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# "Neurotoxic heavy metals in the human brain: 1. The Aluminum-Alzheimer connection"

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## Abstract

Aluminum is environmentally abundant, but not an essential element. We get exposed to it through drinking water with aluminum in it; air pollution from factories; soil with aluminum, harming crops; and dietary sources (many foods and additives). Aluminum is a known toxicant that contributes to cognitive dysfunction. The main reason is that it can enter the brain and be deposited within. It has been associated with several neurodegenerative diseases, such as dialysis encephalopathy, amyotrophic lateral sclerosis, Parkinsonism, and particularly Alzheimer's disease. Although this association remains controversial, there is increasing evidence which suggests the implication of metal homeostasis in the pathogenesis of Alzheimer's disease. Aluminum, zinc, copper, and iron cause the conformational changes of Alzheimer's amyloid-beta protein. It causes the accumulation of tau protein and amyloid-beta protein in experimental animals. It also induces neuronal apoptosis in vivo as well as in vitro. Furthermore, a relationship between aluminum and the iron-homeostasis or calcium-homeostasis has been suggested. Based on these findings, the characteristics of aluminum neurotoxicity are reviewed, and the potential link between aluminum and neurodegenerative diseases including Alzheimer's is reconsidered.

### Abbreviations

AA: Alzheimer's Association; AD: Alzheimer's disease; APP: amyloid precursor protein; ASD: Autism spectrum disorder; AUD: Alcohol use disorder; BAL: British Anti-Lewisite; BBB: Blood-brain barrier; CNS: Central nervous system; CT: Chelation therapy; DE: Dialysis encephalopathy; DESSS: Diet, Exercise, Stress, Sleep, Social interactions; DFO: Deferoxamine; DHHS: (U.S.) Department of Health and Human Services; DMPS: Dimercapto propanesulfonic acid; DPA: D-Penicillamine; DMSA: Mesodimercaptosuccinic acid; EBM: Essential biometals; ErMA: Erythropoietin-resistant microcytic anemia; GEL: Genetics, Environment, Lifestyle; IBS: Irritable bowel syndrome, MRI: Magnetic resonance imaging; MS: Multiple

sclerosis; NEBM: Non-essential biometals; NFT: Neurofibrillary tangles; NTHM: Neurotoxic heavy metals; OS: Oxidative stress; PD: Parkinson's disease; PF: Pulmonary fibrosis; PTH: parathyroid hormone; SOD: Superoxide dismutase; WD: Wilson's disease; WHO: World Health Organization.

**Chemical elements:** Al: Aluminum; Al (OH)3: Aluminum hydroxide; As: Arsenic; Br: Bromine; C: Carbon; Cd: Cadmium; CdTe: Cadmium telluride; Cl: Chlorine; Cu: Copper; Fe: Iron; H: Hydrogen; HCl: Hydrochloric acid; Hg: Mercury; HNO3: Nitric acid; H2SO4: Sulfuric acid; I: Iodine; Mn: Manganese; NaOH: Sodium hydroxide; Pb: Lead: Si: Silicon; Zn: Zinc.

**Diseases listed:** Alcohol use disorder; Alzheimer's disease; Anemia; Asthma; Autism spectrum disorder; Depression; Dialysis encephalopathy; Erythropoietin-resistant microcytic anemia; Irritable bowel syndrome; Multiple sclerosis; Osteomalacia; Parkinson's disease: Pulmonary fibrosis; Wilson's disease.

**Drugs cited:** British Anti-Lewisite (Dimercaprol); Deferoxamine mesylate; Dimercaptopropane sulfonate; Dimercaptopropane sulfonicacid; Dimercaptosuccinic acid; Dipenicillamine; Maltol; Mesodimercaptosuccinic acid.

**Keywords**

Alzheimer's disease; Aluminum; Brain; Chelation; Cognitive disorders; Entry Routes; Deposit.

**-oOo-**

Aluminum (Al) is environmentally ubiquitous. It is the third most abundant element which comprises about 8% of the Earth's crust, after oxygen and silicon. Al is too reactive chemically to occur as a free metal in nature. Instead, it always occurs in combination with other elements such as hydroxide, phosphate, silicate, and sulfate. Al is used in the production of every‑day products such as Al foil, antacids, aspirin, cookware, flour, soda cans, vaccines, etc. This wide distribution ensures the potential for causing human exposure, primarily dietary but also occupational.

The potential for significant Al absorption from the nasal cavity and direct distribution into the brain is concerning and continues to be investigated. Decreased renal function also increases human risk of Al-induced accumulation and toxicity.

## Introduction

Metals in the brain are classified into essential biometals (EBM) which are necessary for normal neurological function, and non-essentials biometals (NEBM) or neurotoxic heavy metals (NTHM), which can cause damage even at low concentrations. EBMs are tightly regulated by the body and are vital for processes like neurotransmission, energy production, and antioxidant defense.

They include: Copper (Cu), a key cofactor for enzymes, which is involved in norepinephrine synthesis and iron metabolism; Iron (Fe), which is essential for oxygen transport, dopamine synthesis, and myelin formation; Manganese (Mn), which is required for antioxidant enzymes like Manganese superoxide (Mn-SOD) in mitochondria; and Zinc (Zn), which is concentrated in the hippocampus and is critical for synaptic transmission and long-term memory formation (Table 1):

| Metal | Neurological effect(s) | Notes |
|---|---|---|
| **Copper (Cu)** | o Norepinephrine synthesis<br>o Iron metabolism | Key factor for enzymes |
| **Iron (Fe)** | Essential for;<br>o Oxygen transport<br>oDopamine synthesis<br>o Myelin formation | Metabolism also involves copper |

| | | |
|---|---|---|
| **Manganese (Mn)** | Required for antioxidant enzymes (e.g., Mn-SOD) | In mitochondria |
| **Zinc (Zn)** | Critical for: o Synaptic transmission oLong-term memory formation | Concentrated in the hippocampus |

**Table 1: Essential biometals and their neurological effects**

In this series of articles, the emphasis will be on neurotoxic heavy metals (NTHM) because exposure to these metals can lead to oxidative stress (OS), inflammation, and disruption of the blood-brain barrier (BBB). These include: Aluminum (Al), which has been historically debated for its link to dementia, though evidence is strongest for extreme, high-level exposures; Arsenic (As) and Cadmium (Cd), which are environmental toxins that can accumulate in the brain, contributing to neurodegeneration; Lead (Pb), which is linked to impaired cognitive function and developmental issues in children; and Mercury (Hg), which is highly neurotoxic and is associated with memory loss and tremors (Table 2). Sidebar 1 summarizes the physicochemical properties of Al.:

| Metal | Neurological effect(s) | Notes |
|---|---|---|
| **Aluminum (Al)** | Link to dementia | Strongest evidence for extreme high-level exposures |
| **Arsenic (As)** | Contributes to neurodegeneration | Environmental toxin that can accumulate in the brain |
| **Cadmium (Cd)** | Contributes to neurodegeneration | Environmental toxin that can accumulate in the brain |
| **Lead (Pb)** | Linked to: o Impaired cognitive function o Developmental issues in children | Environmental toxin emitted from industrial plants and through lead pipes |
| **Mercury (Hg)** | Associated with memory loss and tremors | Highly neurotoxic |

**Table 2: Neurotoxic heavy metals and their neurological effects**

This article will focus on Aluminum (Al) while subsequent articles will deal with the other neurotoxic heavy metals. Al is a recognized neurotoxicant that can penetrate the BBB and accumulate in brain tissue, with a half-life of roughly 150 days. Chronic exposure is associated with cognitive impairment and neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and dementia. It induces neuronal damage through mechanisms like amyloid-beta accumulation, oxidative stress, and neuroinflammation.

## Environmental effects

High Al levels occur near mining sites and small amounts are released to the environment at coal-fired power plants or incinerators. In the air, Al is washed out by the rain or normally settles down but small particles remain in the air for a long time. Acidic precipitation is the main natural factor to mobilize Al from natural sources and the main reason for the environmental effects of Al; however, the main factors of presence of Al in salt and freshwater are the industrial processes that also release Al into air.

Organic complexes of Al may be easily absorbed and interfere with metabolism in mammals and birds, even though this rarely happens in practice. Al is primary among the factors that reduce plant growth on acidic soils. Although it is generally harmless to plant growth in pH-neutral soils, in acid soils the concentration of toxic Al3+ cations increases and disturbs root growth and function.

Al production possesses its own challenges to the environment on each step of the production process.

The major challenge is the emission of greenhouse gases. These gases result from electrical consumption of the smelters and the byproducts of processing. The most potent of these gases are perfluorocarbons, namely CF4 and C2F6, from the smelting process. Biodegradation of metallic Al is extremely rare; most Al-corroding organisms do not directly attack or consume Al but instead produce corrosive wastes.

## Exposure routes

Food is the main source of Al, however, drinking water contains more Al than solid food. Al in food may be absorbed more than from water. Major sources of human oral exposure to Al include food (due to its use in food additives, food and beverage packaging, and cooking utensils), drinking water (due to its use in municipal water treatment), and Al-containing medications (particularly antacid/antiulcer and buffered aspirin formulations).

