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Review Article

Neurotoxic Effects of Electronic Cigarette Exposure on the Central Nervous System: A Scoping Review

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Abstract

Electronic cigarettes (e-cigarettes) have achieved global adoption, with an estimated 82 million users worldwide and disproportionate uptake among adolescents. Despite marketing as a safer tobacco alternative, e-cigarette aerosols contain neurotoxic constituents including nicotine, flavoring agents, carbonyl compounds, and heavy metals. This review maps empirical evidence on CNS effects of e-cigarette exposure across biological model types. A systematic scoping review was conducted per the Arksey and O'Malley framework and reported per PRISMA-ScR guidelines. PubMed and Scopus were searched in January 2026 for studies from 2015 to 2026 examining quantifiable CNS outcomes following e-cigarette exposure in human, animal, or in vitro models. Data were extracted across eight domains and synthesized narratively. Seventy-four studies met inclusion criteria: 49 animal in vivo (66.2%), 17 human (23.0%), and 8 in vitro (10.8%), spanning 14 countries. Seven CNS outcome domains were identified: neuroinflammation and oxidative stress, blood-brain barrier (BBB) integrity, cognitive and behavioral outcomes, neuroimaging and pharmacokinetics, neurotransmitter systems and electrophysiology, developmental neurotoxicology, and other outcomes. Neuroinflammation and BBB disruption showed high directional consistency. Cognitive impairment, hippocampal volume reductions, and reward circuit reorganization were consistently observed. Developmental studies identified epigenomic reprogramming and disrupted GABAergic interneuron migration. Non-nicotine constituents were independently implicated in CNS toxicity. E-cigarette exposure is associated with a consistent and biologically plausible pattern of CNS harm. The developing brain represents a priority risk population. Current evidence does not support the neurological safety of e-cigarettes; regulatory frameworks should mandate CNS-specific toxicity assessment for electronic nicotine delivery systems.

Keywords: e-*Cigarettes; Central Nervous System; Neurotoxicity; Neuroinflammation; Scoping Review*

Introduction

E-Cigarettes and Vaping: Overview and Global Prevalence

Electronic cigarettes (e-cigarettes), also referred to as electronic nicotine delivery systems (ENDS) or vaping devices, represent a rapidly diversifying category of tobacco-related products that have achieved widespread global adoption since their commercial introduction in the mid-2000s. [1] These devices operate by heating a liquid solution, typically comprising nicotine, propylene glycol, vegetable glycerin, and flavoring agents, to generate an inhalable aerosol, thereby bypassing the combustion process that characterizes conventional tobacco cigarettes. [2] Initially marketed as a harm-reduction alternative and a smoking cessation aid, e-cigarettes attracted considerable consumer interest and regulatory ambiguity in equal measures. [3]

Global prevalence data underscore the scale of the phenomenon: an estimated 82 million individuals used e-cigarettes worldwide as of 2021, with projections indicating continued growth across diverse demographic groups. [4] The burden of use is disproportionately concentrated among adolescents and young adults. In the United States, the 2022 National Youth Tobacco Survey identified approximately 2.55 million middle and high school students as current e-cigarette users, representing the most prevalent form of tobacco product use in this age cohort. [5] Comparable patterns have been documented across Europe, Australia, and Southeast Asia, prompting the World Health Organization to characterize youth vaping as a serious and growing public health challenge. [6]

[Figure 1 approximately here]

Figure 1. Global trends in e-cigarette use: estimated worldwide users, U.S. youth current use, and global youth ever-use prevalence, 2000-2026.

The left y-axis represents estimated global e-cigarette users (millions); the right y-axis represents youth use prevalence (%). The dark blue solid line denotes observed global user estimates with 95% uncertainty intervals (shaded band); the dashed line denotes WHO/industry projections for 2025-2026. The red line denotes U.S. middle and high school current use (%) from the National Youth Tobacco Survey (NYTS) with 95% confidence intervals. The dashed blue line denotes pooled global youth ever-use (%) from meta-analytic estimates. Grey shading (2000-2013) indicates the high-uncertainty modeled period preceding systematic survey infrastructure. Milestone annotations: [A] Commercial e-cigarette market entry in Western countries, 2007-2008. [B] Peak U.S. youth use epidemic; JUUL held >70% of the U.S. market prior to FDA enforcement actions, 2019. [C] COVID-19 pandemic onset; transient attenuation of uptake trends, 2020. [D] WHO estimate exceeds 100 million global users, 2024. Note: Pre-2014 global estimates are modeled from limited cross-national survey data and carry wide uncertainty. Sources: [7-11]

Accumulating toxicological evidence has demonstrated that e-cigarette aerosols contain volatile organic compounds, carbonyl species, ultrafine particles, and trace heavy metals including nickel, lead, and chromium. [12,13]

The CNS as a Target of Toxicological Concern

Among organ systems potentially affected by e-cigarette-derived toxicants, the central nervous system (CNS) constitutes a target of particular concern. The brain's high metabolic rate, lipid-rich architecture, and selectively permeable blood-brain barrier (BBB) do not confer immunity from neuroactive substances present in e-cigarette aerosols. [14]

