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James M. McKivigan  
*Touro University Nevada*

Gregory Gilmour

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Neuro-Anatomical Changes of Carbon Monoxide Poisoning on Advanced Imaging: A Literature Review

James McKivigan (Corresponding Author)
College of Health and Human Services Touro University Nevada Henderson, Nevada
Email: jmckivig@touro.edu

Gregory Gilmour
College of Osteopathic Medicine Michigan State University East Lansing, MI

Abstract
Carbon monoxide (CO) poisoning is a major public health issue in the United States that accounts for approximately 50% of poisoning cases in the nation each year and around 50,000 emergency room visits. In most instances of CO poisoning, the culprit is a malfunctioning or poorly tended heating system within the home or, occasionally, commercial building, which causes the system to leak this hazardous gas. One of the more insidious aspects of CO poisoning is that the gas is odorless and colorless, and victims of CO poisoning often do not realize that there is a problem until they begin to experience the effects of poisoning and have no choice but to seek medical attention. Unfortunately, many victims of CO poisoning die before they are able to seek treatment. This paper makes use of a qualitative, systematic literature review to examine the four major parts of the brain that are most severely affected by CO poisoning. Overall, the literature review showed that the white matter, globus pallidus, basal ganglia, and cortex are the parts of the brain most severely impacted by CO poisoning. While many CO poisoning victims do make it to the hospital on time and are treated, they may nonetheless suffer long-term neurological consequences as a result of their exposure. As such, CO poisoning is a major public health issue.

Keywords: Carbon monoxide poisoning; Public health; Neurological health; Brain damage; Household toxins.

1. Introduction
Approximately 50,000 people seek emergency medical help for carbon monoxide (CO) poisoning every year in the United States for varying exposure levels [1]. A colorless, odorless gas, CO is produced from incomplete combustion of certain hydrocarbons. Some common CO exposure sources include charcoal briquettes burned indoors, poorly placed gasoline generators, and low-quality or poorly maintained heating systems [2]. Once CO is inhaled, hemoglobin has a decreased capacity to carry oxygen and release it to body tissues. Common neurological effects include depression, anxiety, cognitive sequelae, sleep problems, gaze abnormalities, trouble balancing, persistent headaches, hearing loss, peripheral neuropathies, and dizziness [1].

CO poisoning is responsible for over 50% of fatal poisonings in many countries [3]. Neurological abnormalities related to CO exposure can be difficult to diagnose if doctors are not aware that exposure has occurred. Many symptoms of CO exposure are common to other substances and conditions. Failure to identify and treat all abnormalities resulting from CO exposure, particularly those affecting the central nervous system (CNS), can lead to additional health complications [2, 4]. Some controversy and ambiguity exist regarding which areas of the brain are affected by CO poisoning, and the diagnosis, treatment, and patient outcomes are affected by this uncertainty. Although existing studies have provided ample evidence of CNS lesions after CO exposure, those findings have not led to a clear understanding of which areas of the brain are affected or the complex nature of CNS lesions [5]. In this systematic literature review, we aimed to determine which areas of the brain are affected by CNS lesions caused by CO exposure. The overall goal was to make it easier for doctors, particularly neuroradiologists, to develop a clear understanding of the complex nature of CNS lesions and the areas of the brain to focus on when CO exposure is suspected.

CO exposure can have many short- and long-term effects on the human brain and may affect different cerebral regions [6-10]. Recent improvements in magnetic resonance imaging (MRI) and other medical technologies have allowed more abnormalities and locations in the brain affected by exposure to be identified [3, 11]. Sometimes, small lesions and atypical manifestations of CO poisoning are overlooked or misidentified by neuropathologists [12, 13]. Failure to identify and treat all abnormalities resulting from CO exposure can lead to additional health complications [2, 4, 14]. As noted above, our general aim in this review was to address the lack of clear understanding of the neuroradiologic abnormalities resulting from CO exposure. A thorough study of the areas in the brain potentially...
affected by CO poisoning and identified through imaging has not yet been performed. The study’s focus is meant to provide a more detailed context concerning the challenges healthcare professionals experience and that can hinder the diagnosis and treatment of CO exposure-related CNS lesions [13].

