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What is the effectiveness of dimethyl glycine in treating Autistic symptoms? A Systematic Review

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What is the effectiveness of dimethyl glycine in treating Autistic symptoms? A Systematic Review

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Abstract

Autism is a chronic neurodevelopmental disorder characterised by a triad of impairments including social communication, abnormal speech and routines. As there is no recognised cure for the condition there is considerable interest in treatment modalities to improve core and common symptoms. The effectiveness of many of these is of doubtful provenance. Across the broad range of modalities a common theme apart from a lack of robust evidence to support any individual intervention is the small size of many of the individual clinical trials, variably poor methodology and the use of heterogeneous outcome measures with uncertain validity.

N, N- dimethyl glycine is a compound related to the amino acid glycine and has been reported to show benefits in children with autism.

This systematic review examines the use of dimethyl glycine to improve the behaviour of children with autism. One RCT reported results from 37 children, taking either dimethyl glycine or placebo. While there was no difference in terms of improved specific behavioural traits between the two arms of the trial there was a non-significant improvement in general behaviour (58% vs. 53%) in those taking dimethyl glycine; however it is quite possible that a lack of power was an issue. Two other trials were found, both with significant methodological limitations were not included, but did report similar beneficial effects. There appear to be no significant side effects but there would be a financial cost associated with using dimethyl glycine in the long term and so its use even in the absence of side effects would need to be supported by further evidence.

Keywords

ASD, Autism, N-Dimethyl glycine, Dimethyl glycine

Introduction

Autism is a chronic neurodevelopmental disorder characterised by a triad of impairments involving social interaction, communication and restricted repetitive behaviour (World Health Organisation,

1992). As there is no recognised cure there is considerable interest in treatment modalities to improve core and common symptoms associated with the condition. This includes conventional medication, health food supplements and non-pharmacological interventions such as music therapy. The effectiveness of many of these modalities is of doubtful provenance. Across this broad range of modalities, a common theme, including a lack of robust evidence to support any individual intervention is the small size of many of the individual clinical trials. This increases the importance of conducting systematic reviews to collate and synthesize research evidence and where possible conduct a meta-analysis.

Dimethylglycine is a drug/health food supplement related to the amino acid glycine. There has been some interest in its ability to improve the behaviour of children with Autism (Bolman et al, 1999). However there do not appear to have been any large scale multi centre studies to address this topic and which conclusively provide evidence to support its use. The aim of this systematic review was to conduct a systematic review to synthesize and clarify if possible the best research evidence on this topic.

The study was the first study to be conducted by the Child Health Applied Research Group: East- Midlands (CHARGE). A group whose aim is to develop the evidence base for community paediatrics by conducting high quality systematic reviews. As such the protocol /methodology had additional checks to ensure that the study was conducted robustly.

Methods

The review was conducted by members of CHARGE. Prior to conducting the study all members received specific additional training in critical appraisal in addition to any previous critical appraisal training. Apart from this, the methodology adopted throughout this review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Moher et al, 2009).

The clinical question, selection criterion, assessment methods and data-analysis approach were all pre-specified within the study protocol which was modified on one occasion prior to commencing the review.

Clinical question

The study question was formulated according to the traditional PICO(S) format, where P=patient, I=intervention, C=comparison, O=outcome S=study type.

In children with autism (<18yrs) (P) does the use of dimethyl glycine (I) compared to no treatment/ placebo (C) improve symptoms of abnormal behaviour (O)

Inclusion/exclusion Criterion

These are shown in table 1 below.

Criterion	Inclusion	Exclusion
patients	*Studies with all patients <18yrs. Patients with a diagnosis of autism based on the ICD-10 or DSM criterion.*	*Studies with adult subjects (>18yrs), where the diagnosis has not been made according to DSM, ICD criterion.*
intervention	*Oral dimethylglycine*	
comparison	*Placebo/no intervention/std treatment.*	*No comparison group or comparison with another intervention.*
outcome	*Behaviour using validated clinical scales. (eg Vineland or ABC) Other objectively measured outcomes e.g hours of uninterrupted sleep.*	*Non validated tools or the use of non-objective outcomes.*
Study type.	*Randomised placebo controlled double blind trials.*	*Any other study type.*

Table 1: Shows the inclusion/exclusion criterion for the systematic review.