Nicotine, the primary pharmacologically active constituent of most e-liquid formulations, exerts well-characterized effects on the CNS through its action at nicotinic acetylcholine receptors (nAChRs), modulating dopaminergic reward circuitry, glutamatergic and GABAergic signaling, synaptic plasticity, and neuronal excitability. [15,16] These neurochemical perturbations underlie the addictive properties of nicotine and carry particular developmental significance: the adolescent brain, which remains in active neurodevelopmental maturation until the mid-twenties, exhibits heightened sensitivity to nicotine-induced neuroadaptation, with lasting consequences for cognition, affect regulation, and addiction vulnerability. [17]

Beyond nicotine, experimental evidence implicates the non-nicotine constituents of e-cigarette aerosols as independent mediators of CNS toxicity. E-cigarette aerosol exposure has been shown to induce mitochondrial dysfunction and endoplasmic reticulum stress in human brain microvascular endothelial cells, effects mediated in part through purinergic P2X7 receptor signaling and disruption of mitochondrial oxidative phosphorylation. [18,19] In vivo aerosol exposure studies have reported impaired hippocampal neurogenesis, reduced prefrontal cortical dendritic density, upregulation of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) in brain

tissue, disruption of tight junction protein expression at the BBB, and behavioral alterations including anxiety, depression-like phenotypes, and deficits in spatial memory and cognitive flexibility. [20,21,22,23] Collectively, these findings establish biological plausibility for CNS harm arising from habitual e-cigarette exposure across both developmental and adult contexts.

Rationale and Research Gap

The field currently lacks a comprehensive synthesis specifically mapping CNS and neurotoxic outcomes attributable to e-cigarette exposure. Existing reviews have focused on pulmonary or cardiovascular endpoints or have addressed nicotine neurotoxicity without differentiating ENDS-specific aerosol exposure from conventional nicotine delivery routes. [24,25]

This distinction carries fundamental scientific importance. E-cigarette aerosols represent a chemically distinct and heterogeneous exposure profile, one that varies substantially by device generation, power output, e-liquid composition, and user behavior, and cannot be validly extrapolated from either isolated nicotine or the combustible tobacco literature. [26] Furthermore, the rapid proliferation of device types, from first-generation cig-a-like products to high-powered sub-ohm devices and nicotine salt-based pod systems, and the continuous reformulation of e-liquid flavoring profiles, necessitate an inclusive and contemporaneous evidence mapping approach rather than a narrow, exposure-specific meta-analysis. [27] A scoping review is therefore the most appropriate methodological vehicle to characterize the current landscape of evidence, identify heterogeneity across study designs and biological models, and delineate the boundaries of knowledge in this domain.

Objectives of This Review

The present scoping review was conducted in accordance with the methodological framework described by Arksey and O'Malley [32] and subsequently refined by Levac and colleagues, 28 and is reported in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). 29 The review addresses the following objectives:

(1) To systematically map the available preclinical and clinical evidence concerning CNS and neurotoxic effects of e-cigarette or vaping exposure;

(2) To characterize the range and nature of CNS outcome domains reported across the included literature;

(3) To identify the predominant study designs, biological exposure models, and populations represented in the existing evidence base;

(4) To delineate gaps in current knowledge and propose priorities for future original research, with particular attention to translational limitations and the developmental neurotoxicology of ENDS exposure.

Materials and Methods:

Study Design

This study was conducted as a scoping review in accordance with the methodological framework proposed by Arksey and O'Malley[32] and subsequently refined by Levac et al., 2010. Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [29] . The review was not pre-registered on a public registry; however, the methodology was defined and documented prior to the screening phase. As this is a scoping review rather than a systematic review, meta-analytic pooling of results was not performed.

The overarching research question guiding this review was: What is the current state of evidence regarding the central nervous system (CNS) neurotoxic effects of electronic cigarette (e-cigarette) and vaping exposure across human, animal, and in vitro (CNS-origin) models?

Search Strategy

A systematic literature search was conducted across two major bibliographic databases: PubMed (MEDLINE) and Scopus. Searches were performed in January 2026, with no start-date restriction applied; however, the publication period was limited to January 2015 to the date of search to capture the period following the commercial introduction of modern e-cigarette devices. No restrictions on study design, species, or biological model type were imposed at the database level, consistent with the broad mapping objectives of a scoping review [30] .

Searches combined e-cigarette/vaping terms with CNS outcome terms (neurotoxicity, neuroinflammation, blood-brain barrier) using equivalent Boolean strategies in both databases:

MeSH terms were intentionally omitted from the PubMed strategy to maximize sensitivity and minimize indexing bias, consistent with scoping review methodology [31] . All retrieved records were imported

into Zotero reference management software (version 7.0; Corporation for Digital Scholarship, Vienna, VA), where duplicate records were identified and removed using automated and manual deduplication procedures prior to screening.

Eligibility Criteria

Inclusion Criteria

Studies were eligible for inclusion if they met the following criteria:

Exposure: Studies must have involved direct exposure to e-cigarette aerosol, vaping products, or electronic nicotine delivery systems (ENDS), including pod-based devices, vape pens, and mod-type systems. Studies examining e-cigarette aerosol extracts administered via the inhalation route were eligible; those in which extracts were delivered intravenously, intraperitoneally, or by other non-inhalation routes were not considered to represent authentic vaping exposure.

Outcome: Studies must have measured at least one quantifiable central nervous system outcome. Eligible outcome domains included, but were not limited to: neuroinflammatory biomarkers (e.g., cytokines, microglial activation); blood-brain barrier (BBB) integrity (e.g., tight junction protein expression, transendothelial electrical resistance); neurotoxic metal accumulation; structural or functional neuroimaging findings (e.g., fMRI, PET, MRI morphometry); electrophysiological outcomes; cognitive or behavioral outcomes with established neurobiological correlates; neurotransmitter system alterations; and epigenetic or transcriptomic changes in CNS tissue.