Dietary exposure in Europeans averages to 0.2–1.5 mg/kg/week but can be as high as 2.3 mg/kg/week. Higher exposure levels of are mostly limited to plumbers, masons, electrical workers, machinists, and … surgeons.

Consumption of antacids, antiperspirants, vaccines, and cosmetics provide possible routes of exposure. Consumption of acidic foods or liquids with Al enhances absorption, and Maltol (a naturally occurring organic compound primarily used as a flavor and aroma enhancer in the food, beverage, and fragrance industries) has been shown to increase the accumulation of Al in nerve and bone tissues.

## Key aspects of Aluminum in the brain

Al can get into our bodies through food, air, and skin. It might reach the brain, but how much and how it gets there is being researched. Key aspects of Al in the brain include:

**Entry routes and deposit**

There are three routes by which Al can enter the brain from systemic circulation or the site of absorption. It fluxes into the brain across the BBB, the choroid plexus and the nasal cavity. It is key to understand how Al interacts with the BBB. This helps us see the risks of Al exposure. Several factors can promote this entry such as increase of the BBB permeability, citric acid and parathyroid hormone (PTH), and vitamin D. But the redistribution of Al out of the brain is slow, allowing it to be deposited for a long time. Key aspects include:

- **Neurotoxicity mechanism:** It acts as a metal toxin, inducing neuronal apoptosis (cell death) and contributing to the formation of protein plaques (amyloid-beta). It has been shown to cause learning and memory impairment.
- **Brain accumulation:** Once in the brain, it is slowly removed, leading to long-term deposition.
- **Disease associations:** While not definitively confirmed as the sole cause, significant associations exist between elevated brain Al and Alzheimer's disease (AD), Parkinson's disease (PD), dialysis encephalopathy (DE), and amyotrophic lateral sclerosis (ALS).
- **Sources of Exposure:** Common sources include food (additives), water, medications (antacids), and occupational exposure.

However, while some research links high Al exposure to AD, the link is still debated, as not all studies consistently find high Al in AD patients. Most ingested Al is filtered by the kidneys and eliminated, with only tiny amounts reaching the brain under normal conditions.

Key factors influencing Al absorption include: the form of Al exposure (e.g., soluble vs. insoluble compounds), the route of exposure (e.g., dietary, inhalation, dermal), and the presence of other metals or compounds that

may interact with Al.

**Toxicity and mechanisms of possible neurotoxicity**

Al is classified as a non-carcinogen by the (U.S.) Department of Health and Human Services (DHHS). A review published in 1988 said that there was little evidence that normal exposure to Al presents a risk to healthy adults. Further, a 2014 multi-element toxicology review was unable to find deleterious effects of Al consumed in amounts not greater than 40 mg/day per kg of body mass. Most Al consumed will leave the body in feces, and any that enters the bloodstream will be excreted via urine.

However, although rarely, Al can cause vitamin D-resistant osteomalacia, erythropoietin-resistant microcytic anemia (ErMA), and central nervous system (CNS) alterations. People with kidney insufficiency are especially at a risk. Chronic ingestion of hydrated Al silicates (for excess gastric acidity control) may result in Al binding to intestinal contents and increased elimination of other metals, such as iron and zinc, sufficiently high doses (>50 g/day) can cause anemia.

During the 1988 Camelford water pollution incident, people in Camelford had their drinking water contaminated with Al-sulfate for several weeks. A final report into the incident in 2013 concluded it was unlikely that this had caused long-term health problems.

Al has been suspected of being a possible cause of AD but, as of 2018, research into this for over 40 years has found no good evidence of causal effect.

Al increases estrogen-related gene expression in human breast cancer cells cultured in the laboratory. In very high doses, Al is associated with altered function of the BBB. A small percentage of people have contact allergies to Al and experience itchy red rashes, headache, muscle pain, joint pain, poor memory, insomnia, depression, asthma, irritable bowel syndrome (IBS), or other symptoms upon contact with products containing Al. Exposure to powdered-Al or Al-welding fumes can cause pulmonary fibrosis. Fine Al powder can ignite or explode, posing another workplace hazard.

There is now substantial evidence indicating that an accumulation of Al occurs in grey matter in diseases associated with Alzheimer neurofibrillary tangles (NFT) degeneration. Four principal accumulation sites have been identified in AD: (1) DNA-containing structures of the nucleus; (2) protein moieties of NFT; (3) amyloid cores of senile plaques; (4) and cerebral ferritin. Consideration of the extensive information now available on the toxic effects of Al in these four loci strengthens the hypothesis that Al could be important in the pathogenesis of this neurodegenerative process. The evidence, however, does not support an etiological role for Al in AD. The primary pathogenic events responsible for AD are presumed to have affected the genetically determined barriers to Al, resulting in increased amounts of this toxic element to vulnerable target sites.

Al might harm the brain in several ways, causing: Induction of oxidative stress; inflammation and immune response modulation; and interaction with proteins and other biomolecules critical for neuronal function.

*Recent studies have highlighted the possible effect of Al on tau protein phosphorylation.* This is linked to neurofibrillary tangle (NFT) formation in Alzheimer's (Table 3):

| Mechanism | Description | Potential impact on AD |
|---|---|---|
| Oxidative Stress | Al induces reactive oxygen species | Neuronal damage and death |
| Inflammation | Al triggers inflammatory responses | Exacerbation of neuroinflammation |
| Protein Interaction | Al binds to critical proteins | Disruption of normal protein function |

**Table 3: Mechanisms of possible neurotoxicity**

## Roles in neurodegenerative diseases

It has been suggested that there is a relationship between chronic routine exposure to Al and increased risk of several neurodegenerative disorders including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and AD‐type dementia in Parkinson patients.

Disruptions in metal homeostasis (balance) are a hallmark of several conditions, including:

• **Alzheimer's disease (AD):** The hallmark amyloid-beta plaques of this disease showed abnormal accumulations of Fe and Zn while recent research has even found elemental metallic Cu and Fe.
• **Parkinson's disease (PD):** Here, significant Fe accumulations have been found in the substantia nigra, which can trigger oxidative stress (OS) and neuronal loss.
• **Wilson's disease (WD):** This genetic disorder causes toxic Cu buildup in the liver and brain (specifically the basal ganglia).

## Is there a link between Alzheimer's and Aluminum?

It is important to know how Al works in our bodies to understand how it might harm the brain and its link to AD. Let us begin with a historical perspective.

### Historical perspective

The idea that Al might cause AD started with observations of dialysis patients. These patients often complex. It involves many cellular and molecular steps. Studies have found that inflammation, oxidative stress, and disrupted cell function are all part of this process.

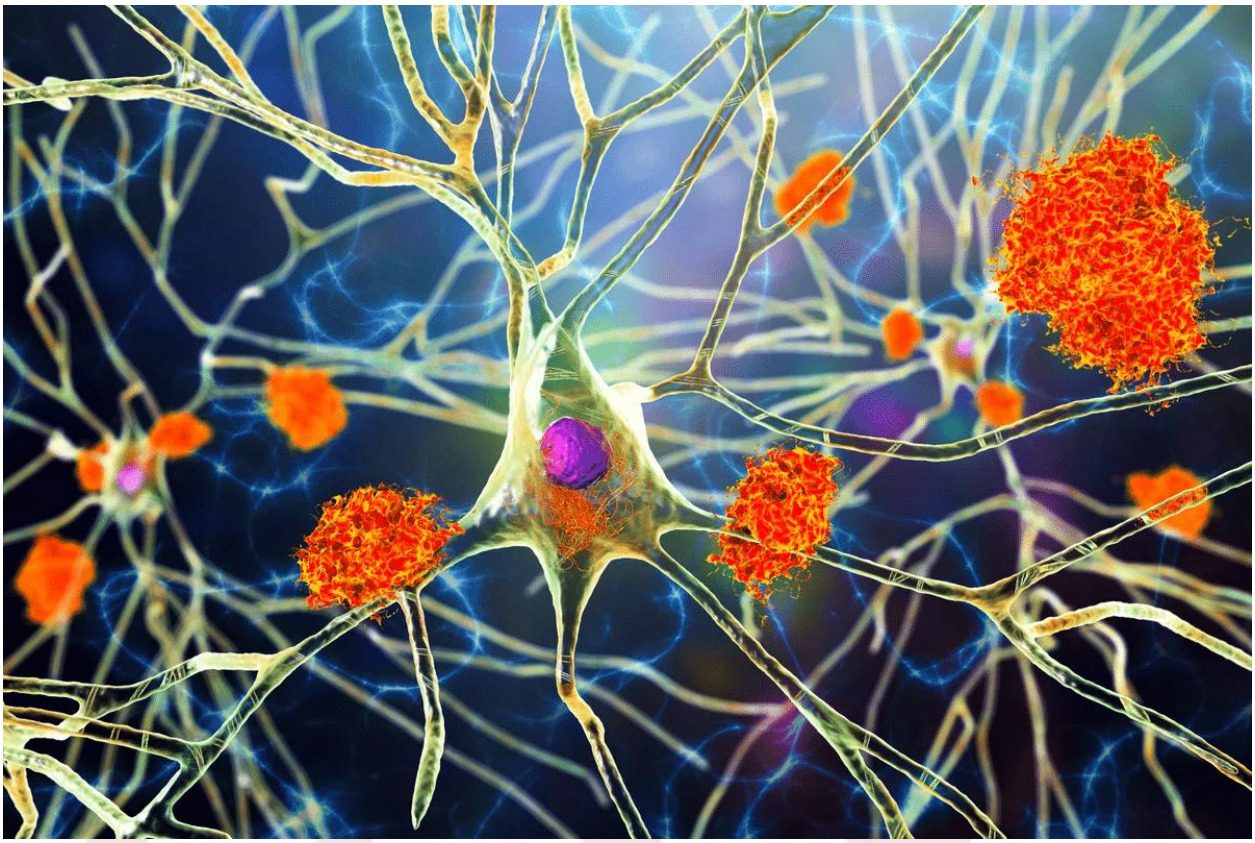
However, failure of amyloid trials has caused many researchers to be more critical of current dogma. Recent developed a condition called dialysis encephalopathy (DE), which caused speech problems, seizures, and memory loss. Finding high Al levels in these patients' brains, researchers linked these conditions to the Al in their treatment and dialysis water and further linked Al to AD. Thus, according to R.C. McLachlan "Aluminum in the brain was a sign of trouble, possibly starting a chain of brain damage". These early findings led to more research on Al's role in AD, specifically whether Al in the brains of AD patients could play a part in the disease. Over the years, that research has grown as related by another expert "The aluminum hypothesis has been a driving force behind much of the research into environmental risk factors for Alzheimer's disease, pushing the field to explore new avenues of investigation and to consider the complex interplay between genetics, environment, and lifestyle in disease development" - as this author characterizes it: "The guilty GEL triad", where G stands for generics, E for environment, and L for lifestyle. Al-AD research is key because of its potential therapeutic aspect. For this, it is important to understand the AD action mechanisms to fathom whether Al exposure plays a role in them.

