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Review

Chelation treatment for autism spectrum disorders: A systematic review

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ABSTRACT

Chelation treatment is used to eliminate specific metals from the body, such as mercury. It has been hypothesized that mercury poisoning may be a factor in autism and data suggest that perhaps 7% of individuals with autism spectrum disorder (ASD) have received chelation treatment. It would therefore seem timely to review studies investigating the effects of chelation treatment for individuals with ASD. To this end, we conducted a systematic search to identify studies that have evaluated the effects of chelation on autism symptomatology. Our search identified five studies, which were analyzed in terms of (a) participant characteristics, (b) dependent variables, (c) study outcomes, and (d) certainty of evidence. Four of the five studies found mixed results and only one study reported positive results. However, given the significant methodological limitations of these studies, the research reviewed here does not support the use of chelation as a treatment for ASD.

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1. Introduction

Autism spectrum disorder (ASD) encompasses a range of developmental disorders, including autism, Asperger syndrome, and Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS; [Sturmey & Fitzer, 2007](#)). An ASD is a lifelong disorder characterized by three core symptoms including deficits in communication skills, impairments in social skills, and restricted and stereotyped patterns of interests and behaviors ([American Psychological Association, 2000](#); [National Research Council, 2001](#)). Currently, the prevalence of ASD is estimated at approximately 1 in every 88 children ([Centers for Disease Control & Prevention, 2012](#)).

Parents and practitioners have a multitude of choices regarding ASD treatments ([Green et al., 2006](#)). While some of the treatment options available for ASD have been supported by well-designed empirical studies published in peer-reviewed journals, other interventions have simply been disseminated and promoted to the public without sufficient empirical testing ([Heflin & Simpson, 1998](#)). Unfortunately, the results of the survey conducted by Green and colleagues concluded that empirical validation of a treatment, or lack thereof, did not appear to have an influence over which treatments parents used.

This abundance of treatment options available may be due, in part, to the fact that ASD etiology remains unknown ([Wing & Potter, 2002](#)). Although the exact etiology is unknown, several hypotheses as to the cause of ASD have been proposed. These hypotheses generally fall into one of two major categories: (a) genetic influences or (b) environmental factors ([Parker, Schwartz, Todd, & Pickering, 2004](#)).

One environmental theory is that ASD is caused by toxic metals in the body ([Adams et al., 2009a](#)). This hypothesis can be traced to [Wakefield et al.'s \(1998\)](#) claim of a link between autism and the Measles–Mumps–Rubella (MMR) vaccine ([Doja & Roberts, 2006](#)). However, due to subsequent disclosure of methodological problems, the Wakefield et al.'s paper was retracted from *The Lancet* in 2010 ([The Editors of the Lancet, 2010](#)). Since then, research has found no link between the MMR vaccine and autism ([Wilson, Mills, Ross, McGowan, & Jadad, 2003](#)). Nevertheless, concerns continued to be raised regarding the use of thimerosal, a preservative that was included in some MMR vaccines. Specifically, thimerosal was considered a potential source of mercury poisoning, which in turn caused ASD ([Doja & Roberts, 2006](#); [Parker et al., 2004](#)). However, research has not shown a link between thimerosal-containing vaccinations and ASD ([Parker et al., 2004](#)). Still, other sources of metal toxicity have been suggested as possible causes of ASD including dental amalgams, mercury-containing fish, and nasal sprays. To date, however, no causal relation has been found between normal exposure to these materials and ASD ([Hertz-Picciotto et al., 2010](#)).