Study design: Original empirical studies were eligible, including controlled in vivo animal studies, human observational or experimental studies, and in vitro studies using cell models of CNS origin (e.g., neuronal cell lines such as SH-SY5Y, primary cortical or hippocampal neurons, brain microvascular endothelial cells, astrocytes, microglia, or brain organoids). In vitro studies employing non-CNS cell lines (e.g., pulmonary epithelial cells, hepatocytes, cardiomyocytes) were excluded unless the model was embedded in a co-culture system with a validated CNS component and CNS-specific outcomes were reported.

Language and date: Articles published in English between January 2015 and January 2026 were eligible.

Exclusion Criteria

Studies were excluded if they met one or more of the following criteria:

No e-cigarette / vaping exposure (Criterion 1): Studies in which the exposure comprised pure (pharmaceutical-grade or research-grade) nicotine solution only, combustible tobacco smoke only, or nicotine/aerosol extract delivered via non-inhalation routes (e.g., intravenous, intraperitoneal, subcutaneous osmotic pump), without a true e-cigarette aerosol inhalation arm.

Irrelevant outcomes (Criterion 2): Studies measuring exclusively abuse liability, reward-related behavioral endpoints without accompanying CNS toxicity measures, cue-reactivity paradigms using visual or olfactory stimuli without real e-cigarette aerosol administration, or self-report mental health scales without objective neurobiological correlations.

Ineligible study design (Criterion 3): Narrative reviews, systematic reviews, meta-analyses, editorials, commentaries, conference abstracts, protocols, and method papers.

Combined exposure / confounding (Criterion 4): Studies in which e-cigarette exposure was inseparably co-administered with another pharmacological or dietary agent (e.g., high-fat diet, alcohol, concurrent illicit drug exposure) and no e-cigarette-alone arm was available for independent data extraction.

Insufficient or non-extractable data (Criterion 5): Studies reporting no extractable quantitative results, hypothesis-only papers, or studies with sample sizes insufficient for meaningful interpretation.

Developmental neurotoxicology studies (including those employing prenatal, perinatal, or early postnatal e-cigarette aerosol exposure models) were retained as an eligible subset and analyzed under a dedicated sub-category (see Section 3.4.6). Although the original exclusion framework listed prenatal/neonatal exposure as a potential exclusion criterion, the mechanistic relevance and volume of available evidence in this domain warranted its inclusion as a distinct thematic area within the review.

Study Selection

Study selection was conducted in two sequential phases by a single reviewer, with systematic application of the predefined eligibility criteria at each phase.

In Phase 1 (Title and Abstract Screening, TA), each record was evaluated against five structured screening questions:

Does the study involve an e-cigarette, vaping product, or ENDS?

Is there a reference to the central nervous system or a related structure (e.g., brain, hippocampus, cortex, neurotransmitter)?

Is a neurotoxic or neurobiological outcome implied (e.g., oxidative stress, neuroinflammation, blood-brain barrier, behavior)?

Does the study appear to be original empirical research (i.e., not a review or commentary)?

Is the study clearly unrelated to CNS outcomes (e.g., exclusively pulmonary or cardiovascular focus)?

Records receiving affirmative responses to at least three of the first four questions, without a clear signal for exclusion on question five, were advanced to full-text review and tagged TA_included. Records not meeting this threshold were tagged with the appropriate TA-level exclusion tag (TA_excluded_notEcig, TA_excluded_noCNS, TA_excluded_review, or TA_excluded_other).
In Phase 2 (Full-Text Screening, FT), retrieved full texts were evaluated against six structured questions:
Is the exposure genuinely e-cigarette or vaping aerosol?

Is a CNS outcome objectively measured (e.g., histology, validated biomarker, neuroimaging, behavioral assay)?

Are results clearly reported (i.e., not hypothesis-only)?

Is the study design sufficiently rigorous (i.e., in vivo or in vitro with appropriate controls)?

Is the full text available in English?

Does the study provide extractable data relevant to this review's research question? Studies receiving affirmative responses to at least four of the six questions were included in the final synthesis and tagged FT_included. Studies not meeting this threshold were tagged with the applicable FT exclusion code (FT_excluded_wrongExposure, FT_excluded_noCNSOutcome, FT_excluded_noData, FT_excluded_methods, or FT_excluded_review).

The study selection process and record flow are presented in the PRISMA-ScR flow diagram (Figure 1).

Data Extraction

A structured data extraction framework was developed a priori, organized across eight thematic domains:
bibliographic and identity information (study ID, author, year, title, journal, DOI, PMID);

study design and sample characteristics (study design, biological model, sample size, age/developmental stage, sex, control group description);

exposure details (exposure type, product details, nicotine concentration, flavoring, administration method, puff protocol, exposure duration, dose metrics);

measured outcomes (outcome category, specific outcome, assay or method, outcome units, effect size, p-value or confidence interval, direction of effect, statistical significance);

mechanisms and biomarkers (biomarkers reported, proposed mechanism);

quality and notation (risk of bias assessment, methodological issues, funding source, conflict of interest);

management notes (extraction date, comments); and risk of bias scoring (domain-specific and overall ratings).