### Hallmarks of AD

Alzheimer's is a complex disorder with many factors at play (see Fymat 2018-2025). It is marked by two key features: amyloid-β plaques and neurofibrillary tangles (NFT). Amyloid plaques are made of beta-amyloid protein that builds up outside neurons. NFTs are made of tau protein that builds up inside neurons. Both are linked to damage and death of neurons, causing memory loss and other cognitive problems.

The process of forming these plaques and tangles is
studies have suggested that neuroinflammation and neuronal loss precede amyloid-β plaque deposition. The earliest damage in humans with AD occurs as NFTs in the entorhinal cortex cells of origin for the performant pathway. NFT formation involves Al interactions with hyperphosphorylated tau (Figure 1; orange color: NFTs;

purple color: amyloid-beta plaques).



*Source: Unknown*

**Figure 1: Understanding Al exposure in the brain**

**Established AD risk factors**

Several known factors increase the risk of getting AD, including:

• **Age:** The risk goes up a lot after age 65.

• **Genetics:** Family history and certain genetic mutations, like those in the APOE gene, are big factors.

• **Lifestyle:** This author's acronym DESSSS, where D stands for Diet, E for Exercise, S for Stress, Sleep, and Social interactions can also raise the risk.

**Evidence supporting the Al–AD connection**

Research has shown a link between Al and AD. Studies from different fields support this connection.

**Elevated Al levels in brain tissue studies**

A key study reported in the journal *Environmental Health Perspectives* showed higher levels in Alzheimer patients' brains. It is thus stated: *"The accumulation of aluminum in the brain may contribute to the pathogenesis of Alzheimer's disease by promoting the*

*formation of amyloid plaques and neurofibrillary tangles"*. More research backs these findings, showing Al buildup in the brain may help cause Alzheimer's.

Animal studies have likewise shown Al's harm. They found cognitive and neuropathological changes like in Alzheimer's. A study on mice fed Al showed memory and learning issues. It also found more amyloid precursor protein (APP). These results suggest Al can cause Alzheimer-like problems. Recent studies also found that Al speeds up tau protein aggregation, showing that Al can worsen Alzheimer's.

In summary, evidence from many studies supports Al's link to AD. As research grows, we will learn more about this connection. This could help find ways to prevent and treat Alzheimer's, at least in those cases where Al is the main contributor to the disease.

**Notable water-based studies**

A UK study found a positive correlation between high Al levels in drinking water and increased Alzheimer's risk. Other research suggests a link, but results vary. Studies linking Al in water to Alzheimer's have limitations. Meta-analyses use different methodologies regarding the inclusion/exclusion criteria of participants, the specific sources of Al like water or food, the quality of the evidence, the measurement of Al exposure, the outcomes considered, etc. Differences in such factors are limiting, can change the results, and determine the reliability of the study.

Factors like *individual exposure levels, dietary habits, and other environmental exposures* can affect results. Also, other substances in water might interact with Al, to understanding Alzheimer's risk factors (Table 4).

changing its health effects. It is difficult to prove a direct link between water and AD - a complex disease with many risk factors.

**Evidence against the Al-AD connection**

However, other recent studies have questioned the idea that Al is a big risk for AD. The exact causes of AD are complex and not fully understood. Indeed, this author has opined that it is a runaway autoimmune disease in which the celebrated hallmarks (plaques and tangles) are but symptoms or consequences of the disease, not its cause(s) (Fymat 2018-2025). Nonetheless, the debate about Al's role has been intense. The evidence that goes against the Al-AD link consists mainly of study limitations and other possible reasons for correlations.

Many systematic reviews and meta-analyses on Al exposure have investigated the Al-AD link, but results are mixed. Some studies suggest a link, but the evidence is not strong enough to be sure.

For example, a large study reported in the *Journal of Alzheimer's Disease* found no link between Al in water and Alzheimer's risk. This suggests the connection might be more complicated than thought. A meta-analysis of 15 studies on Al exposure and Alzheimer's risk found no strong evidence of a link. Further, studies on workers in industries with high Al exposure have also shown mixed results. Some found no higher risk of Alzheimer's among those exposed to more Al. As one leading researcher in the field described it: *"The evidence on aluminum and Alzheimer's is not as straightforward as we thought. We need more research to understand the complex factors involved".* This complexity highlights the need for a detailed approach

| Study | Number of Participants | Main Findings |
|---|---|---|
| **Meta-Analysis 1** | 10,000 | No significant association found between Al exposure and Alzheimer's risk. |
| **Meta-Analysis 2** | 5,000 | Moderate association between high Al exposure and |

| | | |
|---|---|---|
| | | increased Alzheimer's risk. |
| **Meta-Analysis 3** | 8,000 | Mixed results, with some studies showing an association and others not. |

**Table 4: Summary of key meta-analyses on Al exposure and AD**

Studies of Al and AD face big challenges, e.g. it is difficult to accurately measure past Al exposure, which can lead to biased results. Also, many studies use self-reported data or indirect measures of exposure, adding more uncertainty. *"The challenge in studying aluminum exposure and Alzheimer's risk lies in accurately capturing long-term exposure data and controlling for confounding variables".*

In addition, some studies linking Al to AD might be influenced by other factors, e.g., places with high Al in water might also have other harmful substances. Further, some research suggests that the connection could be due to other factors.

These meta-analyses use different methodologies regarding the inclusion/exclusion criteria of participants, the specific sources of Al like water or food, the quality of the evidence, the measurement of Al exposure, the outcomes considered, etc. Differences in such factors are limiting, can change the results, and determine the reliability of the study.

## Position statements from medical organizations

Al in drinking water has raised concerns about AD in that high levels of Al in water might increase Alzheimer's risk. The recommended maximum limit is 0.2 mg/L for Al from Al-based coagulants. The World Health Organization (WHO) has issued guidelines and safety thresholds to help keep water safe and reduce health risks from Al. "The WHO guidelines provide a critical framework for assessing the safety of drinking water in relation to aluminum content, helping to mitigate potentially harmful effects." Table 5 encapsulates the position statements of several medical organizations including the WHO:

| **Organization** | **Position on Aluminum-Alzheimer's link** |
|---|---|
| Alzheimer's Association (AA) | o Inconclusive evidence<br>o More research needed |
| World Health Organization (WHO) | o Acknowledges controversy<br>o Further research required |
| National Institute on Aging (NIA) | o Supports research into environmental risk factors, including Aluminum |

**Table 5: Position statements from medical organizations on Al effects in the brain**

Nonetheless, despite disagreements, researchers in the scientific community all agree that Alzheimer's is caused by both genes and the environment, Al being seen as one part of this larger picture. More studies are needed to understand this complex issue better. Key areas of consensus include: (1) The complexity of AD's etiology; (2) the need for more rigorous and longitudinal studies; and (3) the importance of considering multiple risk factors. Ongoing controversies and research gaps concern the different ways studies are done. It is difficult to measure Al exposure accurately and how it might cause AD is not clear. Some studies hint at a possible link between Al and AD. Yet others have found no clear proof. The argument over Aluminum dementia and Alzheimer's aluminium keeps going. The findings are complex and varied. By understanding how Al and AD interact, we can find ways to lower the risk of this serious disease.

## Treatment

### Pharmacotherapy

In case of suspected sudden intake of a large amount of Al, the only treatment is Deferoxamine mesylate, which may be given to help eliminate Al from the body by chelation therapy. However, it should be applied with caution as this reduces not only Al body levels, but also those of other metals such as copper or iron.