Despite the lack of supporting evidence, the hypothesized link between toxic levels of metals in the body and ASD is likely one reason why chelation treatment has been applied to many individuals with ASD. Chelation treatment involves giving an individual various chemical substances for the purpose of binding and then withdrawing specific metals from the person's body ([Risher & Amler, 2005](#)). The chemical substances utilized in chelation treatment have a myriad of potential and potentially serious, side effects, including fever, vomiting, diarrhea, loss of appetite, hypertension, hemorrhoid symptoms, metallic taste, hypotension, cardiac arrhythmias, hypocalcemia, the latter of which can in turn cause fatal cardiac arrest ([Beauchamp et al., 2006](#); [Doja & Roberts, 2006](#); [Moel & Kumar, 1982](#); [Physician's Desk Reference, 2011](#)). In 2005, for example, a 5-year-old boy with ASD died from cardiac arrest caused by hypocalcemia while receiving intravenous chelation ([Beauchamp et al., 2006](#); [Brown, Willis, Omalu, & Leiker, 2006](#)). The potential safety risks associated with chelation recently resulted in a suspension of a clinical study of chelation treatment for autism ([Mitka, 2008](#)). Additional safety issues arose from a rodent study that found lasting cognitive impairment from the use of succimer (i.e., oral DMSA – 2,3 dimercaptosuccinic acid); a chelating agent ([Stangle et al., 2007](#)).

Despite these safety issues, an internet survey of 552 parents found that 7.4% of the parent respondents reported that their child with ASD had received chelation treatment ([Green et al., 2006](#)). In a similar, but smaller survey of 74 parents of children with ASD, [Harrington, Rosen, Garnecho, and Patrick \(2006\)](#) found that 8% of the children had received chelation treatment. With respect to survey of medical professionals, [Golnik and Ireland's \(2009\)](#) survey found that, while none of the physicians encouraged the use of chelation for children with ASD, 26% reported that they did not have enough knowledge to make a recommendation in reference to chelation treatment. Given the significant potential side effects, the multiple theories which connect metal poisoning to ASD, and the current trends regarding use of chelation as an ASD treatment, a systematic review of the current chelation treatment literature is warranted. Further, such a review stands to benefit parents and other caregivers of children with ASD, given the numerous treatment options available and importance of selecting empirically validated treatments.

To our knowledge, there has not been a systematic literature review on the effects of chelation on symptoms associated with ASD. The purpose of the review is to describe the characteristics and evaluate the results of the available research on the effects of chelation treatment on symptoms associated with ASD, in order to assist caregivers and practitioners in making informed decisions regarding the use of chelation as an ASD treatment.

2. Method

This review consisted of a systematic search and analysis of studies that utilized chelation for the treatment of ASD. The results of the analysis are summarized in the following categories: (a) participant characteristics, (b) dependent variables, (c) study outcomes, and (d) certainty of evidence. Due to the limited number of studies available, the intent of this review was to include all available studies. As a result, the quality and type of research designs varied.

2.1. Search procedures

A systematic search of electronic databases was conducted including: PsycINFO, Psychology and Behavioral Sciences Collection, PsychARTICLES, Educational Resources Information Clearing House (ERIC), Education Research Complete, Academic Search Complete, MAS Ultra – School Edition, MasterFILE Premier, MEDLINE, Science & Technology Collection, and the Cumulative Index to Nursing and Allied Health Literature (CINHAL). On all databases, the following free-text terms were inserted into the keyword fields in pairs utilizing Boolean operators and truncation: “developmental disability”, “disability”, “autism”, “Asperger”, “Pervasive Developmental Disorder”, and “PDD-NOS” paired with “metal”, “metal poison”, “heavy metal”, “detoxification”, “chelation”, “succimer”, “dimercaptopropane sulfonate”, “DMPS”, “dimercaptosuccinic acid”, and “DMSA” (e.g., “developmental disability” paired with “metal” and “autism” paired with “DMPS”). The search was restricted to English language journals. The abstracts of the resulting articles were reviewed to identify studies for inclusion. An ancestry search was then completed on all studies in order to identify additional articles. Finally, hand searches covering January 2009–December 2011 were conducted for the four journals that had published the already included studies in an effort to identify additional studies for inclusion in this review.