Data were extracted by a single reviewer directly into a structured extraction spreadsheet (Microsoft Excel). For studies reporting multiple exposure conditions, data were extracted separately for each relevant arm. Where necessary information was absent from the article text, this was recorded as 'Not Reported (NR).'

Risk of Bias Assessment

Given the heterogeneity of study designs included in this review (in vivo animal, human observational/experimental, and in vitro), a standardized formal risk of bias tool applicable across all study types was not available. Accordingly, a domain-adapted risk of bias framework was developed for this review, comprising five domains:
Exposure Characterization: whether dose, device, and duration were clearly defined;

Control Group Adequacy: whether a true or appropriate control group was present;

Outcome Measurement: whether outcomes were assessed using objective, validated methods;

Statistical Reporting: whether appropriate statistical tests, p-values, and/or confidence intervals were reported; and

Selective Reporting: whether all intended outcomes were reported.

Each domain was rated as Low Risk, Unclear Risk, or High Risk. Overall risk of bias was determined according to the following algorithm: studies with three or more High-risk domain ratings were classified as High overall risk of bias; studies with two High-risk ratings were classified as Moderate; and studies with zero or one High-risk rating were classified as Low. Risk of bias assessment was performed by a single reviewer and is reported narratively in the results.

Data Synthesis

Given the substantial heterogeneity in biological models, exposure protocols, outcome categories, and measurement methods, quantitative synthesis (meta-analysis) was not appropriate or attempted. Instead, a qualitative thematic synthesis was performed in accordance with standard scoping review methodology [32,30]. Included studies were categorized by biological model type (human, animal, in vitro), and findings were further organized according to CNS outcome domain (neuroinflammation and oxidative stress; blood-brain barrier integrity; cognitive and behavioral outcomes; neuroimaging and pharmacokinetics; neurotransmitter systems and electrophysiology; developmental neurotoxicology; and other/miscellaneous). A narrative synthesis of key findings, directions of effect, and consistency of evidence across studies is presented in Section 3.

Results

Study Selection

The systematic literature search identified a total of 866 records across the two databases. No records were retrieved from trial registers. Following automated deduplication, 259 duplicate records were removed, resulting in 607 unique records being taken forward to title and abstract screening. After application of the pre-specified title/abstract eligibility criteria, 332 records were excluded, leaving 275 reports sought for full-text retrieval. All 275 full-text articles were successfully obtained. On full-text assessment against the eligibility criteria, a further 201 reports were excluded, and 74 studies met all inclusion criteria and were incorporated into the final evidence synthesis. The complete selection process is presented in Figure 1 and summarized in Table 1, following the PRISMA 2020 guidelines 33.

At full-text exclusion, the most frequent reasons were insufficient or non-extractable data (n = 140) and no e-cigarette / vaping exposure (n = 140), followed by ineligible study design (n = 61), irrelevant outcomes (n = 54), combined exposure / confounding / confounding (n = 22), and wrong population / model (n = 21). Summed exclusions exceed excluded reports (n = 201) because many studies received multiple exclusion reasons.

[Figure 2 approximately here]

Figure 2. PRISMA 2020 flow diagram for the systematic scoping review.

Database search conducted January 2026. Records identified: n = 866; after duplicate removal: n = 607; title/abstract screening exclusions: n = 332; full-text screening sought: n = 275; full-text exclusions: n = 201; studies included in synthesis: n = 74.

Study Characteristics

Study Design and Biological Model Distribution

The 74 included studies comprised three broad methodological categories: preclinical in vivo animal studies (n = 49, 66.2%), human studies (n = 17, 23.0%), and in vitro cell-based studies (n = 8, 10.8%). A single study employed a non-human primate (NHP) model. Rodent models were the dominant preclinical platform: mice (predominantly C57BL/6J, Balb/c, and CD-1 strains) were used in approximately 28 studies, and rats (Sprague-Dawley, Fischer 344, and HIV-1 transgenic lines) in approximately 21 studies. In vitro models utilized human cerebral microvascular endothelial cell lines (hCMEC/D3, bEnd.3), primary rodent neurons, microglia, induced pluripotent stem cell (iPSC)-derived neural progenitors, and lung epithelial cell lines.

Human studies employed resting-state and task-based fMRI, PET with nicotine-specific tracers, structural MRI, cognitive test batteries, and cross-sectional epidemiological designs. Sex was treated as a biological variable in 31 studies; several preclinical studies identified significant sex differences in CNS outcome magnitude or direction.

[Figure 3 approximately here]

Figure 3. Annual distribution of included studies by publication year (n = 74).

Bar height is proportional to study count. Dark blue = maximum output year (n = 19, 2025); mid blue = n ≥ 10; light blue = n < 10; grey = no included studies (2017). Dashed trend line represents polynomial fit. The 2019 EVALI crisis and subsequent regulatory scrutiny contributed to sustained research growth from 2020 onward. The 2025 data point includes studies published through the January 2026 search date.

[Figure 4 approximately here]

Figure 4. Biological model distribution of included studies (n = 74).

Left panel: horizontal bar chart showing absolute study counts by model type. Right panel: proportional pie chart. Animal in vivo studies dominate the corpus (n = 49; 66.2%), followed by human studies (n = 17; 23.0%) and in vitro CNS cell-based models (n = 8; 10.8%).

Geographic and Temporal Distribution

The literature spanned 14 countries. The United States contributed approximately 38 studies (51.4%), followed by Italy (n ≈ 6, 8.1%), China (n = 5, 6.8%), and Lebanon, Indonesia, Australia, and nine additional countries contributing smaller numbers.