The clinical choices made during the research of Hart, et al. [6] provide context for how imaging techniques like MRI and computed tomography (CT) are used to determine the location and extent of neurological abnormalities resulting from exposure. In this systematic review, we aimed to answer the following question: Which areas of the brain are affected by carbon monoxide exposure?

2. Methods

This section describes in detail the methodology chosen for this study. This research did not involve recruiting and collecting data from participants but instead was a systematic, qualitative review [15] of the existing literature.

2.1. Conducting a Systematic Literature Review

Specific procedures and criteria were followed during this systematic review to ensure that the resulting ontology was developed in an academically rigorous manner. No ethical challenges were anticipated because no human participants took part in the study. This systematic literature review was performed in four phases consisting of eight sub-steps, as suggested by Okoli [15] (Figure 1).

Figure 1. Overview of the steps conducted in this systematic literature review

2.2. Planning

During the planning stage, the steps included identifying the purpose of the study and drafting the protocol. The planning stage helped refine the selection of literature used in this review, narrowing the search to references related to areas of the brain affected by CNS lesions caused by CO exposure. Knowing the purpose of the study helped to keep the research aligned. The protocol for this review involved training in the use of Excel spreadsheets (Microsoft Corp. Redmond, WA, USA) and NVivo 12 Pro (www.qsrinternational.com). Time was allocated for learning documentation using the required protocol to address the research goals. All collected data were accounted for, contributing to the credibility and dependability of this study.

2.3. Selection

Selection involved outlining the inclusion criteria and searching for existing literature. The inclusion criteria were predetermined before the literature search based on the purpose of the review. The inclusion criteria were as follows: (1) peer-reviewed articles available in full text accessible full text open access; (2) published between January 1, 1999, and June 30, 2018; (3) published in English; and (4) included only human participants.

The search process involved a systematic, manual search of specific evidence-based studies and reviews from journal papers published since 1999. Two search engines, Elsevier (ScienceDirect) and PubMed, were used to minimize publication bias [16]; and some search strings were used in an attempt to conduct a balance of broad and specific searches [16]. The search strings involved the keywords “carbon monoxide poisoning,” combined with one of the following: “brain lesions,” “CNS lesions,” or “brain injury.” The search was initially performed in PubMed using the search string “carbon monoxide poisoning, brain lesions.” The initial search generated 400 results that were then filtered using the criteria mentioned above, which narrowed the study to 25 relevant articles. The abstracts of all 25 articles were evaluated to determine which were useful to the review. Thus, the fourth step, the literature search, yielded 21 relevant articles to be used in this review. Table 1 shows the number of relevant results generated in PubMed and Elsevier (ScienceDirect) using different search strings.
### Table 1. Search Strategy

<table>
<thead>
<tr>
<th>Engine</th>
<th>Search String</th>
<th>Initial Results</th>
<th>Filtered Results</th>
<th>Excluded due to unrelated content</th>
<th>Excluded due to inability to access</th>
<th>Excluded due to duplication</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>Carbon monoxide poisoning, brain lesions</td>
<td>400</td>
<td>25</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>PubMed</td>
<td>Carbon monoxide poisoning, CNS lesions</td>
<td>124</td>
<td>61</td>
<td>7</td>
<td>44</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>PubMed</td>
<td>Carbon monoxide poisoning, brain injury</td>
<td>199</td>
<td>94</td>
<td>8</td>
<td>65</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Elsevier</td>
<td>Carbon monoxide poisoning, brain lesions</td>
<td>303</td>
<td>50</td>
<td>1</td>
<td>48</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Elsevier</td>
<td>Carbon monoxide poisoning, CNS lesions</td>
<td>17</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Elsevier</td>
<td>Carbon monoxide poisoning, brain injury</td>
<td>581</td>
<td>165</td>
<td>10</td>
<td>136</td>
<td>0</td>
<td>19</td>
</tr>
</tbody>
</table>

