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INPLASY

Association Between Injectable Depot Medroxyprogesterone Acetate and Intracranial Meningioma: Protocol for a Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - N/A.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 4 March 2026 and was last updated on 4 March 2026.

INTRODUCTION

Review question / Objective To systematically assess the association between injectable depot medroxyprogesterone acetate (DMPA) and the risk of intracranial meningioma in adult women compared to oral progestin-containing contraceptive products and non-use comparators.

Rationale Recent pharmacoepidemiologic studies and case reports suggest a potential association between long-term use of progestin-containing medications and increased risk of intracranial meningioma. Injectable depot medroxyprogesterone acetate (DMPA; Depo-Provera) is widely used for contraception and other indications, yet its association with meningioma risk remains incompletely characterized compared to oral formulations. Given the frequency of DMPA use globally and the clinical burden of intracranial meningioma, a systematic synthesis of available observational evidence is needed to inform clinical decision-making and regulatory guidance.

Condition being studied Intracranial meningioma is a typically benign central nervous system tumor arising from the meninges. Progestogenic medications, including injectable DMPA commonly used for contraception, have been implicated as potential risk factors for meningioma development or growth due to hormone receptor expression in meningioma cells. This review aims to quantify the risk associated specifically with injectable DMPA exposure.

METHODS

Search strategy (meningioma*) AND ("medroxyprogesterone acetate" OR "depot medroxyprogesterone" OR Depo-Provera OR DMPA OR MPA).

Participant or population Adult women aged ≥18 years (studies focusing primarily on adults but not explicitly excluding younger participants will be included). Confirmed diagnosis of intracranial meningioma by neuroimaging, histopathology,

surgical records, or validated registry/ administrative codes.

Intervention Injectable depot medroxyprogesterone acetate (DMPA). Exposure occurring at any time prior to meningioma diagnosis; studies with explicit pre-diagnosis lag periods (≥1 year) will be prioritized in sensitivity analyses, but studies without a clearly documented lag window may still be included in the primary ever-use synthesis.

Comparator Oral progestin-containing contraceptive products, including: Progestin-only pills (e.g., norethindrone, levonorgestrel), Combined oral contraceptives (e.g., ethinylestradiol-levonorgestrel), and Oral medroxyprogesterone acetate. Other hormonal contraceptive comparators: Other oral contraceptive formulations containing levonorgestrel, norethindrone, or other progestins, alone or in combination with estrogen. Non-use comparators: Women with no hormonal exposure, no contraceptive use, or documented non-use of hormonal contraceptives, where reported.

Study designs to be included Retrospective cohort studies, Prospective cohort studies, Case-control studies (nested and non-nested), Database or registry-based studies.

Eligibility criteria eyond the PICOS framework, we applied the following additional eligibility criteria. We restricted inclusion to observational studies providing adjusted effect estimates (odds ratios, relative risks, hazard ratios, or incidence rate ratios) for DMPA exposure and meningioma risk; studies reporting only crude estimates were not pooled but could be retained for narrative context. We excluded analyses in which DMPA exposure could not be disentangled from other progestogen formulations or routes (e.g., levonorgestrel intrauterine devices, subdermal implants) and studies in which meningioma outcomes were not clearly separable from other central nervous system tumors. When multiple publications analyzed overlapping datasets, we included the report with the largest sample size, the broadest observation window, and the most detailed characterization of DMPA exposure and outcome ascertainment, and we excluded companion or duplicate analyses to avoid double-counting participants.

Information sources
CINAHL Ultimate (via EBSCOhost)
MEDLINE with Full Text (via EBSCOhost)
Academic Search Premier (via EBSCOhost)
Cochrane Database of Systematic Reviews
PubMed
Grey literature: bioRxiv.org, medRxiv.org
Trial registries: ClinicalTrials.gov, WHO International Clinical Trials Registry Platform
Regulatory documents: Drugs@FDA prescribing information.

Main outcome(s)
Primary outcome:
Diagnosis of intracranial meningioma, confirmed by at least one of the following:
Neuroimaging (MRI or CT)
Histopathology
Surgical records (including surgery-confirmed diagnoses)
Validated registry or administrative diagnostic codes (ICD-9/10).

Additional outcome(s)
Secondary outcomes (when available):
Tumor location (intracranial/cerebral vs spinal; skull base vs non-skull base)
Tumor grade or histologic subtype
Tumor multiplicity.

Data management Search results will be imported into Zotero and Covidence for duplicate removal and study management.

Screening process:
Two reviewers will independently screen titles and abstracts
Two reviewers will independently conduct full-text review
Discrepancies will be resolved through discussion until consensus is reached
A third reviewer will be consulted if consensus cannot be achieved.

Quality assessment / Risk of bias analysis All included studies will be assessed using the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool (Version 2 where applicable), which is appropriate for observational studies of exposures.

Authors will use a GRADE-based framework to rate the overall certainty of evidence for the primary outcome (intracranial meningioma diagnosis) as high, moderate, low, or very low.

Strategy of data synthesis If ≥3 clinically and methodologically comparable studies are identified, we will perform a random-effects meta-analysis using the DerSimonian-Laird method via generic inverse variance in Review Manager (RevMan) 5.4. If statistical pooling is not appropriate due to substantial heterogeneity, limited data, or clinical heterogeneity, we will provide a structured narrative synthesis organized

by study design, exposure definition, and risk of bias.

Subgroup analysis Pre-specified subgroup analyses (if data permit):
Duration of DMPA use (e.g., <1 year, 1–3 years, ≥3 years, or study-specific longest exposure categories)
Cumulative dose (when reported)
Age at first DMPA exposure
Tumor location (intracranial/cerebral-only vs mixed site; skull base vs non-skull base)
Presence or absence of prior cranial irradiation
Outcome ascertainment method (surgery-confirmed vs diagnosis-based using administrative codes)
Active-comparator analyses (DMPA vs other hormonal contraceptives, where studies report parallel estimates vs a shared non-exposed reference).

Sensitivity analysis
Pre-specified sensitivity analyses:
Excluding studies at critical or serious risk of bias
Excluding studies without imaging-confirmed or surgery-confirmed diagnoses
Excluding preprints or grey literature
Restricting to studies with ≥1 year pre-diagnosis exposure lag clearly documented
Excluding individual large database studies that drive substantial heterogeneity (post hoc sensitivity analyses will be transparently labelled as exploratory).

Language restriction English language only. Non-English abstracts will be screened; if potentially eligible, we will attempt to obtain translation or will exclude and document the citation for transparency.

Country(ies) involved United States of America.

Keywords Depot medroxyprogesterone acetate; DMPA; Depo-Provera; Meningioma; Intracranial tumors; Progestin contraceptives; Hormonal contraception; Observational studies; Systematic review; Meta-analysis.

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