Temporally, the distribution of publications demonstrated a pronounced upward trend over the review period (2015-2025). Only two studies were published before 2018. Output accelerated markedly from 2018 onward, with the highest annual counts recorded in 2025 (n = 19), 2024 (n = 10), and 2022 (n = 10). The 73% of studies published from 2020 onward reflects the field's rapid expansion in the wake of the global EVALI (e-cigarette or vaping product use-associated lung injury) crisis of 2019, which generated substantial scientific and regulatory attention regarding the broader health consequences of vaping.

Figure 5. Geographic distribution of included studies by country of corresponding author institution (n = 74 studies, 14 countries).

Bar length is proportional to study count. color gradient reflects study volume: dark blue = USA (n = 49); mid blue = Italy (n = 6); medium = China, Jordan (n = 3 each); light blue = Australia, Indonesia, Lebanon (n = 2 each); pale = single-country contributors (n = 1 each). Country attribution is based on institutional affiliation, not study population origin.

Exposure Characteristics

Exposure modalities varied considerably across studies. In vivo studies employed forced inhalation exposure chambers (the most common method), nose-only inhalation systems, and, in human studies, ad libitum use of commercially available e-cigarette products. Self-administration paradigms (electronic vapour self-administration, EVSA) were used in several rodent studies examining addiction-related behavior. In vitro studies exposed cell cultures to whole aerosol condensate, commercially obtained e-liquid extracts, or individual e-liquid constituents.

Nicotine concentrations ranged from 0 to 60 mg/mL; animal models most commonly used 2.4-6 mg/mL, and human studies used 20-59 mg/mL (nicotine-salt). Flavoring was examined in 43 studies (58.1%), with menthol (n = 8) and fruit/sweet flavors (n ≈ 12) most common. Exposure duration ranged from single acute sessions to six months.

The complete characteristics of all 74 included studies, including exposure details, primary CNS outcome domains, and direction of effect for each study, are presented in Supplementary Table S1.

Risk of Bias Summary

Overall risk of bias was rated as low in 72 of the 74 included studies (97.3%) and moderate in 2 studies [34,35] . No study was rated as high overall risk of bias. Detailed domain-level RoB ratings are presented in Table 1.

Domain-level ratings are presented in Table 1. Exposure characterization was rated high risk in 4 studies (5.4%) where aerosol chemistry or dose were inadequately described. Selective reporting showed the highest uncertainty, with 41 studies (55.4%) receiving unclear ratings due to the common absence of pre-registered analysis plans.

Table 1. *Risk of Bias Domain-Level Summary (n = 74 studies)*

RoB*	Lo	Uncle	High
Exposure	60	10	4
Control	61	11	1
Outcome	65	9	0
Statistical	63	7	4
Selective	33	41	0
Overall	72	N/A	2

**RoB = Risk of Bias. 'Moderate' overall RoB was assigned when at least one domain received a high-risk rating without sufficiently compromising the study's core findings.*

CNS Outcomes by Domain

Across the 74 included studies, findings were organized into seven thematic domains: neuroinflammation and oxidative stress, blood-brain barrier integrity, cognitive and behavioral outcomes, neuroimaging and pharmacokinetics, neurotransmitter systems and electrophysiology, developmental neurotoxicology, and other outcomes encompassing brain lipidome, epigenetics, and heavy metal accumulation. Each domain is addressed in turn below.

Table 2. Summary of CNS Outcome Findings by Domain

[Table 2]

Synthesis of evidence across seven thematic CNS outcome domains. 'Consistency' reflects the degree of directional agreement across independent studies within the domain. Study counts include overlapping studies where multiple domains were reported.

Representative biomarkers are listed; see Supplementary Table S1 for study-level details.

Table 2. Thematic synthesis of CNS outcome domains across the 74 included studies. Green = High consistency (directional agreement in ≥75% of studies); yellow = Moderate (50-74%); n = number of studies reporting within the domain (some studies contributed to multiple domains). BBB = blood-brain barrier; NAc = nucleus accumbens; VTA = ventral tegmental area; mPFC = medial prefrontal cortex; DHA = docosahexaenoic acid; EV = extracellular vesicles; MAO = monoamine oxidase; GABA = gamma-aminobutyric acid; iPSC = induced pluripotent stem cells.

Neuroinflammation and Oxidative Stress

Neuroinflammation and oxidative stress were the most consistently reported molecular outcomes. Moshensky et al.[36] showed chronic e-cigarette inhalation upregulated Tnfa, Il1b, and Il6 in the NAc and elevated HMGB1/RAGE in the hippocampus, consistent with sustained neuroimmune activation.

Hammad et al.[37] reported hippocampal and amygdala NF-κB/IL-6 upregulation with anxiety-like behavior during withdrawal. Zelikoff et al.[38] observed microglial activation and reduced Ngfr/Bdnf in adolescent mice, and Church et al.[88] reported elevated hippocampal IL-6 with impaired novel object recognition in perinatally exposed offspring.

Oxidative stress was a key mechanism: Yaseen et al.[39] showed hippocampal SOD, GPx, and GSH depletion reversed by Vitamin E; Bradley et al.[40] found flavored condensate produced dose-dependent microglial toxicity with elevated ROS and cytokines; and Oliver et al.[41] reported third-hand vapor impaired short-term memory and elevated cortical microglial activation.