### 2.4. Extraction

During the extraction phase, relevant data from the literature were noted and screened for exclusion. Excluded materials included non-peer-reviewed materials that were written before 2000. Articles that were not written in English were also excluded because the authors are English speaking. All information reviewed this limited to changes in the central nervous system due to carbon monoxide exposure. A conventional content analysis was used to determine critical codes and categories and identify articles containing data pertinent to this review. This process involved reading each article carefully to establish the diagnosis and treatment of CNS lesions caused by CO exposure. During the analysis, we determined four categories representing four brain areas that were considered significant to the review: (1) white matter, (2) globus pallidus, (3) basal ganglia, and (4) cortex. The categories were determined through an NVivo word-search query in which the brain’s most mentioned areas were selected for closer exploration. The categories are further described in the Results and Discussion section, including how the specified regions of the brain were affected by CO poisoning.

In carefully reading the articles, we determined their quality and relevance to the review. In this phase, several articles were excluded due to the absence of CO poisoning cases.

### 2.5. Execution

The execution phase involved synthesizing the results and writing the review. To integrate the results, facts extracted from the literature were combined. The manuscripts were examined for their relation to one another and relevance to the research question. The next section contains the findings of this systematic literature review.

### 3. Results and Discussion

Through a qualitative content analysis of 65 pieces of pertinent literature, we attempted to answer the following question: Which areas of the brain are affected by carbon monoxide exposure? Descriptions of the four categories representing the brain (i.e., white matter, globus pallidus, basal ganglia, and cortex) that emerged from the content analysis were relevant in answering the research question. The categories showed how CO exposure affected these areas of the brain. Each category will be individually described before describing the synthesized results. The synthesized results were developed by analyzing how the four categories were related to each other to answer the research question.

#### 3.1. White Matter

Based on the literature gathered in this review, the area of the brain most widely affected by CO exposure is the white matter. In most cases, brain injuries were not restricted to this area alone. In particular, damage to the white matter was generally associated with delayed encephalopathy, affecting the globus pallidus, cortex, and thalamus [17]. Damage to the white matter can often be identified through MRI [13], and the white matter may be more prone to ischemia during the early stages of CO poisoning [18].
Cases reviewed by Sener [18] revealed that white matter lesions often reversed in approximately 16 days, and lesions to the basal ganglia may manifest belatedly [18]. CT and MRI scans were usually performed on patients exposed to CO despite the lack of CNS lesion symptoms or CO exposure-related symptoms. Delays in symptom presentation often led to late diagnoses [19-22].

Kim, et al. [21], stated that CO poisoning has no indicative signs or symptoms, and diagnosis may be difficult without the patient's CO exposure history. Devine, et al. [23], and Kahan, et al. [24] added that patients exposed or presumed to have been exposed to CO should be monitored over the long term through a series of neuropsychological tests. Devine, et al. [23], claim that routine neurologic examinations might not adequately detect neurological sequelae.

If undetected, CO poisoning may affect white matter severely, including demyelination, leading to loss of vision, speech impairment, and physical disability [25]. Demyelination is believed to result from delayed encephalopathy [22]. Devine, et al. [23], argued that demyelination of white matter is often more reversible than lesions of the globus pallidus. Ozcan, et al. [25], argued that demyelination reaching the white matter is found only in severe cases.

In other cases, some patients suffered from long-term issues associated with lesions in the white matter. Huisa, et al. [20], presented two cases of white matter lesions caused by CO poisoning; in one case, the patient recovered fully, and in the other, the patient only partly recovered. The authors concluded that the different outcomes were influenced by several factors, including the length of hypoxic exposure, individual responses to white matter hypoxic injury, and even genetics [20]. Ozcan, et al. [25], Raub, et al. [26], and Yoshiike, et al. [17], also reported cases of patients suffering from white matter lesions caused by CO poisoning in which long-term cognitive deficiencies resulted. Murata, et al. [27], discussed a patient with white matter lesions who suffered neuronal necrosis progressing from demyelinating membrane destruction.