Search strategy

The search strategy was conducted in order to locate both published and unpublished/grey literature. Included were primary medical databases (Medline [1946-2012], Embase[1974-2012]; psychinfo [1999-2007],) meta-search engines (Sumsearch, TRIP), evidence

based medicine databases (Cochrane database). All searches were conducted during June 2011 and were not restricted by language. (One final search of Embase and Medline was re-executed in January 2012.)

Search terms were based on text-words and MeSH terms where appropriate and the search strategy for primary databases was designed based on the PICO question. The Embase search is shown in figure.1

1. pangamic acid.mp.
2. vitamin B15.mp.
3. N,N-dimethylglycine.mp. or exp dimethylglycine/
4. dimethylglycine/ or dimethylglycine.mp.
5. exp glycine/ or exp glycine derivative/
6. exp infantile autism/ or exp autism/ or Autism.mp.
7. autistic spectrum disorder.mp. or exp autism/
8. aspergers syndrome.mp. or exp Asperger syndrome/
9. pervasive developmental disorder.mp. or exp autism/
10. exp Asperger syndrome/ or exp autism/ or kanner's syndrome.mp. or exp infantile autism/
11. (1or 2 or 3 or 4 or 5) and (6 or 7 or 8 or 9 or 10)

Figure 1. Shows the search strategy for a search of Embase.

The search was executed by one author. All included papers had their references examined to look for additional citations and were also entered into a citation search using the Web of Science. Grey literature was searched by contacting experts in the field, the pharmaceutical industry (Cambridge Commodities) and searching conference abstracts from Archives of Disease in Childhood from 2007-2011.

Assessment of studies and study quality

All relevant abstracts from searches were obtained and reviewed by two authors independently to decide whether full papers should be obtained for assessment. Although the search for studies was unrestricted by language to identify the widest possible pool of research we did not have the resources to translate into foreign languages.

Reviews of full text papers were carried out independently, by two authors, to decide whether these papers met the eligibility criteria

for inclusion and were then appraised for study quality using the Cochrane Collaboration tool (Higgins & Green, 2009). Studies were included based upon both reviewers agreeing that a study met the eligibility criterion. Where disagreement occurred with regards to inclusion or study quality a third review was carried out by one author who was the final arbiter.

Given the relatively new group structure, where there was a potential concern about the quality of the actual review carried out by an author an additional author was asked to carry out an independent review instead.

Data-extraction

All reviewers used a standardised data extraction tool to record study details for both inclusion/exclusion criterion (as per the clinical question and the PICO format) and quality based on the Cochrane tool.

One author collated all reviews to derive a summary risk of bias assessment graph, and then extracted all relevant data for the study.

Synthesis

The protocol outlined in advance that where possible studies would be examined for clinical and statistical heterogeneity and meta-analysis performed where this was possible. Comparison on the basis of point estimates, confidence intervals and where relevant funnel plots and a chi-square test for heterogeneity were detailed. In the absence of sufficient homogeneity of included studies analysis was to be restricted to a qualitative synthesis.