Blood-Brain Barrier Integrity

Seven studies examined BBB integrity. Sivandzade & Cucullo[42] showed e-cigarette condensate increased ROS, decreased ZO-1 and TEER, and increased paracellular permeability via Nrf2/PPARγ pathway downregulation. Kadry et al.[43] confirmed TEER reductions with metformin protection, implicating mitochondrial pathways. Jadhav et al.[44] found combined nicotine and flavoring produced the greatest ZO-1 downregulation (~43.5%) with insufficient compensatory antioxidant upregulation. Cardenas et al.[45] identified a pro-vasoconstrictive endothelial phenotype, reduced NO and elevated endothelin-1, with cerebrovascular implications. Hammad et al.[46] reported efflux transporter (ABCB1, ABCG2) upregulation in limbic regions, affecting CNS drug bioavailability.

Cognitive and Behavioral Outcomes

Memory impairment was the most consistently documented behavioral endpoint. Spatial memory deficits reversed by Vitamin E [39], reduced novel object recognition with hippocampal synaptic marker loss [47], and perinatal nicotine vapor-induced memory deficits [48,49] were consistently reported. Ponzoni et al.[50] and Delshad et al.[51] documented co-occurring anxiety phenotypes and selective hippocampal impairment, respectively. Anxiety outcomes were context-dependent: Hammad et al.[37] and Martínez et al.[52] reported withdrawal anxiety and elevated ICSS thresholds (anhedonia), while Smith et al.[53] found paradoxically reduced anxiety in perinatally exposed offspring, highlighting exposure timing as a key variable. Reward-related behaviors included menthol-enhanced EVSA responding with NAc dopamine release and mPFC hyperexcitability 54, flavor-dependent dopaminergic effects 55, flavor component-driven reinforcement 56, and cross-sensitisation with $\Delta^{[9]}$-THC 57. Prior vaping increased ischaemic infarct volume by 94% in female rats [58] and worsened cerebral glucose utilisation after stroke [59], indicating e-cigarettes may worsen cerebrovascular outcomes.

Neuroimaging and Pharmacokinetics

Happer et al.[60,61] found earlier e-cigarette onset and greater addiction severity associated with hippocampal volume reduction. Boparai et al.[62] found grey matter reductions in smokers but not e-cigarette users, suggesting differential structural effects.

Resting-state fMRI identified network-level alterations: acute nicotine increased ECN and suppressed DMN activity [63]; chronic use elevated insular synchrony while reducing NAc connectivity [64]; and amygdala-insula rsFC mediated pathways from sleep and depression to e-cigarette use, with blunted lPFC activation predicting alexithymia [35,65].

Task-based fMRI showed vaping transiently improved attention with augmented task-positive BOLD [66], while conventional cigarettes produced greater craving reduction than e-cigarettes [67].

PET studies confirmed dose-dependent β2-nAChR occupancy [68]. Freebase e-cigarettes deliver less brain nicotine than combustibles, while nicotine-salt products achieve equivalent profiles, with females showing higher Cmax and AUC [69,70]. Lactate-salt formulations produce faster brain peak than freebase [71].

Neurotransmitter Systems and Electrophysiology

Nicotine vapor and flavored e-liquids enhanced NAc dopamine release via VTA α4α6* nAChR sensitisation, with a flavor- and sex-dependent effect [55]. High-fat diet compounded self-administration and produced divergent VTA/mPFC electrophysiological effects [72]. Acute CeA activation habituated with chronic exposure while hypothermia persisted [73]. Sanchez et al.[74] identified sex and formulation interactions in reward-aversion circuitry, and Martinez et al.[52] demonstrated hypodopaminergic withdrawal via elevated ICSS thresholds. Cholinergic effects included nAChR subunit modulation by both nicotine-containing and nicotine-free vapor [75], VTA myelination-related gene dysregulation [76], and MAO-A/B inhibition by commercial e-liquids with monoaminergic implications [77]. Menthol condensate reduced spontaneous spike frequency in neuronal networks [78]. Sub-toxic nicotine reduced GLUT1/GLUT3 expression and impaired neuronal glycolytic and mitochondrial function [79].

Developmental Neurotoxicology

Fifteen studies examined developmentally sensitive exposure windows. Walayat et al.[80,81] showed prenatal exposure increased ischaemic vulnerability and produced region-specific DNA methylation changes disrupting axon guidance. Chen et al.[82,83] demonstrated prenatal-equivalent nicotine shifted the E/I neuronal ratio and disrupted bivalent histone marks at developmental gene promoters. Parnell et al.[84] showed e-cigarette aerosol reduced GABAergic interneuron migration via alpha7 nAChR activation during embryonic windows, disrupting cortical inhibitory circuits. Lee et al.[85] demonstrated mTOR pathway activation in the developing brain, and Awada et al.[86] reported hypothalamic glutamatergic disruption following maternal exposure. Perinatal nicotine vapor produced persistent memory deficits and DNA methylation reductions 48,49, frontal transcriptomic disruption 87, and persistent hippocampal neuroimmune abnormalities in offspring [38,88].

Other Outcomes: Brain Lipidome, Epigenetics, and Heavy Metal Accumulation

Additional studies examined cerebrovascular function, brain lipid metabolism, and heavy metal accumulation. Mills et al.[89,90] documented impaired MCA dilation, elevated EV release, and offspring amyloid beta accumulation and circadian clock dysregulation following maternal exposure. Ben Taleb et al.[91] demonstrated acute cerebrovascular impairment in human users, and Kuntic et al.[92] confirmed NOX2-dependent oxidative stress. Cardenia et al.[93] identified an atherogenic brain lipid profile with reduced DHA in exposed rats. Re et al.[94] reported Ni, Cr, and Pb accumulation in mouse brain tissue from device heating coils, identifying metal deposition as a CNS injury mechanism independent of nicotine.