2.2. Inclusion and exclusion criteria

To be included in this review, the study had to have evaluated the effects of chelation treatment with at least one child with ASD. ASD included children with autism, Asperger syndrome, or PDD-NOS. Any study that used the term chelation to describe one or more of the treatment components was included as were studies that included chelation as part of a treatment package. One study included in this review (Adams et al., 2009b) did not specifically refer to chelation, but rather described the use of specific chelating agents (i.e., dimercaptosuccinic acid – DMSA). The paper was included because the authors went on to characterize this treatment as chelation in an accompanying paper reporting the same medical investigation and results (Adams et al., 2009a). In addition to the above inclusion criteria, the study design had to have included measurement of at least one dependent variable related to a core symptom of ASD, that is, communication skills, social skills, and/or repetitive and stereotyped patterns of behavior. Studies focusing only on biomedical outcomes (e.g., reduction in metals) were excluded because the impact on ASD symptomatology was not measured.

2.3. Data extraction

Each potential study was assessed against the inclusion criteria and data extracted on (a) participant characteristics, (b) dependent variables, (c) study outcomes, and (d) certainty of evidence. These analyses were conducted by the first, eighth, and ninth authors. The data extracted to analyze participant characteristics included gender, age, diagnosis, and documentation of high levels of metals. Dependent variables included those associated with deficits in communication and social skills and restricted and stereotyped patterns of interests and behaviors. Study outcomes were coded as “positive”, “negative”, or “mixed”. Studies were coded as having positive results if all participants made improvements on all dependent variables or if statistically significant improvements were found for all dependent variables in a group design (using the alpha levels stated in the reviewed study). Studies were coded as having negative results if none of the dependent variables improved for any participant or if a group design failed to find statistically significant improvement. Studies were coded as mixed if some participants improved and others did not or if improvement was found in some dependent variables, but not in others. Mixed results for group design studies applied if some improvements among dependent variables were statistically significant, but others failed to reach statistical significance (using alpha levels stated in the reviewed study). Certainty of evidence was rated as “insufficient”, “preponderant”, or “conclusive” based upon definitions utilized in other works (e.g., Mulloy et al., 2010; Simeonsson & Bailey, 1991; Smith, 1981). Studies were classified at the insufficient level of certainty if they did not utilize a true experimental design (e.g., case studies, AB designs, and group designs without a control group) and/or did not meet the criteria of the next level of certainty. In order to be classified at the preponderance level of certainty, a study had to: (a) demonstrate experimental control in a single case research design or use an experimental group design, (b) provide adequate inter-observer agreement, when applicable (i.e., 20% or more of sessions with mean agreement 80% or higher), (c) operationally define dependent variables, and (d) provide enough detail to enable replication. Studies classified at the preponderance level could contain limitations regarding alternative explanations for results (e.g., concurrent intervention or multi-component interventions). The final level of certainty (i.e., conclusive) was reserved for studies that met the first four requirements of preponderance of evidence with an additional attempt to control for confounding variables (e.g., double-blind and placebo controlled).

2.4. Inter-rater agreement

To assess reliability of our application of the inclusion criteria, the eighth and ninth authors independently conducted the searches and then independently applied the inclusion and exclusion criteria to studies identified by the search procedures. Agreement was 83% and the one disputed study was then reviewed to reach a consensus. To assess reliability of data extraction, two articles were jointly summarized by the first, eighth, and ninth authors and the remaining three studies (60%) were then independently summarized by two authors to assess agreement. There were 30 items in which there could be

Table 1
Summary of reviewed studies.