Results

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┌─────────────────────────────────────┐          ┌─────────────────────────────────────┐
│ Records identified from databases    │          │ Records identified through other    │
│ searched.                            │          │ sources                             │
│                                      │          │                                     │
│ Medline 27                           │          │ Experts in the field n=1            │
│                                      │          │                                     │
│ Embase 67                            │          │ Hand search n=0                     │
│                                      │          │                                     │
│ Psyclit 4                            │          │ Snowballing n=1                     │
│                                      │          │                                     │
│ SUMsearch 4                          │          └─────────────────────────────────────┘
│                                      │
│ Tripdatabase 3                       │
│                                      │
│ Cochrane database 5                  │
│                                      │
└─────────────────────────────────────┘
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┌─────────────────────────────────────┐
│ Records screened after duplicates    │
│ removed n=67                         │
└─────────────────────────────────────┘
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┌─────────────────────────────────────┐          ┌─────────────────────────────────────┐
│ Records screened at title/abstract   │  ──────> │ Records excluded n= 65              │
│ n=67                                 │          │                                     │
│                                      │          │ Reasons for exclusion: foreign      │
│                                      │          │ language n=1.  Case report          │
│                                      │          │ n=1.Others clearly not relevant or  │
│                                      │          │ clearly not trials.                 │
└─────────────────────────────────────┘          └─────────────────────────────────────┘
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┌─────────────────────────────────────┐          ┌─────────────────────────────────────┐
│ Records assessed as full text n=2    │  ──────> │ Records excluded n=1                │
│                                      │          │                                     │
│                                      │          │ Reason for exclusion: did not meet  │
│                                      │          │ PICO.                               │
└─────────────────────────────────────┘          └─────────────────────────────────────┘
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┌─────────────────────────────────────┐          ┌─────────────────────────────────────┐
│ Records included for citation search │  ──────> │ Records reviewed from ISI web of    │
│                                      │          │ science citation search. N=25       │
│ N=1                                  │          │                                     │
└─────────────────────────────────────┘          └─────────────────────────────────────┘
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                    ┌─────────────────────────────────────┐
                    │ Final study total.  N=1.            │
                    │                                     │
                    └─────────────────────────────────────┘
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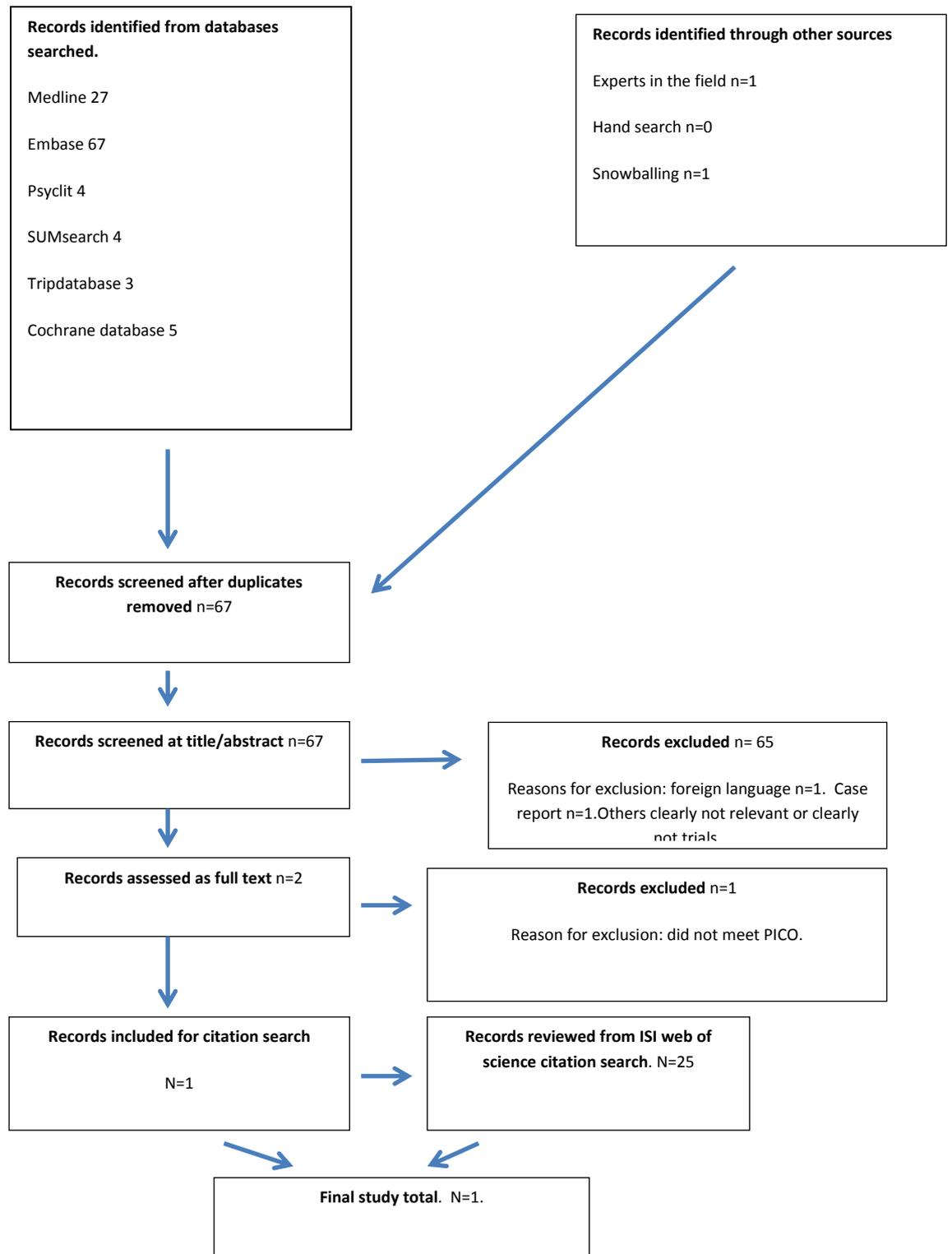
Figure 2: Flow of information and search results.