### Chelation therapy

Chelation (or, more generally, metallo-pharmacology) is the use of metals to restore the normal healthy physiology of the body either by direct administration of essential metals, or by chelating out excess or toxic metals, or using them as carriers for targeted drug delivery, or else for tagging biomolecules for diagnostics.

Metal toxicity may occur due to essential metal overload or exposure to heavy metals from various sources. Chelation therapy (CT) is an important concept and tool for modifying metal concentrations in the body. Metals and metal compounds interfere with functions of various organ systems like the central nervous system (CNS), the hematopoietic system, liver, kidneys, etc. More details are provided in Sidebar 2.

## How to protect oneself?

Al can get into our bodies through food, air, and skin. It might reach the brain, but how much and how it gets there is being researched.

The key factors influencing aluminum absorption include:

• Form of Al exposure (e.g., soluble vs. insoluble compounds);
• Route of exposure (e.g., dietary, inhalation, dermal); and
• Presence of other metals or compounds that may interact with Al.

Many products have Al, adding to our daily exposure. These include:

• Cookware and utensils made from Al;
• Antacids and buffered aspirin with Al;
• Antiperspirants and deodorants with Al salts;
• Cosmetics and personal care products; etc.

Knowing where Al comes from is key. Our bodies can get rid of it, but too much can be harmful. This is true for people with kidney problems or those who work with Al. Sidebar 3 answers some frequently asked questions on this topic.

## Summary conclusions and takeaways

- As the third most abundant element on Earth, Aluminum is environmentally ubiquitous. Too reactive chemically to occur as a free metal in nature., it always occurs in combination with other elements such as hydroxide, phosphate, silicate, and sulfate.
- Al is used in the production of every‐day products, such as Al foil, antacids, aspirin, cookware, ensuring the potential for causing human exposure, primarily dietary but also occupational.
- The potential for significant Al absorption from the nasal cavity and direct distribution into the brain is concerning and continues to be investigated. Decreased renal function also increases human risk of Al-induced accumulation and toxicity.
- Metals in the brain are classified into essential biometals which are necessary for normal neurological function, and non-essentials biometals or neurotoxic heavy metals, which

can cause damage even at low concentrations. The former are tightly regulated by the body and are vital for processes like neurotransmission, energy production, and antioxidant defense. The latter (including Al) can lead to oxidative stress, inflammation, and disruption of the blood-brain barrier

- Environmental effects involve high Al levels occurring near mining sites and small amounts released to the environment at coal-fired power plants or incinerators. In the air, Al is washed out by the rain or normally settles down but small particles remain in the air for a long time. Acidic precipitation is the main natural factor to mobilize Al from natural sources and the main reason for the environmental effects of Al; however, the main factors of presence of Al in salt and freshwater are the industrial processes that also release Al into air.
- Al production possesses its own challenges to the environment on each step of the production process. The major challenge is the emission of greenhouse gases. Biodegradation of metallic Al is extremely rare; most Al-corroding organisms do not directly attack or consume Al but instead produce corrosive wastes.
- Major sources of human oral exposure to Al include food (due to its use in food additives, food and beverage packaging, and cooking utensils), drinking water (due to its use in municipal water treatment), and Al-containing medications (particularly antacid/antiulcer and buffered aspirin formulations). Consumption of antacids, antiperspirants, vaccines, and cosmetics provide possible routes of exposure.
- There are three routes by which Al can enter the brain from systemic circulation or the site of absorption. It fluxes into the brain across the blood-brain barrier, the choroid plexus, and the nasal cavity. Key aspects include: Neurotoxicity mechanism, brain accumulation, disease associations, and sources of exposure.
- While some research links high Al exposure to AD, the link is still debated, as not all studies consistently find high Al in AD patients. Most ingested Al is filtered by the kidneys and eliminated, with only tiny amounts reaching the brain under normal conditions.
- Key factors influencing Al absorption include: the form of Al exposure (e.g., soluble vs. insoluble compounds), the route of exposure (e.g., dietary, inhalation, dermal), and the presence of other metals or compounds that may interact with Al.
- While classified as non-carcinogen, Al presents a risk to healthy adults. Although rarely, Al can cause vitamin D-resistant osteomalacia, erythropoietin-resistant microcytic anemia, and central nervous system alterations. People with kidney insufficiency are especially at a risk.
- Al has been suspected of being a possible cause of AD but, as of 2018, research into this for over 40 years has found no good evidence of causal effect. Nonetheless, it indicates elevated Al levels in Alzheimer’s patients’ brain tissue.
- The argument over Aluminum dementia and Alzheimer’s keeps going. The findings are complex and varied. By understanding how Al and AD interact, we can find ways to lower the risk of this serious disease. Understanding the link between Al and Alzheimer’s is key for prevention.
- In case of suspected sudden intake of a large amount of Al, the only treatment is Deferoxamine mesylate, which may be given to help eliminate Al from the body by chelation therapy. However, it should be applied with caution as this reduces not only Al body levels, but also those of other metals such as copper or iron.
- Several sidebars are provided for the interested

readers regarding the physicochemical properties of Al, chelation therapy, and answers to frequently asked questions.

## Sidebar 1 - Physicochemical properties of Aluminum

The discovery of Aluminum was announced in 1825 by Danish physicist Hans Christian Orstedt. (1777-1851). Its first industrial production was initiated by French chemist Henri Etienne Sainte-Claire Deville (1818-1881) in 1856. It became much more available to the public in 1886 with the Hall-Heroult process developed independently by French engineer Paul Heroult (1863-1914) and American engineer Charles Martin Hall (1863-1914). Its mass production led to its extensive use in industry and everyday life. In 1954, Al became the most produced non-ferrous metal, surpassing copper (Cu). In the 21st century, most Al was consumed in transportation, engineering, construction, and packaging in the U.S., Western Europe, and Japan.

Despite its prevalence in the environment, Al has no known function in biology and no living thing is known to metabolize Al salts although Al is well tolerated by plants and animals. Nonetheless, because of the abundance of these salts, the potential for a biological role for them is of interest, and studies are ongoing. At pH 6–9 (relevant for most natural waters), Al precipitates out of water as a hydroxide and is hence not available. Most elements behaving this way have no biological role or are toxic.

**Isotopes**

Al has one stable, highly abundant isotope ($^{27}Al$), making it the 12th most abundant element in the Universe. It is quite useful in magnetic resonance imaging (MRI) for which it has a high sensitivity. All other isotopes are radioactive, the radioactivity being such that 26Al is used in radiometric dating. The most stable of these isotopes is 26Al, with a half-life of 717,000 years. While it was present along with stable 27Al in the interstellar medium from which the Solar System formed, no detectable amount could have survived the time since the formation of the planet. However, minute traces of 26Al are still produced from the decay of argon in the atmosphere induced by ionizing radiation of cosmic rays. The other known isotopes, with mass numbers ranging from 20 to 43, all have half-lives less than 7 minutes, as do the four detected metastable states.

**Physical characteristics**

Al is the third most common element and the most ubiquitous metal of the Earth's crust, constituting over 8% of its mass. It is a highly reactive post-transition metal in Group 13 of the periodic table, characterized by its high affinity for oxygen and its amphoteric nature, meaning it reacts with both acids and bases. While it is inherently very active, it typically behaves as a stable material in everyday environments due to the rapid formation of a thin, protective oxide layer on its surface, a process known as *passivation*.

The physical properties of Al are low density ($2.70 g/cm^3$), melting point 660.32"° C," silvery-white in color, high electrical and thermal conductivity, and high malleability and ductility. Its low standard atomic weight of 13 (low in comparison with many other common metals; about one-third that of steel - an ally of iron and carbon (C) gives it the low density responsible for many of its uses. Its great affinity toward oxygen explains the common occurrence of its oxides in nature, primarily in rocks in the Earth's crust, where it is the third most abundant element after oxygen and silicon (Si).

Pure Al is quite soft, lacking in strength, nonmagnetic, and ductile. Its density is 2.70 g/cm3, about one-third that of steel, much lower than other commonly encountered metals, making Al parts easily identifiable through their lightness. Al's low density compared to most other metals explains its use in the aerospace

industry and for many other applications where light weight and relatively high strength are crucial.

Al is an excellent thermal and electrical conductor. However, the high electrical conductivity means that it is strongly affected by alternating magnetic fields through the induction of eddy currents.

**Chemical characteristics**

Al has a high chemical affinity to oxygen. At normal conditions, fine powder of Al reacts explosively on contact with liquid oxygen; however, it forms a thin oxide layer (~5 nm at room temperature) that protects the metal from further corrosion by oxygen, water, or dilute acid, a process termed *passivation*. Al is not attacked by oxidizing acids because of its passivation. This allows Al to be used to store reagents such as nitric acid (HNO3), concentrated sulfuric acid (H2SO4), and some organic acids. It reacts with most nonmetals upon heating, forming a wide range of intermetallic compounds involving metals from every group on the periodic table.