Citation	Participants	Dependent variable measurement	Study outcomes	Certainty of evidence
Adams et al. (2009b)	38 male, 3 female 3–8 years 40 diagnosed with autism 1 Asperger syndrome	ATEC, PDD-BI, SAS, ADOS, PGI	Mixed	Insufficient: comparison of one group who received one round of DMSA and one group that received seven rounds rather than a control group that received no chelation treatment, multi-component intervention suggests improvements could be a result of another component (e.g., vitamin and mineral supplement and glutathione lotion)
Eppright et al. (1996)	1 male 4 years Autism	Anecdotal parent report	Positive	Insufficient: no experimental design (case study report), not enough detail to replicate, no IOA, multi-component intervention suggests improvements could be a result of another component (e.g., early intervention program)
Geier and Geier (2006)	10 male, 1 female 6–14 years 9 autism 2 PDD-NOS	ATEC	Mixed	Insufficient: no control group, multi-component intervention suggests improvements could be a result of another component (e.g., vitamin and mineral supplements), authors report potential conflict of interest in that authors served as consultants and expert witness in cases before National Vaccine Injury Compensation Program and civil litigation
Patel and Curtis (2007)	9 male, 1 female 4–10 years 5 autism/PDD 5 Asperger syndrome	Anecdotal parent report	Mixed	Insufficient: no experimental design, no IOA, multi-component intervention suggests improvements could be a result of another component (e.g., behavior therapy)
Senel (2010)	19 participants Unknown gender Unknown age range 19 ASD	Anecdotal parent report via researcher-made survey	Mixed	Insufficient: no experimental design, no IOA, parent survey of experiences with chelation provides no detail regarding chelation treatment, possibility of multiple interventions

Abbreviations: ATEC, Autism Treatment Evaluation Checklist; PDD-BI, Pervasive Developmental Disorder-Behavior Inventory; SAS, Severity of Autism Scale; ADOS, Autism Diagnostic Observation Schedule; PGI, Parent Global Impressions; IOA, interobserver agreement; PDD-NOS, Pervasive Developmental Disorder-Not Otherwise Specified; PDD, Pervasive Developmental Disorder; ASD, autism spectrum disorder.

agreement or disagreement (i.e., 3 studies with 10 items per study). Agreement for the summarized items was 87%. All disagreements were resolved by discussion until consensus was reached.

3. Results

A total of five studies met the criteria for inclusion in this review (Adams et al., 2009b; Eppright, Sanfacon, & Horwitz, 1996; Geier & Geier, 2006; Patel & Curtis, 2007; Senel, 2010). Table 1 summarizes these five studies in terms of participant characteristics, dependent variables, study outcomes, and certainty of evidence.

3.1. Participants

A total of 82 participants received chelation treatment across the five studies. The sample size per study ranged from 1 to 41 participants. Of the 82 participants, 58 participants were male (72%) and five were female (6%). The gender was not reported for the remaining 19 participants. All participants were children, ranging from 3 to 14 years of age. Of the 82 participants, 50 (61%) were diagnosed with autism, six (7%) with Asperger syndrome, five (6%) with autism/PDD, and two (2%) with PDD-NOS. Nineteen participants (23%) were reported to have an ASD, but no specific diagnosis (e.g., autism, Asperger syndrome, or PDD-NOS) was provided. In addition to ASD diagnoses, eleven participants (12%) were reported to have attention deficit hyperactivity disorder (ADHD), three participants had an undisclosed neurological problem, one participant had a seizure disorder, and one participant presented with oppositional defiant behavior.

Verification of high levels of metals was a requirement for participation in only one, two-phase study (Adams et al., 2009b). During the first phase, all 41 participants received one round of chelation. Only participants with a high excretion of toxic metals after the first round continued to the second phase, in which participants were divided into two groups, one group received additional rounds of chelation treatment, while the other group received placebo. Additionally, Geier and Geier (2006) required exposure to mercury in the medical history for participation. Finally, Eppright et al. (1996) reported that the participant in their study had a documented elevated blood lead level.