Xu et al.[95] found menthol with nicotine produced distinct hippocampal AMPK/ERK disruption, and Carboni et al.[96] described neuropeptide gene alterations. These findings expand the neurotoxicity landscape to lipidomic remodelling, trace metal deposition, and epigenomic dysregulation.

Discussion

Summary of Key Findings

This scoping review identified 74 empirical studies characterising CNS consequences of e-cigarette exposure across human, animal, and in vitro models. Across all model systems, exposure was associated with neuroinflammation, BBB disruption, cognitive and behavioral impairment, reward circuit reorganisation, neurotransmitter dysregulation, and neurodevelopmental misprogramming.

Neuroinflammation was the most uniformly documented response, with pro-inflammatory cytokine upregulation and antioxidant enzyme depletion observed across acute and chronic exposures. BBB integrity was compromised in all seven studies assessing it. Cognitive findings were dominated by memory deficits, anxiety-like phenotypes, and reward sensitisation, with additional evidence linking vaping to worsened ischaemic brain injury. Human neuroimaging studies documented hippocampal volume reductions, altered resting-state and task-related functional connectivity, and PET-confirmed dose-dependent nicotinic receptor occupancy. Developmental neurotoxicology studies identified epigenomic reprogramming, disrupted GABAergic interneuron migration, and transgenerational neurodevelopmental vulnerability as mechanisms through which early-life vaping exposure may exert lasting effects on brain structure and function. Together, these findings establish robust biological plausibility for CNS harm from e-cigarette use, while also revealing significant translational gaps and methodological inconsistencies that limit the confidence with which preclinical findings can be extrapolated to human populations.

Neuroinflammation and BBB: Converging Evidence

The co-occurrence of neuroinflammation and BBB disruption across mechanistically independent experimental systems constitutes one of the most

internally consistent observations in this review. Critically, these two phenomena are not merely co-reported, they are mechanistically linked. ROS-mediated suppression of the Nrf2/PPARγ cytoprotective axis drives simultaneous upregulation of pro-inflammatory cytokines and downregulation of tight junction proteins, creating a self-reinforcing neuroimmune-vascular cycle. The regional specificity of this pattern, preferentially affecting the hippocampus, nucleus accumbens, and amygdala, is noteworthy given these structures' central roles in memory encoding, reward processing, and affective regulation, providing a mechanistic substrate for the behavioral deficits observed across Section 3.4.3.

The translational significance of the BBB findings is amplified by Hammad et al.'s (2025b) in vivo demonstration of ABCB1 and ABCG2 efflux transporter upregulation in limbic brain regions, a finding with direct clinical implications. Upregulation of these transporters would be expected to reduce CNS penetration of therapeutic agents (including anticonvulsants, antidepressants, and antipsychotics) while potentially facilitating CNS entry of lipophilic aerosol toxicants that are not transporter substrates. This pharmacokinetic vulnerability has received insufficient attention in the clinical literature and warrants prospective investigation in habitual e-cigarette users.

Cardenas et al.'s (2023) identification of a pro-vasoconstrictive, pro-thrombotic endothelial phenotype, characterized by reduced NO bioavailability and elevated endothelin-1, bridges the neuroinflammatory and cerebrovascular literatures. Sustained vasoconstriction in cerebral microvasculature would be expected to reduce regional cerebral blood flow, potentially exacerbating both neuroinflammatory injury and the ischaemic vulnerability documented by Pradhyumnan et al.[58] and Sifat et al.[59].

Human vs. Animal Evidence: Translational Gap

A fundamental tension in the evidence base is the methodological distance between preclinical and human literatures. Animal studies employ forced inhalation paradigms that bear limited resemblance to volitional human use; aerosol concentrations and device characteristics frequently differ from consumer products, complicating dose-response extrapolation.

Human studies are predominantly cross-sectional, with small neuroimaging samples (typically n < 100) that cannot establish causal inference and are confounded by prior tobacco use. PET pharmacokinetic studies [69,70] provide the strongest translational bridge, demonstrating nicotine-salt products achieve brain pharmacokinetics equivalent to combustibles.

For neuroinflammation, BBB disruption, and neurodevelopmental toxicity, direct human evidence remains sparse. Hippocampal volume reductions [60,61] and acute cerebrovascular impairment [91] provide partial validation, but the translational gap remains a key limitation.

Role of Nicotine vs. Non-Nicotine Aerosol Components

A recurrent and unresolved question throughout this review is the relative contribution of nicotine versus the non-nicotine constituents of e-cigarette aerosols to the observed CNS toxicity. The majority of studies in this review employed nicotine-containing e-liquids, and several did not include nicotine-free vehicle controls, rendering it impossible to disentangle nicotine-specific effects from those attributable to propylene glycol, vegetable glycerin, flavoring compounds, carbonyl byproducts, or trace metals.

Where nicotine-free controls were included, vehicle aerosol alone produced significant CNS effects including altered microglial density and nAChR expression [75] and neuroinflammatory disruption [22].