There are four notable Al key chemical reactions:

• **With air (oxygen):** Al is a highly reactive metal with a strong affinity for oxygen. It reacts almost instantly with oxygen in the air to quickly form a protective, self-healing oxide layer of aluminum oxide. This layer is transparent, extremely thin (2–5 nm), and self-healing. While it prevents further corrosion under normal conditions, fine Al powder can react explosively with liquid oxygen or catch fire easily when exposed to a flame.

• **With water:** Normally, Al is unaffected by water because of its oxide film. However, if this layer is removed or if the water is hot, it reacts vigorously to produce hydrogen (H) gas and aluminum hydroxide Al(OH)3. At high temperatures, the reaction with steam produces aluminum oxide and hydrogen gas.

• **With acids and bases (Amphoterism):** Aluminum dissolves in both acidic and alkaline solutions, making its behavior unusual compared to many other metals. With mineral acids like hydrochloric acid (HCl), it reacts to form aluminum salts and release hydrogen gas. On the other hand, with bases, it reacts with strong bases like sodium hydroxide (NaOH) to produce aluminates and hydrogen gas.

• **With halogens and nonmetals:** Upon heating, Al reacts with all halogens (chlorine Cl bromine Br, iodine I) to form aluminum halides. It also reacts with other nonmetals at high temperatures to form compounds such as aluminum nitride.

However, it is not essential for human metabolism but can adversely be toxic for the human organism, including the brain. This fact is worrying, considering that we live in the 'Aluminum age', where exposure to this extensively used metal is inevitable and burgeoning. Absorbed via various routes, Al can display toxic properties, some of which can be associated with the pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and others such as autism spectrum disorder (ASD), alcohol use disorder (AUD), and dialysis encephalopathy (DE). Therefore, Al concentration could be used as a marker of certain diseases (AD, PD), and possible benefits from the use of Al chelators (AD, AUD, MS, DE) are possible.

## Sidebar 2 – On chelation therapy

**History**

During the Second World War, Dimercaprol was developed as an experimental antidote against the arsenic-based poison gas Lewisite. After World War II, mass lead poisoning was observed in a large number of navy personnel, later identified because of their jobs repainting the hulls of ships. This introduced the medical use of Ethylenediaminetetraacetic acid (EDTA) as a lead chelating agent. British Anti-Lewisite

(Dimercaprol) (BAL) has dominated medical prescriptions for general metal intoxication due to its high efficacy for human arsenic and mercury poisoning. In the 1960s, BAL was modified into meso 2,3-dimercaptosuccinic acid (DMSA), a related dithiol with far fewer side effects. Another dithiol, sodium 2,3-dimercaptopropane 1-sulfonate (DMPS), was introduced as a mercury-chelating agent by researchers in the former Soviet Union.

**Basic concept**

Although the concept of chelation is based on simple coordination chemistry, evolution of an ideal chelator and chelation therapy that completely removes specific toxic metal from desired site in the body involves an integrated drug design approach. Chelating agents are organic or inorganic compounds capable of binding metal ions to form complex ring-like structure called 'chelates' that possess "ligand" binding atoms to form either two covalent linkages or one covalent and one co-ordinate or two co-ordinate linkages (Figure 2).

Further, pH also is an important factor influencing complex formation and stability. Most chelating agents are unstable at low pH whereas, at high pH, metals tend to form insoluble hydroxides which are less accessible to chelating agents. This feature becomes significant in pathological conditions leading to acidosis or alkalosis.

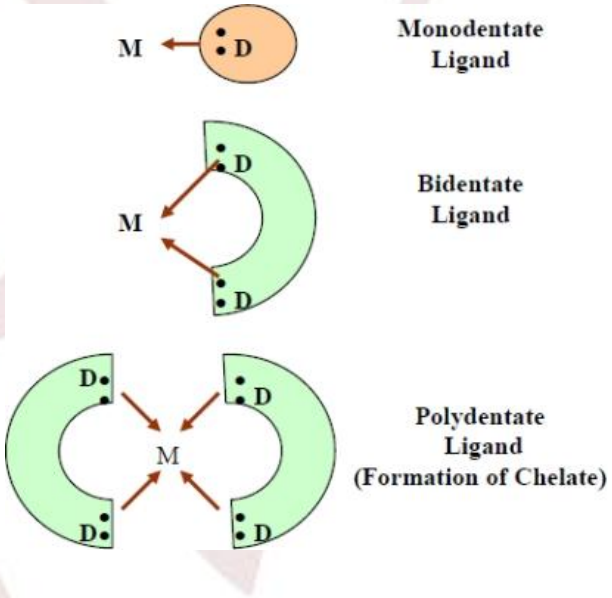
**Optimally effective chelation**

Optimally effective chelation can be achieved by virtue of some combination of the basic properties of both the metal ions and the chelating agents, and the resulting metal complex. It is important that a chelator satisfy

**Characteristics of an ideal chelator**

Chelation therapy has historically been used in attempts to reduce the body burden of toxic metals in highly symptomatic patients with elevated biological markers. Chelating agents can affect metal toxicity by mobilizing

criteria that allow it to: (1) transport across physiological barriers into compartments where a toxic metal ion is concentrated, (2) form a stable complex with the metal after removing it from the biological chelator, if required at the site and (3) form a chelation complex whose properties render it non-toxic and facilitate its excretion, not only from the site of deposition, but also from the body.




*Source: Flora SJS and Pachauri V (2010)*

**Figure 2: Formation of metal ligand complexes using mono, bi and polydentate ligands**

the toxic metal mainly into urine. A chelating agent forming a stable complex with a toxic metal may shield biological targets from the metal ion, thereby reducing the local toxicity. However, sometimes a chelator may expose the metal to the biological environment and thus increase the toxicity of the metal. An ideal chelator

should have: (1) high solubility in water; (2) resistance to biotransformation; (3) ability to reach the sites of metal storage, (4) ability to retain chelating ability at the pH of body fluids; and (5) the property of forming metal complexes that are less toxic than the free metal ion.

**Benefits and drawbacks of chelation therapy**

Most of the currently used chelating agents have serious side effects. Edetate Calcium Disodium (CaNa2EDTA) is a general chelating agent used primarily to treat severe lead poisoning in adults and children by binding to lead and facilitating its excretion through urine. Administered via intravenous or intramuscular injection, it acts as an antidote to reduce heavy metal body burden. It is used clinically despite associated risks.

Similarly, although considered safer, DMSA shares the limitation of extracellular distribution, rendering the drug effective in cases of slow, low dose, chronic metal poisoning (especially lead and arsenic) since metal reaches the cellular compartments behind the physiological barriers including the BBB. Thus, it is of immediate environmental health concern to identify the limitations of currently available chelating agents and develop new drugs that are more effective in the cases of low, long-term exposure to toxic metal. Although treatment with DMSA and Dimercapto propanesulfonic acid (DMPS) has shown lesser adverse effects, essential metal loss of Cu and Zn may be considered as one of the serious notable limitations. Specificity for the target metal may be another domain that needs to be addressed during new drug development. DPA exhibits disadvantage of possible risk to cause anaphylactic reaction in patient allergic to penicillin. Also prolonged use of DPA may induce several cutaneous lesions, dermatomyosites, adverse effects on collagen, dryness, *etc*. (Figure 3).

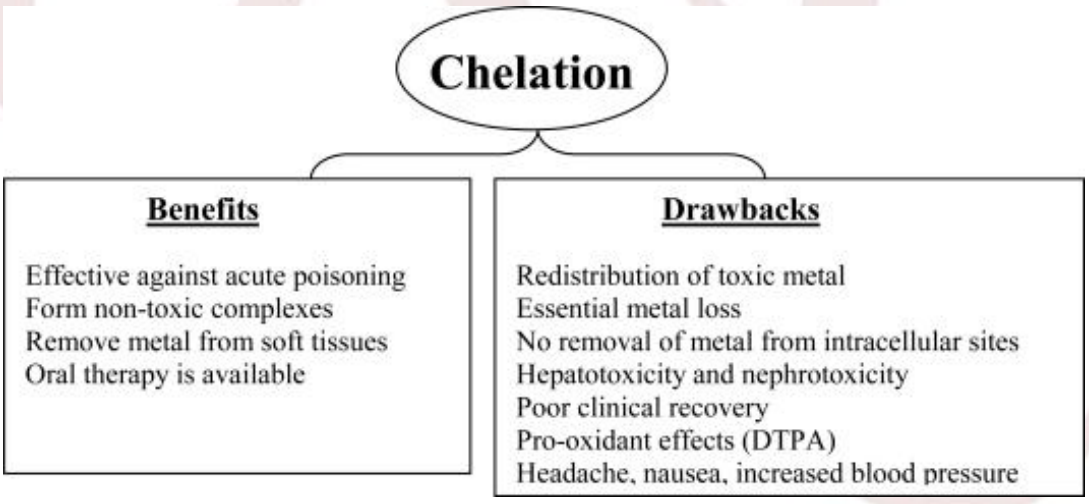



**Figure 3: Benefits and drawbacks associated with chelation therapy**

**Chelation therapy for aluminum toxicity**

Chelation therapy for Al toxicity exists, with Deferoxamine (DFO) being the primary, standard medical treatment to remove excess Al from the body. It is primarily used for acute or chronic Al poisoning, often in patients with kidney failure, and is administered via injection to bind Al and increase its excretion. Key details on Al chelation are the following:

- **Primary Agent:** Deferoxamine (DFO) is the established, effective chelator, often used to treat Al-

associated bone and brain diseases.