### 3.2. Globus Pallidus

CO poisoning also appears to affect the globus pallidus. Damage to the globus pallidus is associated with several symptoms, including parkinsonism or Parkinson-like symptoms [13, 19, 28]. Chen, et al. [28], described a case in which MRI showed lesions in the globus pallidus 7 months after CO poisoning. The patient developed parkinsonism, particularly akinesia and rigidity, which were not improved by treatment with levodopa. The patient was further examined using gradient echo, which showed lesions in the substantia nigra. Chen, et al. [28], differentiated their case from other CO poisoning cases with parkinsonism symptoms by this finding. Conventional MRI is generally unable to detect delayed pallido-reticular lesions; however, the authors concluded that pallidal lesions usually contribute to parkinsonian symptoms [28]. Jeon, et al. [29] recommended diffusion-weighted (DW) imaging to assess CO poisoning damage; out of a total of 387 patients, 104 developed acute brain lesions. Out of those 104 patients, 77 had lesions in the globus pallidus.

Parkinsonism may also be related to cerebral atrophy in CO poisoning, resulting in other issues such as dementia and psychosis. Such symptoms generally appear in only 10% to 30% of patients [30]. In one of the cases reported in Huisa, et al. [20], a 32-year-old male found unconscious after CO exposure had normal MRI results and was discharged from hospital after 10 days. Five days later, the patient was readmitted due to confusion, insomnia, and hallucinations. He was given antipsychotic medications, but an evaluation 90 days later revealed he had severe executive dysfunction and mild memory deficits. The patient only partially recovered.

Bilateral globus pallidus lesions are associated with alexithymia (a lack of emotional awareness) [31]. Huang, et al. [31] noted that psychological complications, particularly mood and behavior problems, are common in patients following CO poisoning.

Unilateral damage to the globus pallidus has been associated with disruption to the sleep-wake pattern [17]. In severe cases, CO poisoning may result in cytotoxic edema or swelling of brain cells [23].

Among the cases analyzed for this review, two patients who suffered damage to the globus pallidus made full recoveries [18, 25]. Only one case, presented in Baud, et al. [32], died. Other studies noted that patients could make full recoveries [18, 20, 25]. Some studies revealed that several patients suffered long-term effects of CNS lesions caused by CO poisoning [17, 20-24, 31, 33, 34]. There are few similarities in patients reported to have made full recoveries. In the case presented in Ozcan, et al. [25], a 52-year-old woman was found unconscious after accidental CO exposure, with a reported Glasgow Coma Scale (GCS) score of 9/15. Initial scans showed bilateral hypodensity in the globus pallidus. The patient showed improvements in the first 3 days and was discharged on day 8. At her 90-day evaluation, the patient showed no signs of neurological sequelae. In Sener [18], the patient was a 9-year-old girl found unconscious after accidental CO exposure. The initial MRI showed slightly abnormal signal intensity in the posterior portions of the globus pallidus. After 16 days of hyperbaric treatment, the patient showed no signs of lesions.

### 3.3. Basal Ganglia

Another area of the brain profoundly affected by CO poisoning is the basal ganglia. Kasbekar and Gonzalez-Martin [33], presented a case in which damage to the basal ganglia from CO poisoning was linked to visual impairment. However, they noted that the patient was chronically exposed to CO. Lim, et al. [35], also reported that chronic exposure to CO might affect the basal ganglia but reiterated that damage caused by CO poisoning is not limited to this region. The cortex, white matter, thalamus, and pons should also be examined for lesions to prevent coma or death. These authors recommended radiological techniques such as DW MRI and magnetic resonance spectroscopy (MRS) to determine damage. Hopkins, et al. [36], found that a wide range (between 4% and 88%) of
The basal ganglia have high energy requirements, and a lack of oxygen and glucose following CO exposure generally led to their damage [37]. Lim, et al. [35], noted that damage to the basal ganglia might be determined through changes in cerebral metabolism. The region’s high energy requirements mean that neurotransmitters and trace metals are utilized at specific rates. Alteration of these rates was uniquely associated with lesions in the basal ganglia. Damage to the basal ganglia may also affect decision-making and executive function [23, 24], along with movement [35]. Devine, et al. [23], noted that patients with lesions of the basal ganglia might present with headaches, flu-like symptoms, and memory retrieval issues.