3.2. Interventions

Various forms of chelation treatment were implemented across the studies, with all studies except the one by Senel (2010) identifying specific chelating agents. The duration of chelation treatment ranged from approximately 1.5–7 months. Frequencies of administration ranged from 1 to 12 times weekly. In four studies, chelation treatment was one component of a multi-component treatment program (Adams et al., 2009b; Eppright et al., 1996; Geier & Geier, 2006; Patel & Curtis, 2007). For example, the treatment package provided by Patel and Curtis (2007) included eight components, such as an organic diet and nutritional supplements including vitamins, minerals, amino acids, and peptides. Participants also continued their usual therapies including special education, speech therapy, occupational therapy, and physical therapy. Other treatment package components included intramuscular injections of LUPRON DEPOT[®] (Geier & Geier, 2006), subcutaneous injections of LUPRON[®] (Geier & Geier, 2006), vitamin and mineral supplements (Adams et al., 2009b; Geier & Geier, 2006), dextroamphetamine (Eppright et al., 1996), Ritalin (Eppright et al., 1996), Clonidine (Eppright et al., 1996), and early intervention services (Eppright et al., 1996). Two studies noted that participants continued with current treatments in addition to the treatment components that were included as part of the study (Adams et al., 2009b; Patel & Curtis, 2007). Senel (2010) did not report whether participants received other treatments at the time when they received chelation.

3.3. Dependent variables

Although biomedical dependent variables were reported in many studies, the purpose of this review was to summarize the effects of chelation on ASD symptoms. Four of the five studies included in the review reported on the effects on communication (e.g., speech, expressive language, and phonological skills). Three studies reported on social skills (e.g., eye contact, social interaction, and play participation). And, all five studies reported on the effects of chelation on repetitive and stereotyped patterns of behavior and/or problematic behaviors (e.g., ritualism, resistance to change, restrictive interests, and stereotyped tactile activities).

These dependent variables were measured in a variety of ways. Three studies utilized anecdotal reports or researcher-created questionnaires to measure change (Eppright et al., 1996; Patel & Curtis, 2007; Senel, 2010). Adams et al. (2009b) used researcher-created measures in addition to other standardized measures. These authors created both the Severity of Autism Scale and Parent Global Impressions for their study. Geier and Geier (2006) also utilized standardized tests or questionnaires. Such tests and questionnaires included the Autism Treatment Evaluation Checklist (ATEC; Rimland & Edelson, 2000), Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 1999), and Pervasive Developmental Disorder-Behavior Inventory (PDD-BI; Cohen & Sudhalter, 2005). None of the reviewed studies utilized direct observation to measure these dependent variables.

3.4. Study outcomes

Four of the five studies found mixed results (Adams et al., 2009b; Geier & Geier, 2006; Patel & Curtis, 2007; Senel, 2010) and one study reported positive results (Eppright et al., 1996). Geier and Geier (2006) reported results on all three of the core symptoms associated with ASD. They found negative results for communication and positive results for social skills and repetitive and stereotyped behavior. Patel and Curtis (2007) reported mixed results for communication and repetitive and stereotyped behaviors, but positive results for social skills. Senel (2010) reported mixed results for communication and repetitive/stereotyped behaviors. Adams et al. (2009b) reported mixed results for communication and social skills and for repetitive/problem behavior. Eppright et al. (1996) only reported results of repetitive and stereotyped behaviors, which were positive and noted that behavior problems returned after treatment was discontinued.

3.5. Certainty of evidence

All five studies were classified as insufficient, the lowest level of certainty, for various reasons. Adams et al. (2009b) received this classification as their study implemented a multi-component intervention, which precludes the ability to attribute changes solely to the chelation intervention. The lack of an experimental design was the predominant factor for an insufficient classification in the case of Eppright et al. (1996) and Senel (2010). In the first case, they presented a case study. In the second case, they relied on parent survey. Additional concerns regarding certainty of evidence included insufficient detail to enable replication and the potential for multiple treatment interference. Finally, absence of a control group and the potential multiple treatment interference were the main reasons for the insufficient classification of the studies by Geier and Geier (2006) and Patel and Curtis (2007).

4. Discussion

This systematic review identified five studies that evaluated the effects of chelation treatment on ASD symptomatology. Overall, the literature base must be considered extremely limited in terms of the quantity and quality of existing research. Given the small number of studies and their methodological weaknesses, the results of this review do not support the use of chelation as a treatment for ASD.