Bradley et al.[40] found flavored e-cigarette condensate significantly more toxic than unflavored controls in microglia, implicating flavoring agents as independent neurotoxic agents. Re et al.[94] reported Ni, Cr, and Pb accumulation in mouse brain tissue, and Cardenia et al.[93] documented atherogenic lipidomic remodelling. These confirm multi-mechanistic CNS toxicity extending beyond nicotine; future studies must include nicotine-free controls and defined flavoring exposures.

Developmental Vulnerability

The developmental neurotoxicology findings in this review constitute what may be its most urgent public health signal. Fifteen studies examined CNS outcomes following prenatal, perinatal, or adolescent e-cigarette exposure, and the evidence across these studies is remarkably consistent in demonstrating that the developing brain is disproportionately vulnerable to e-cigarette-associated harm, with effects that may be both persistent and epigenetically transmitted.

Walayat et al.[81] and Chen et al.[82,83] showed nicotine-mediated DNA methylation and histone modification changes persistently shift neuronal lineage. Parnell et al.[84] identified alpha7 nAChR-mediated GABAergic interneuron migration disruption as a mechanism for cortical inhibitory circuit alteration.

These findings are significant given disproportionate e-cigarette use among adolescents and pregnant individuals. Mills et al.[90] documented offspring amyloid beta accumulation and circadian dysregulation following maternal exposure, raising the possibility of transgenerational neurodevelopmental sequelae.

Limitations of the Available Literature

Several limitations constrain the conclusions. First, exposure heterogeneity is pervasive: studies employed diverse device types, e-liquid formulations, and protocols, making cross-study comparisons unreliable. Many animal studies used aerosol concentrations dissimilar to human use and failed to characterise aerosol composition, precluding dose-response analysis.

Second, longitudinal human CNS data are essentially absent. The cross-sectional designs predominant in human studies cannot establish temporal precedence and are susceptible to confounding by prior tobacco use and comorbid substance use.

Third, sex is inconsistently addressed. Significant sex differences in reward circuit activation and ischaemic vulnerability have been identified [74,58], yet many studies used male-only cohorts, making sex-disaggregated analysis methodologically necessary.

Fourth, validated human biomarkers for CNS-specific e-cigarette toxicity are absent, impeding translation of preclinical findings into clinical surveillance frameworks.

Limitations of This Review

This review was conducted by a single reviewer, introducing a risk of selection and extraction bias that dual-reviewer processes would mitigate.

The search was restricted to two bibliographic databases with English-language publication filters. Studies published in languages other than English, indexed exclusively in regional databases, or published as grey literature, including government reports, regulatory agency documents, and conference proceedings, were not captured. Given the global distribution of the included literature, language-restricted searching may have introduced geographic and institutional publication bias, potentially under-representing research from non-anglophone academic traditions.

The review was not pre-registered on PROSPERO, limiting independent verification of methodological fidelity and auditing of interpretive choices including the decision to include developmental exposure studies.

As a scoping review, this work does not assess effect sizes or weight evidence by quality. The narrative synthesis is descriptive rather than inferential; reporting frequency does not reflect magnitude or clinical relevance.

Implications for Public Health and Future Research

The evidence carries important implications for policy and practice. Regulatory frameworks should mandate CNS-specific toxicity assessment, particularly for flavored products appealing to adolescents, as a precondition for ENDS market entry, with emphasis on developmental exposure scenarios.

Clinicians should communicate that e-cigarettes are not neurologically safe alternatives to combustible tobacco, particularly for adolescents and pregnant individuals. PET evidence confirms nicotine-salt products achieve brain nicotine exposures equivalent to conventional cigarettes, while flavoring agents and heavy metals extend the risk profile beyond nicotine.

Research priorities include: (1) prospective longitudinal neuroimaging studies in human users; (2) mechanistic studies systematically comparing nicotine-containing versus nicotine-free aerosols with defined flavoring compounds; (3) standardisation of animal aerosol exposure protocols; (4) characterization of epigenomic and intergenerational neurodevelopmental effects; and (5) development of peripheral biomarkers of CNS-specific ENDS toxicity.

Conclusion

This scoping review maps CNS and neurotoxic effects of e-cigarette exposure across 74 empirical studies. Neuroinflammation, BBB disruption, cognitive deficits, reward circuit reorganisation, and neurodevelopmental misprogramming emerge as the principal outcome domains.

The adolescent and developmentally exposed brain is identified as the primary priority concern. Non-nicotine aerosol components, flavoring agents, carbonyl species, and trace metals, are implicated as independent neurotoxic agents, with direct relevance to the regulatory treatment of flavored products.

Several critical gaps remain, most notably the absence of longitudinal human CNS outcome data, the limited representativeness of animal exposure paradigms, and the inconsistent treatment of sex as a biological variable. The translational gap between robust preclinical evidence and sparse clinical literature constitutes the most significant obstacle to evidence-based CNS risk communication and regulation.

Notwithstanding these limitations, the weight of evidence synthesized here is sufficient to support a

precautionary public health stance toward e-cigarette use, particularly in populations with developing or vulnerable brains. E-cigarettes cannot be considered neurologically safe on the basis of existing evidence. The scientific and regulatory community should treat CNS toxicity as a primary rather than ancillary concern in the evaluation and governance of electronic nicotine delivery systems.

Patient informed consent
There is no need for patient informed consent.

Ethics committee approval
There is no need for ethics committee approval.

Conflict of interest
There is no conflict of interest to declare.

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Emre Taner Özcan (100%): Design the research, data collection and wrote the whole manuscript.

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