• **Other Agents:** EDTA and succimer have also been explored for Al detoxification.

• **Administration:** Because it is not well-absorbed orally, DFO is typically given via intramuscular, subcutaneous, or intravenous routes.

• **Process:** The chelator binds to Al in the blood, forming a compound that is then cleared by the kidneys or through dialysis.

• **Usage:** It is only used for diagnosed, high-level, or toxic Al accumulation, not for removing low-level background environmental exposure.

**Newer strategies: Combination therapies**

A new trend in chelation therapy is to use two structurally different chelators. This concept lies on the fact that two prescribed drugs will act through different mechanisms of action, thus resulting in additional effect, or sometimes they may support each other's mode of action leading to synergism.

The idea of using combined treatment assumes that various chelating agents are likely to mobilize toxic metals from different tissue compartments and therefore better results could be expected. This combination approach ensures: (1) Enhanced metal mobilization from the body; (2) reduction in the dose of potential toxic chelators; and (3) no redistribution of toxic metal from one organ to another following chronic metal exposure.

**Sidebar 3 – Frequently asked questions**

**What are the main sources of aluminum exposure in daily life?**

You can get exposed to aluminum from many places. This includes the environment, food, and products like antacids and cosmetics. Knowing these sources helps us understand our aluminum intake and its health risks.

**Is there a link between aluminum exposure and Alzheimer's disease?**

Some studies hint at a possible link between aluminum and Alzheimer's. But the proof is not solid yet. Research has found aluminum in Alzheimer's brains. It suggests that too much aluminum might raise the risk of getting the disease.

**How does aluminum potentially contribute to Alzheimer's disease pathology?**

Aluminum might worsen Alzheimer's by interacting with known risk factors. It can build up in the brain. This might help create amyloid plaques and tangles, key signs of Alzheimer's.

**Can aluminum in drinking water increase the risk of Alzheimer's disease?**

Some research links aluminum in water to Alzheimer's risk. But the findings are not clear-cut. The World Health Organization has set guidelines for safe aluminum levels in water.

**Are there any occupations that are at higher risk of aluminum exposure?**

Yes, jobs like mining, manufacturing, and welding expose people to more aluminum. Long-term exposure in these jobs might raise the risk of neurological problems, including Alzheimer's.

**What do medical organizations say about the aluminum-Alzheimer's link?**

Medical groups have different views on the aluminum-Alzheimer's link. Some see a possible connection, while others call for more research. The debate shows how complex the relationship between aluminum and Alzheimer's is.

**Can reducing aluminum exposure help prevent Alzheimer's disease?**

Cutting down on aluminum might be good for health. But it is not clear if it can stop Alzheimer's. More studies are needed to see if reducing aluminum helps prevent the disease.

**What are the current research gaps in understanding the aluminum-Alzheimer's link?**

There are many research gaps. We need to understand how aluminum harms the brain, how the blood-brain barrier works with aluminum, and the effects of long-term low-level exposure. More studies are essential to fill these gaps.

**Does aluminum cause dementia?**

Research on aluminum and dementia is ongoing. Some studies suggest a link, but the evidence is not strong. More research is needed to understand the relationship between aluminum and dementia risk.

**Are there any protective measures against aluminum exposure?**

Yes, there are ways to lower aluminum exposure. Using aluminum-free cookware and products, avoiding aluminum in antacids, and following safety guidelines in aluminum-related jobs can help.

## References

**Selected neurodegenerative diseases:**

1. Coyle JT and Puttfarcken P (1993). "Oxidative stress, glutamate, and neurodegenerative disorders". Science (New York, NY) 262:689–95.
2. Fymat, AL (2017). "Nanoneurology: Drug delivery across the brain protective barriers", Journal of Nanomedicine Research (2017). 5(1):1-4, 00105. doi: 10:15406/jnmr/2017.05.00105.
3. Fymat, AL (2017). "Therapeutics delivery behind, through and beyond the blood-brain barrier", Open Access Journal of Surgery (2017). 5(1): 1-9; 555654. doi: 10.19080/OAJS.2017.05.555654.
4. Fymat AL (2017). "Immunotherapy of brain cancers and neurological disorders", Journal of Cancer Prevention & Current Research (2017). 8(6):1-7; 00301. doi: 10.15406/jcpcr2017.08.00301.
5. Fymat AL (2018). "Blood-brain barrier permeability and neurological diseases", Journal of Current Opinions in Neurological Science (Invited Editorial). (2018). 2(2);411-4.
6. Fymat AL (2018). "Regulating the brain's autoimmune system: The end of all neurological disorders?" Journal of Current Opinions in Neurological Science (2018). 2(3):475-9.
7. Fymat, AL (2018). "Neutrophils-mediated treatment of neurodegenerative and other inflammatory diseases", Journal of Clinical Research in Neurology 1(1):1-5.
8. Fymat AL (2018). "Harnessing the immune system to treat cancers and neurodegenerative diseases", Journal of Clinical Research in Neurology 1(1):1-14, 2018.
9. Fymat AL (2019). "On the pathogenic hypothesis of neurodegenerative diseases", Journal of Clinical Research in Neurology 2(1):1-7.
10. Fymat, AL (2019). "Our two interacting brains – Etiologic modulations of neurodegenerative and gastroenteric diseases", Journal of Current Opinions in Neurological Science 4(2):50-4.
11. Fymat, AL (2019). "Electromagnetic therapy for neurological and neurodegenerative diseases: I. Peripheral brain stimulations". Open Access Journal of Neurology and Neurosurgery 12(2):30-47.

12. doi:10.19080/OAJNN.2019.12.555833.
13. Fymat AL (2019). ”Alzhei … Who? Demystifying the disease and what you can do about it”, Tellwell Talent Publishers, pp 236. ISBN: 978-0-2288-2420-6; 978-0-2288-2419-0.
14. Fymat AL (2020). “Dementia: Fending off the menacing disease... and what you can do about it”, Tellwell Talent Publishers, pp 488. ISBN: 978-0-2288-4146-3; 978-0-2288-4145-6.
15. Fymat AL (2020). “Neuroradiology and its role in neurodegenerative diseases”, Journal of Radiology and Imaging Science 1(1):1-14. Journal closed and transferred to: Journal of Neuroradiology and Nanomedicine 5(1):1-14.
16. Fymat AL (2020). “Electromagnetic therapy for neurological and neurodegenerative diseases: II. Deep brain stimulation.” Open Access Journal of Neurology and Neurosurgery 13(1):1-17.
17. doi: 19080/OAJNN.2020.13.555855.
18. Fymat AL (2020). “Nanobiotechnology-based drugs for the treatment of neurological disorders”, Journal of Pharmaceutical Bioprocessing 8(3):1-3.
19. Fymat, AL (2023). “Pathogens in the brain and neurodegenerative diseases’, Journal of Neurology and Psychology Research 5(1):1-14.
20. Fymat AL (2023). “Pathogens in the brain and neurodegenerative diseases”, Journal of Neurology and Psychology Research 5(1):1-14.
21. Fymat AL (2024). “The diseased brain: Neurodegenerative and other diseases”, Journal of Neurology and Psychology Research 5(1);1-54.
22. Fymat AL (2026). “Immunotherapy of neurodegenerative diseases”, Journal of Neurology and Psychology Research 7(1);1-23.

**Alzheimer’s disease:**

23. Bancher C, Lassmann H, Breitschopf H, and Jellinger KA (1997). “Mechanisms of cell death in Alzheimer's disease.” J Neural Transm Suppl 50:141–52.
24. Brooks WM, Lynch PJ, Ingle CC, Hatton A, Emson PC, Faull RL et al (2007)/ “Gene expression profiles of metabolic enzyme transcripts in Alzheimer's disease”. Brain Res 1127:127–35.
25. Bu G (2009). “Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy”. Nat Rev Neurosci 10:333–44.
26. Domingo JL (1995). “Adverse effects of potential agents for the treatment of Alzheimer's disease: a review.” Adverse Drug Reactions Toxicol Rev 14:101–15.
27. Fymat AL (2018). “Alzheimer's Disease: A Review, Journal of Current Opinions in Neurological Science 2(2);415-36.
28. Fymat, AL (2018). “Alzheimer's disease: Prevention, delay, minimization, and reversal,” Journal of Clinical Research in Neurology 1(1):1-16.
29. Fymat, AL (2018). “Is Alzheimer's an autoimmune disease gone rogue?”, Journal of Clinical Research in Neurology 2(1):1-4.
30. Fymat AL (2018). “Is Alzheimer's a runaway autoimmune disease? And how to cure it?” Proceedings of the European Union Academy of Sciences, 2018 Newsletter, pages 379-83.
31. Fymat, AL (2020). “Alzheimer's: What do we know about the disease and what can be done about it?” EC Journal of Psychology & Psychiatry 9(11):69-74.
32. Fymat AL (2020). “Is Alzheimer's an autoimmune disease gone rogue? The role of brain immunotherapy”, Journal of Clinical Research in Neurology 3(2):1-3.
33. Fymat AL (2020). “Alzheimer's: Will there ever be a cure?” Journal of Clinical Psychiatry and Neuroscience 3(4): 1-5.