Execution of the search detected no more than 27 studies, of which only 2 were deemed suitable for full review. 23 of the 25 others were not reviewed because the abstract/title reviews clearly demonstrated that the papers did not fulfil the clinical question.

One of the 25 abstracts excluded was a trial whose full text was reported in Chinese, and only the abstract was available in English and so the decision was made to review the abstract but not to include the paper in the review as we did not have the resources to translate the paper.

Another abstract was a case report and so again failed the inclusion criterion.

One of two studies included for full review included adults and children and results could not be separated for the two. As a result it was not formally included in the final synthesis but was still critically appraised as per the protocol and is still discussed in some detail in the section on excluded papers.

Risk of bias within all included studies

One study was included in our analysis (Kern et al, 2001)
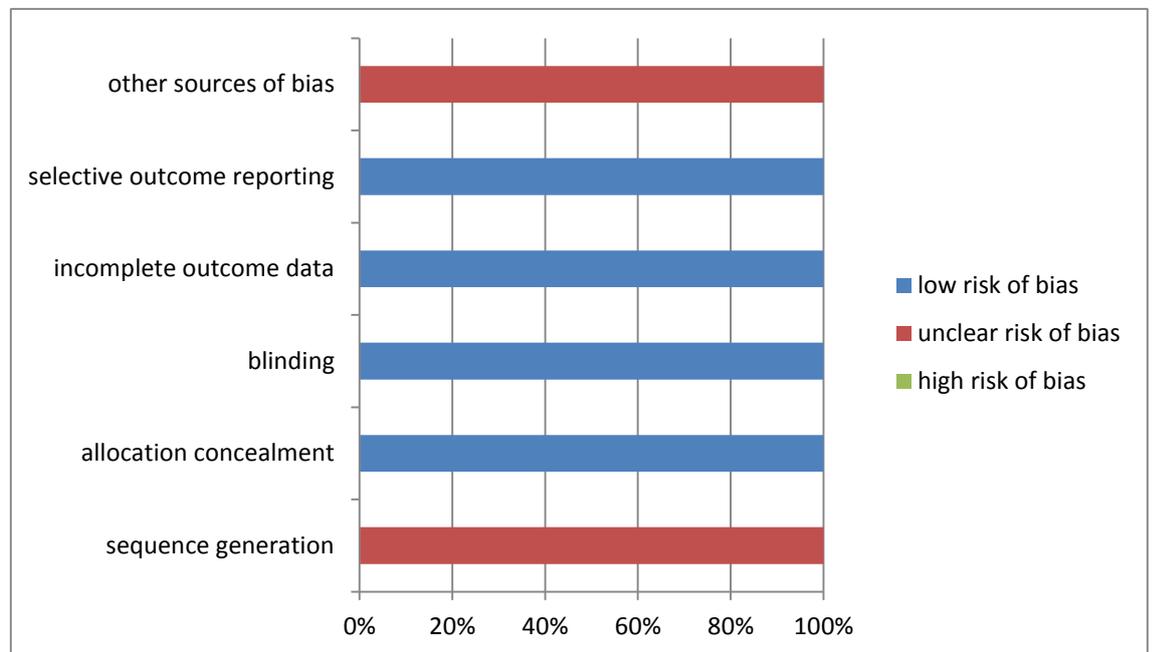
Figure 3: The risk of bias across six different areas for Kern et al. There was a low risk of bias across 4 four areas but an unclear risk across two areas (sequence generation and other sources of bias).

In this study 39 children were recruited to receive either dimethylglycine or placebo. There was incomplete baseline data for both groups to enable a fair comparison between the two groups to be made (the groups did differ for one behavioural measure, with the treatment arm more severely affected) and recruitment was carried out in a number of ways including by advertisement. A power calculation did not appear to have been carried out beforehand, and thus in a clinical trial with only 39 patients there was a clear concern about the results being affected by low power.