All studies reviewed had considerable threats to internal validity, which renders their findings inconclusive. Specifically, the studies lacked proper experimental designs. For example, Eppright et al. (1996), which is the only study reporting positive results, was an uncontrolled case study. Of the four studies reporting mixed results, three did not include a control group (Adams et al., 2009b; Geier & Geier, 2006; Patel & Curtis, 2007), and the fourth study was non-experimental and based the conclusions about chelation treatment effects solely on an indirect third-party (parent) reports (Senel, 2010). In addition to the lack of proper experimental design, many studies included multiple treatment components, which make it impossible to assess the effects of chelation alone. For example, early intervention, in-home parent training, Ritalin, and Clonidine were all implemented alongside chelation in the only study reporting positive results (Eppright et al., 1996). Of the four remaining studies, which reported mixed results, three documented the inclusion of other treatments in addition to chelation (Adams et al., 2009b; Geier & Geier, 2006; Patel & Curtis, 2007). The fourth study reported that participants received an average of five treatments making multiple treatment interference highly likely (Senel, 2010). Thus, it is possible that the effects these researchers attributed to chelation could have been due to other independent or extraneous variable, such as maturation, education (e.g., special education and early intervention programs), or the other treatment components (e.g., psychotropic medication and vitamin supplements).

All of the studies utilized measurement methods that could have biased the results, including lack of blind data collection procedures, use of researcher-developed measurement instruments, and/or reliance on respondent memory. The only study reporting positive results (Eppright et al., 1996) and three of the four studies that reported mixed results (Geier & Geier, 2006; Patel & Curtis, 2007; Senel, 2010) employed indirect measures (i.e., solicited the perceptions of parents and of other respondents who were not blind to the treatment). Moreover, three of the four studies that did not utilize blind data collection procedures also implemented a multi-component treatment intervention; therefore, respondents may have held a strong belief in one or more of the treatment components that influenced subjective perceptions.

Researcher-developed measures were utilized in three of the four studies that reported mixed results (Adams et al., 2009b; Patel & Curtis, 2007; Senel, 2010). In fact, researcher-developed surveys were the only measurement instruments utilized by Patel and Curtis (2007) and Senel (2010). Eppright et al. (1996), the only study reporting positive results, utilized informal parent report as the only means of measurement of the symptoms associated with ASD. Adams et al. (2009b) utilized the Parent Global Impressions and the Severity of Autism Scale, both of which were created by the authors for the purpose of their study (i.e., without any prior evidence on the psychometric properties of such measures). Two studies, which reported mixed results (Geier & Geier, 2006; Patel & Curtis, 2007), required respondents to report changes in dependent variables based on recall memory (i.e., from periods of 3 months or longer).

Perhaps the greatest concern in regards to the selection of chelation treatment for children ASD is the lack of construct validity. In some ways, chelation therapy represents the “cart before the horse” scenario in that the hypothesis supporting of the use of chelation treatment failed to be validated prior to the application of chelation. Chelation treatment aims to eliminate specific metals from the body. However, empirical evidence has yet to support the hypothesis that the core ASD symptoms are caused by the presence of such metals in the body. Because empirical evidence does not support the hypothesis that the core ASD symptoms are associated with specific levels of metals in the body, the use of chelation to remove metals from the body in order to ameliorate ASD symptoms could be seen as unfounded and illogical.

Moreover, even if metal poisoning contributed to the ASD symptoms, it would still be unclear whether chelation treatment would have the ability to reverse existing neurological problems caused by such exposure, or whether it would only be able to prevent further damage (i.e., worsening of symptoms). In other words, even if the metal poisoning theories held true, it does not necessarily lead to an expectation that chelation would ameliorate current communication and social skills deficits and behavioral impairments, rather than prevent additional or more extensive impairments.

Based on the results of this review, evidence to support the use of chelation as a treatment for children with ASD is extremely weak. The weakness of the evidence base, the lack of a sound rationale for use of chelation as an ASD treatment, and the potential negative side effects strongly argue against the use of chelation treatment for ASD.

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