34. Fymat AL (2022). “Alzheimer's disease: A path to a cure”, Journal of Neurology and Psychology Research 3(1):1-15. https://researchnovelty.com/articles.php?journal_id=5.
35. Fymat, AL (2022). “Alzheimer's disease: A path to a cure”, Current Opinions in Neurological Science 3(1):1-16.
36. Fymat AL (2025). “Alzheimer’s disease: Potential application of hyperbaric oxygen therapy”, Journal of Neurology and Psychology Research 5(6):1-20.
37. Fymat AL (2025). “Prion-like mechanisms in neurodegenerative diseases: I. Alzheimer’s disease”, Journal of Neurology & Psychology Research 6(4):1-22.
38. Neve RL, Robakis NK (1998). “Alzheimer's disease: a re-examination of the amyloid hypothesis”. Trends Neurosci 21:15–9.
39. Roush W (1995). “Protein studies try to puzzle out Alzheimer's tangles”. Science (New York, NY) 267:793–4.

**Dementia:**

40. Fymat, AL (2018). “Dementia treatment: Where do we stand?” Journal of Current Opinions in Neurological Science 3(1):1-3. 599.603.
41. Fymat. AL (2019). “On dementia and other cognitive disorders”, Journal of Clinical Research in Neurology 2(1):1-14.
42. Fymat AL (2019). “Dementia: A review”, Journal of Clinical Psychiatry and Neuroscience 1(3):27-34.
43. Fymat, AL )2019). “Dementia with Lewy Bodies: A review”, Journal of Current Opinions in Neurological Science 4(1);15-32.
44. Fymat AL (2019). “What do we know about Lewy body dementia?” Journal of Psychiatry and Psychotherapy (Invited Editorial) 2(1)-013:1-4.
45. doi:10.31579/JPP.2019/018.
46. Fymat, AL (2020). “Dementia: Should we reorient our approach to treatment?” EC Journal of Psychology & Psychiatry 9(12):1-3.
47. Fymat, AL (2020). “Dementia: What is its causal etiology?” International Journal of Neuropsychology and Behavioral Sciences 1(1):19-22.
48. Fymat, AL (2021). “On potentially reversible forms of dementia”, Journal of Current Opinions in Neurological Science 6(1):101-8, 2021.
49. Fymat AL (2021). “Dementia: Eliminating its potentially reversible forms”, Proc. European Union Academy of Sciences. Pages 270-7.
50. Fymat, AL (2024). “The coming dementia pandemic: Prescription for a cure”, Current Opinions in Neurological Science (Invited Editorial), 9(1):1-5.
51. Fymat AL (2025). “A novel form of dementia: Limbic-predominant age-related TDP-43 encephalopathy”, Journal of Neurology and Psychology Research 6(3):1-13.

**Aluminum in the brain and Alzheimer’s disease:**

52. Becaria A, Campbell A, and Bondy SC (2002). “Aluminum as a toxicant”. Toxicol Ind Health 18:309–20.
53. Bondy SC (2014). “Prolonged exposure to low levels of aluminum leads to changes associated with brain aging and neurodegeneration”. Toxicology 315:1–7.
54. Bondy SC, Guo-Ross SX, and Pien J (1998). “Mechanisms underlying the aluminum-induced potentiation of the pro-oxidant properties of transition metals”. Neurotoxicology 19:65–71.
55. Campbell A (2002). “The potential role of aluminum in Alzheimer's disease”. Nephrol, Dial, Transplant 17(Suppl. 2):17–20.
56. Candy JM, Oakley AE, Klinowski J, Carpenter TA, Perry RH, Atack JR et al (1986). “Aluminosilicates and senile plaque formation in Alzheimer's disease”. Lancet (London, England) 1:354–7.

57. Connor DJ, Harrell LE, Jope RS (1989) Reversal of an aluminum-induced behavioral deficit by administration of deferoxamine". Behav Neurosci 103:779–83.
58. Crapper DR, Krishnan SS, and Dalton AJ (1973). "Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration". Science (New York, NY) 180:511–3.
59. Domingo JL (1995). "Reproductive and developmental toxicity of aluminum: a review". Neurotoxicol Teratol 17:515–21.
60. Doroszkiewicz J, Farhan JA, Mroczko J, Winkel I, Perkowski M, and Mroczko B (2023). "Common and trace metals in Alzheimer's and Parkinson's diseases", Int J Mol Sci. 24(21):15721.
61. doi: 10.3390/ijms242115721.
62. Drago D, Bettella M, Bolognin S, Cendron L, Scancar J, Milacic R et al (2008). "Potential pathogenic role of beta-amyloid (1-42) - aluminum complex in Alzheimer's disease". Int J Biochem Cell Biol 40:731–46.
63. Edwardson JA, Klinowski J, Oakley AE, Perry RH, and Candy JM (1986). "Aluminosilicates and the ageing brain: implications for the pathogenesis of Alzheimer's disease". Ciba Found Symp 121:160–79.
64. Exley C (2007). "Aluminum, tau and Alzheimer's disease". J Alzheimer's Dis 12:313–5; author reply 7–8.
65. Exley C (2013). "Human exposure to aluminum". Environ Sci Process Impacts 15:1807–16.
66. Exley C (1999). "A molecular mechanism of aluminum-induced Alzheimer's disease?" J Inorg Biochem 76:133–40.
67. Flaten TP (2001). "Aluminum as a risk factor in Alzheimer's disease, with emphasis on drinking water". Brain Res Bull 55:187–96.
68. Forbes WF LS and Gentleman JF (1995). "Geochemical risk factors for mental functioning, based on the Ontario Longitudinal Study of Aging (LSA) V. Comparisons of the results, relevant to Al water concentrations, obtained from the LSA and from death certificates mentioning dementia". Can J Aging 14:642–56.
69. Forbes WF MC and Hayward LM, Agwani (1994). "Geochemical risk factors for mental functioning based on the Ontario Longitudinal Study of Aging (LSA) II. The role of pH". Can J Aging 13:249–67.
70. Frisardi V, Solfrizzi V, Capurso C, Kehoe PG, Imbimbo BP, Santamato A et al (2010). " Aluminum in the diet and Alzheimer's disease: from current epidemiology to possible disease-modifying treatment". J Alzheimer's Dis 20:17–30.
71. Garruto RM and Brown P (1994). "Tau protein, aluminum, and Alzheimer's disease". Lancet (London, England) 343:989.
72. Giorgianni C, Faranda M, Brecciaroli R, Beninato G, Saffioti G, Muraca G et al (2003). "Cognitive disorders among welders exposed to aluminum". Giornale italiano Medicina Lavoro Ergonomia 25(Suppl. 3):102–3.
73. Greger JL (1993). "Aluminum metabolism". Annu Rev Nutr 13:43–63.
74. Huang Y, Herman MM, Liu J, Katsetos CD, Wills MR, and Savory J (1997). "Neurofibrillary lesions in experimental aluminum-induced encephalopathy and Alzheimer's disease share immunoreactivity for amyloid precursor protein, A beta, alpha 1-antichymotrypsin and ubiquitin-protein conjugates". Brain Res 771:213–20.
75. Iregren A, Sjogren B, Gustafsson K, Hagman M, Nylen L, Frech W et al (2001). "Effects on the nervous system in different groups of workers exposed to aluminum". Occup Environ Med 58:453–60.
76. Julka D, Gill KD (1996). "Altered calcium homeostasis: a possible mechanism of

aluminum-induced neurotoxicity". Biochim Biophys Acta 1315:47–54.