While randomisation was stated as having occurred the method employed by the pharmacists doing this was unclear, although allocation concealment seemed adequate as did blinding. Out of the 39 children only 2 dropped out and this is unlikely to have affected the results. While the study looked at a number of outcomes all of these seem to have been reported, but with incomplete statistical data reported for some of the outcomes.

Results from included studies

The included study looked at several outcomes:

1. Behavioural assessments. These were conducted using the Vineland Maladaptive Behaviour domain, and the Aberrant Behaviour Checklist (ABC). These were done using a combination of examination and parental input (with recording of assessments to validate findings during examiner assessment.)

2. Neurological assessments. Carried out by one examiner.

3. Parental report.

Behavioural assessments

The 'ABC' was analysed via a three factor analysis of variance using 1. Pre/post assessment scores, 2. Behavioural assessment measure (eg Vineland/ABC) and 3. Dimethylglycine versus placebo. While an overall improvement across all subjects was noted (treatment and placebo) there was no difference between the two groups.

Each behavioural measure was also evaluated using one-tailed t-tests showing no difference between the two groups.

Neurological assessments

Dimethylglycine did not affect pre/post neurological assessment compared to placebo. (chi sq test =0.31, p<0.57; n=31).

Parental reports

Overall improvements were seen in the treatment group (58%) compared to the placebo group (53%) but this was not statistically significant. Similarly more children in the placebo group (32%) had negative effects compared to the treatment group (16%).

Excluded Studies

Two studies which were not included are discussed below as they have some bearing upon the discussion and the reasons for their exclusion and some of their findings merit further discussion.

One study (Bolman et al, 1999) was a small, double blind, placebo controlled cross over study. The schedule was to use either a placebo or dimethylglycine (from 125mg to 375mg depending on weight) with a 2 week baseline, 4 week placebo or treatment, 2 week washout period and then a 4 week cross over. This study was excluded because the ten patients included 2 adults – and it was not possible to analyse the children's results separately. There were nevertheless several additional potential and likely sources of bias which would have severely restricted the applicability of their findings. This includes, unclear randomisation, and allocation concealment, the use of smaller dosages compared to our included study, and the very small number of subjects in the study (n=10) of whom 2 dropped out (probably children.)

The second excluded study (Jung et al, 2000) was a larger (n=106) cross over study again employing a cross-over design with 4 weeks of either placebo or treatment followed by 2 weeks of washout then cross-over for 4 weeks. (10 weeks total.) The complete report for this study was only available in Chinese. While we used an unrestricted language search to best identify the amount of research in this field, translating services were beyond the scope and scale of our study group.

 It is not possibly to adequate judge the quality of the study based on the abstract which was available in English however several factors are clear. While the authors report a clear improvement in behaviour in the dimethylglycine group there was a significant drop-out rate for this study with 21% of subjects dropping out at 4 weeks (the results are reported from this time period) and 58% of subjects

dropping out at the end of 10 weeks. This alone puts the study at a very high risk of bias and is noted by the authors who recommend further study. It may also explain why this study was not published in an English language journal.

This study raises the spectre of publication bias and is further discussed in the next section.

Discussion

At present there is not enough evidence to clearly recommend the use of dimethylglycine in children with autism. We have found one study with some methodological limitations which showed some improvement in parental reported behaviour (58% vs. 53%) but this was not statistically significant, however an important limiting factor was the size of the study with only 37 patients making this trial probably underpowered.

Two other studies which were not included, and which had major methodological problems also suggested that there may be some benefit in treatment.

Taken together these three studies illustrate the trouble with conducting small sized trials which then report statistically insignificant results- are they truly insignificant or just underpowered? Taken together they emphasize the need to conduct robust and adequately powered studies. Another difficulty relates to which outcomes to measure- there is no, single, clearly validated tool and there are criticisms that can be levelled against some of the outcomes measures already described. This difficulty is compounded further when an attempt is made to compare trials with heterogeneous outcomes.

Given the relative heterogeneity in reported outcomes and the differences in methodologies and quality of trials to date conducting further small studies are unlikely to be of as much benefit as it is unlikely that meta-analysis using the already extant studies will be useful or probable.

The results to date however *do* suggest that dimethylglycine may have some value. Given that the drug does not seem to have any adverse side effects, is relatively costly, and that autism is an incurable condition with few effective evidence based interventions, the results to date make a reasonably compelling case

for a well conducted adequately powered randomised controlled
trial to address this issue.

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