to 1g in the former and the dose of venlafaxine to 37.5 mg in the latter. Aside from these two cases, all studies consistently report side effects as being mild, transient and not clearly related to treatment.

Sarcosine occurs naturally in a range of foods and is sold without restriction. For example, 100 g at 98% purity can be purchased for £20 ($26) (https://www.sigmaaldrich.com/catalog/product/aldrich/131776). It is widely promoted on the internet as a "brain health supplement" (https://brainvitaminz.com/collections/all), for a variety of mental health problems (https://selfhacked.com/blog/sarcosine/, https://www.reddit.com/r/Anhedonia_Recovery/comments/77vvyz/sarcosine_nac_nacetylcysteine_success_stories_for/) and specifically for schizophrenia (http://www.schizophrenia.com/glycinetreat.htm).

Sarcosine differs from the drugs which can be prescribed to treat schizophrenia in that patients can obtain it for themselves. Even though it is may be sold as a dietary supplement, there is reasonable evidence that it has a real pharmacological effect which may produce useful benefits in some patients. Psychiatrists should know how they would respond if a patient asks whether they should try taking sarcosine in addition to their antipsychotic medication. They could even consider whether they should actively recommend it. In fact, since it does not require a prescription, any member of the multidisciplinary team might have this role and mental health services may well want to develop agreed policies on communicating what they regard as the benefits and risks. It should be borne in mind that some patients may regard sarcosine as a relatively attractive option. They may regard it as a "natural" product and they may feel more autonomy in consuming something which they purchase for themselves rather than only taking a medication which is prescribed to them. Both doctors and patients may be attracted to the idea that sarcosine represents a rational treatment intervention, given that it seems to act by enhancing the functioning of a receptor which is impaired in schizophrenia. Including sarcosine as part of the treatment package may be seen as in some ways implementing a more holistic approach than simply prescribing antipsychotic medication on its own. It might even to some extent be perceived as a lifestyle intervention and as a part of "healthy diet".

It seems clear that there is a need for larger trials to produce a better understanding of the likely benefits and risks of sarcosine treatment. In terms of current practice, it seems that there is reasonable evidence that it can produce an improvement in schizophrenia symptoms when added to conventional antipsychotic treatment. Indeed, the evidence in favour of sarcosine is arguably already stronger than for some of the other interventions offered by mental health services. It seems to be almost universally well-tolerated with an absence of significant side effects, with the exception of two cases of transient hypomania on patients who were taking antidepressants. These

cases suggest that caution should be exercised in patients taking serotonergic medication. A potential risk is that patients might try taking sarcosine instead of, rather than as well as, their usual medication. This could well lead to deterioration or relapse and patients should be advised against trying this without close supervision. Another risk is that patients with unsatisfactory symptom control might try to self-medicate with high doses. It is unclear what, if any, problems this might cause but it seems sensible to advise caution. A final suggestion is that in discussions with patients, carers and other health professionals one should always speak of sarcosine as enhancing the activity of glutamate receptors rather than NMDA receptors, since otherwise there will inevitably be people who gain the impression that one is referring to receptors for ecstasy.

Individual professionals and services will draw their own conclusions but it seems reasonable to conclude that suggesting sarcosine to patients with schizophrenia would be a defensible, evidence-based intervention.

Acknowledgments

Thanks to James Innes for helpful comments.

Declaration of interest

The author is involved in genetics research which implicates the same system as is targeted by sarcosine. He declares no other interest.

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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).

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	Initially improved but developed hypomania which resolved after reducing dose of sarcosine to 1 g, after which patient

500 mg and citalopram 10 mg to which was added sarcosine 2 g. (Strzelecki et al. 2014)	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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