77. Kawahara M (2005). "Effects of aluminum on the nervous system and its possible link with neurodegenerative diseases". J Alzheimer's Dis 8:171–182; discussion 209–15. doi: 10.3233/jad-2005-8210.
78. Landsberg JP, McDonald B, and Watt F (1992). "Absence of aluminium in neuritic plaque cores in Alzheimer's disease". Nature 60:65–8.
79. Levallois P (1995). "Aluminum and Alzheimer's disease". Can Med Assoc J 152:467–8.
80. Lu X, Liang R, Jia Z, Wang H, Pan B, Zhang Q et al (2014). "Cognitive disorders and tau-protein expression among retired aluminum smelting workers". J Occup Environ Med/Am Coll Occup Environ Med 56:155–60.
81. Mantyh PW, Ghilardi JR, Rogers S, DeMaster E, Allen CJ, Stimson ER et al (1993). "Aluminum, iron, and zinc ions promote aggregation of physiological concentrations of beta-amyloid peptide". J Neurochem 61:1171–4.
82. Martyn CN, Barker DJ, Osmond C, Harris EC, Edwardson JA, and Lacey RF (1989). "Geographical relation between Alzheimer's disease and aluminum in drinking water". Lancet (London, England) 1:59–62.
83. Martyn CN, Coggon DN, Inskip H, Lacey RF, and Young WF (1997). "Aluminum concentrations in drinking water and risk of Alzheimer's disease". Epidemiology (Cambridge, MA) 8:281–6.
84. McLachlan DR, Bergeron C, Smith JE, Boomer D, and Rifat SL (1996). "Risk for neuropathologically confirmed Alzheimer's disease and residual aluminum in municipal drinking water employing weighted residential histories". Neurology 46:401–5.
85. Miu AC, Olteanu AI, Miclea M (2004). "A behavioral and ultrastructural dissection of the interference of aluminum with aging". J Alzheimer's Dis 6:315–28.
86. Molloy DW, Standish TI, Nieboer E, Turnbull JD, Smith SD, and Dubois S (2007). "Effects of acute exposure to aluminum on cognition in humans". J Toxicol Environ Health Part A 70:2011–9.
87. Muma NA and Singer SM (1996). "Aluminum-induced neuropathology: transient changes in microtubule-associated proteins". Neurotoxicol Teratol 18:679–90.
88. Munoz DG (1995). "Aluminum and Alzheimer's disease". Can Med Assoc J. 152:468–9.
89. Murayama H, Shin RW, Higuchi J, Shibuya S, Muramoto T, and Kitamoto T (1999). "Interaction of aluminum with PHFtau in Alzheimer's disease neurofibrillary degeneration evidenced by deferoxamine-assisted chelating autoclave method". Am J Pathol 155:877–85.
90. Neri LC, Hewitt D (1991). "Aluminum, Alzheimer's disease, and drinking water". Lancet (London, England) 338:90.
91. Ricchelli F, Drago D, Filippi B, Tognon G, and Zatta P (2005). "Aluminum-triggered structural modifications and aggregation of beta-amyloids". Cell Mol Life Sci 62:1724–33.
92. Rifat SL, Eastwood MR, McLachlan DR, and Corey PN (1990). "Effect of exposure of miners to aluminum powder". Lancet (London, England) 336:1162–5.
93. Riihimaki V, and Aitio A (2012). "Occupational exposure to aluminum and its biomonitoring in perspective". Crit Rev Toxicol 42:827–53.
94. Rogers MA and Simon DG (1999). "A preliminary study of dietary aluminum intake and risk of Alzheimer's disease". Ageing 28:205–9.
95. Rondeau V, Commenges D, Jacqmin-Gadda H,

and Dartigues JF (2000). “Relation between aluminum concentrations in drinking water and Alzheimer's disease: an 8-year follow-up study”. Am J Epidemiol 152:59–66.

96. Savory J, Exley C, Forbes WF, Huang Y, Joshi JG, Kruck T et al (1996). “Can the controversy of the role of aluminum in Alzheimer's disease be resolved? What are the suggested approaches to this controversy and methodological issues to be considered?” J Toxicol Environ Health 48:615–35.
97. Savory J, and Ghribi O (2007). “Can studies of aluminum toxicity in vivo and in vitro provide relevant information on the pathogenesis and etiology of Alzheimer's disease?” J Alzheimer's Dis 11:429–30; discussion 31–2.
98. Shcherbatykh I and Carpenter DO (2007). “The role of metals in the etiology of Alzheimer's disease”. J Alzheimer's Dis 11:191–205.
99. Shin RW, Lee VM, and Trojanowski JQ (1994). “Aluminum modifies the properties of Alzheimer's disease PHF tau proteins in vivo and in vitro”. J Neurosci 14(Part 2):7221–33.
100. Shin RW, Lee VM, and Trojanowski JQ (1995). “Neurofibrillary pathology and aluminum in Alzheimer's disease”. Histol Histopathol 10:969–78.
101. Singer SM, Chambers CB, Newfry GA, Norlund MA, and Muma NA (1997). “Tau in aluminum-induced neurofibrillary tangles”. Neurotoxicology 18:63–76.
102. Sjogren B, Iregren A, Frech W, Hagman M, Johansson L, Tesarz M et al (1996). “Effects on the nervous system among welders exposed to aluminum and manganese”. Occup Environ Med 53:32–40.
103. Still CN (1994). “Aluminum neurotoxicity and Alzheimer’s disease”, J S C Med Assoc. 90(11):560-4.
104. Vogt (1986). “Water quality and health: Study of a possible relation between Al in drinking water and dementia”. Sosiale og Okonomiske Studier. Oslo: Statistics Norway 61.
105. Walton JR (2010). “Evidence for participation of aluminum in neurofibrillary tangle formation and growth in Alzheimer's disease”. J Alzheimer's Dis 22:65–72.
106. Walton JR (2014). “Chronic aluminum intake causes Alzheimer's disease: applying Sir Austin Bradford Hill's causality criteria”. J Alzheimer's Dis 40:765–838.
107. Wang L (2018). “Entry and deposit of Aluminum in the brain”, Adv Exp Med Biol 1091:39-51. doi: 10.1007/978-981-13-1370-7_3.
108. Wettstein A, Aeppli J, Gautschi K, and Peters M (1991). “Failure to find a relationship between mnestic skills of octogenarians and aluminum in drinking water”. Int Arch Occup Environ Health 63:97–103.
109. Wisniewski HM, Shek JW, Gruca S, and Sturman JA (1984). “Aluminum-induced neurofibrillary changes in axons and dendrites”. Acta Neuropathol 63:190–7.
110. Wong MH, Fung KF, and Carr HP (2003). “Aluminum and fluoride contents of tea, with emphasis on brick tea and their health implications”. Toxicol Lett 137:111–20.
111. World_Health Organization (1997). “Aluminum”. Geneva: WHO. Environmental Health Criteria 194.
112. Yokel RA (2000). “The toxicology of aluminum in the brain: a review”. Neurotoxicology 21:813–28.
113. Yokel RA (2006). “Blood-brain barrier flux of Aluminum, manganese, iron and other metals suspected to contribute to metal-induced neurodegeneration”, J Alzheimer’s Dis. 10(2-3):223-53. doi: 10.3233/jad-2006-102-309.
114. Yumoto S, Kakimi S, Ohsaki A, and Ishikawa A (2009). “Demonstration of aluminum in amyloid fibers in the cores of senile plaques in the brains of patients with Alzheimer's

disease". J Inorg Biochem 103:1579–84.

115. Zatta PF (1995). "Aluminum binds to the hyperphosphorylated tau in Alzheimer's disease: a hypothesis". Med Hypotheses 44:169–72.

**Chelation therapy:**

116. Alan L and Miller ND (1998). "Dimercaptosuccinic Acid (DMSA), a non-toxic, water-soluble treatment for heavy metal toxicity. Altern. Med. Rev. 3:199–207.

117. Andersen O (1999). "Principles and recent developments in chelation treatment of metal intoxication". Chem. Rev.2683–710. doi: 10.1021/cr980453a.

118. Andersen O (2004). "Chemical and biological considerations in the treatment of metal intoxications by chelating agents". Mini Rev. Med. Chem. 4:11–21. doi: 10.2174/1389557043487583.

119. Angle CR (1996). "Chelation therapies for metal intoxication". In: Chang LW, editor. Toxicology of Metals. CRC Press; Boca Raton, FL, USA: 1996. pp. 487–504.

120. Aposhian HV (1983). "DMSA and DMPS—Water soluble antidotes for heavy metal poisoning. Ann. Rev. Pharmacol. Toxicol. 123:193–215.

121. doi: 10.1146/annurev.pa.23.040183.001205.

122. Blanusa M, Varnai VM, Piasek M, and Kostial K (2005). "Chelators as antidotes of metal toxicity: Therapeutic and experimental aspects". Curr. Med. Chem. 12:2771–94.

123. doi: 10.2174/092986705774462987.

124. Flora SJS and Pachauri V (2010). "Chelation in metal intoxication". Int J Environ Res Public Health 7(7):2745–88. doi: 10.3390/ijerph7072745.

125. Fournier L, Thomas G, Garnier R, Buisine A, Houze P, and Pradier F (1988). "2, 3-Dimercaptosuccinic acid treatment of heavy metal poisoning in humans." Med. Toxicol. 3:499–504. doi: 10.1007/BF03259898.

126. Jones MM (1994)."Design of new chelating agents for removal of intracellular toxic metals". In: Kauffman GB, editor. Coordination Chemistry: A Century of Progress. The American Chemical Society; Washington, DC, USA: 1994. pp. 427–38.

127. Kazantzis G (1990). "Diagnosis and treatment of metal poisoning-General aspect". In: Friberg G, Nordberg GF, Vouk VB, editors. Handbook on the Toxicology of Metals. Elsevier; Amsterdam, The Netherland: 1990. pp. 302–17.

128. Klaassen CD (2006). "Heavy metals and heavy metal antagonists." In: Goodman L, Gilman A, editors. The Pharmacological Basis of Therapeutics. McGraw Hill, Medical Publishing Division; New York, NY, USA: 2006. pp. 1825–72.

129. Nordberg GF, Fowler BA, Nordberg M, and Friberg L, editors (2007). "Handbook on the toxicology of metals". 3rd ed. Academic Press; San Diego, CA, USA: 2007. pp. 577–98.

130. Spoor NL (1977). "The use of EDTA and DTPA for accelerating the removal of deposited transuranic elements from human". Harwell; Didcot, UK: 1977.

131. Winship KA (1993). "Toxicity of aluminium: a historical review, Part 2. Adverse Drug Reaction". Toxicol. Rev. 12:177–211.