3.4. Cortex

CO poisoning also affects the cortex in general and is associated with demyelination resulting in “disorientation, confusion, cogwheel rigidity, opisthotonic posturing, extremity flaccidity or spasticity, extensor plantar response, and coma” [26]. Damage to the cortex may not manifest symptoms immediately after CO poisoning. Generally, patients undergo an MRI to check for brain lesions after exposure. Some patients demonstrate normal MRI results after CO exposure and do not show cognitive deficiencies until days or months later. For instance, in the case presented in Devine, et al. [23], a 45-year-old woman who went to the hospital 6 hours after confirmed CO exposure showed normal MRI results. The patient had experienced flu-like symptoms, including balance issues, severe headaches, and facial pain for at least 6 months before the confirmed CO exposure. Further examination of the case showed that the patient might have been continuously exposed to CO for an unknown long-term period. Seventeen months after the first MRI, the patient’s test results showed “subtle” frontal lobe dysfunction, leading to difficulty in reading, writing, and speaking.

Following the testing of vital signs such as blood pressure, heart rate, and carboxyhemoglobin levels, and undergoing CT scans and MRI, patients are often given hyperbaric oxygen therapy. In the case presented in Baud, et al. [32], a female patient found unconscious after CO exposure received endotracheal intubation and was ventilated with 100% oxygen.

4. Discussion

In this review, we attempted to identify the areas of the brain affected by carbon monoxide exposure. A review of 65 papers revealed that CO exposure most prominently affects the white matter, globus pallidus, basal ganglia, and cortex. Each area responds differently to CO exposure; research suggests that the effects of CO exposure can be systemic or specific to a particular system [26]. Therefore, to identify the brain areas affected by CO exposure, doctors are advised to watch for specific symptoms associated with particular lesions.

The table in Appendix A provides a summary of CO lesions by anatomical location, as presented in the literature reviewed. For instance, akinetic-mutism is generally linked to white matter lesions, whereas parkinsonism is usually associated with globus pallidus lesions [19]. Murata, et al. [27] and Lim, et al. [35] noted the usefulness of serial DW MRI plus proton magnetic resonance spectroscopy (1H-MRS) measurements in identifying tissue damage, which may help detect delayed sequelae associated with CO poisoning. Lim, et al. [35], emphasized that monitoring the brain after CO exposure should not be limited to CT scans. Furthermore, the literature revealed that successful diagnosis of CNS lesions caused by CO exposure is achieved not only by checking neurological symptoms via a blood sample, CT scan, and MRI, but also by including long-term monitoring of neuropsychological symptoms using a full battery of neuropsychological tests.

Although some patients made full recoveries after treating CNS lesions, others displayed alexithymia [31], Ganser syndrome [24], and loss of sleep [17], related their specific neurologic lesions. Immediate short-term treatment for CNS lesions caused by CO exposure often involves therapy with 100% hyperbaric oxygen. Long-term treatment may be more effective when combined with neuropsychological treatment and drugs, as some patients exhibit psychological symptoms.

5. Conclusion

This literature review of 65 papers identified the brain's areas most prominently affected by carbon monoxide exposure, the white matter, globus pallidus, basal ganglia, and cortex. Clinicians can use this knowledge when evaluating patients where carbon monoxide exposure is suspected to screen patients and initiate treatment more effectively, especially where advanced imaging is not readily available. In clinical centers where MRI is feasible, clinicians may use this information to review images more efficiently with a better understanding of the brain's locations to evaluate in the setting of possible carbon monoxide exposure.

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