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REVIEW

Development and Growth of Intracranial Meningiomas in Transgender Women Taking Cyproterone Acetate as Gender-Affirming Progestogen Therapy: A Systematic Review

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Abstract

Background: Gender-affirming hormone therapy is critical to the management of transgender persons. Cyproterone acetate (CPA) is a synthetic, progesterone-like compound commonly used in high doses as gender-affirming progestogen therapy in transgender women. An association between high-dose CPA and the development and growth of intracranial meningioma, including case reports in transgender women, has been described. This systematic review summarizes these cases at the patient level and discusses their management.

Methods: This systematic review was registered with PROSPERO (CRD42020191965). A detailed search of the PubMed, EMBASE, and Web of Science electronic bibliographic databases was performed (inception—December 20, 2020). Two review authors independently completed screening, data extraction, and risk of bias assessment in duplicate.

Results: Nine records were included describing ($n = 12$) individual case reports and ($n = 35$) intracranial meningiomas. The median age at presentation was 48 years (interquartile range [IQR], 43–55 years), most frequent daily CPA doses were 50 mg/day ($n = 5$) and 100 mg/day ($n = 5$), and the median duration of CPA use was 9.5 years (IQR, 6.5–17.5 years). Multiple meningiomas were common ($n = 7$). For most cases ($n = 10$), surgical resection was the initial preferred management strategy, but two were successfully managed by CPA cessation.

Conclusions: Transgender women receiving high doses of CPA may be at increased risk of intracranial meningioma development and/or growth, although this remains a rare disease. For presumed CPA-associated meningioma, drug cessation appears to be an appropriate management strategy when surgery is not imminently required to manage raised intracranial pressure or prevent neurological deterioration. Given the importance of gender-affirming hormone therapy to transgender persons, a suitable alternative hormone regimen should be offered, although the use of CPA in both high doses and for prolonged periods of time is now in decline.

Keywords: cyproterone acetate; estradiol; gender-affirming hormone therapy; meningioma; transgender

Introduction

Gender-affirming hormone therapy is critical to the welfare of transgender persons. There are three major goals of hormonal therapy prescribed for transgender women. First, to reduce endogenous sex hormone levels, thereby reducing the secondary sex characteristics of the transgender persons' designated gender; second, to replace endogenous sex hormone levels consistent with the transgender persons' gender identity (as per the principles of hormone replacement treatment of hypogonadal patients); and finally, to reduce gender dysphoria.[1] Cyproterone acetate (CPA) has been

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widely prescribed in Europe as gender-affirming progestogen therapy in combination with estradiol, although its utilization for this purpose is in decline or has already stopped in many countries.[1] CPA is a synthetic, progesterone-like drug that displays antiandrogenic properties through competitive inhibition of testosterone binding sites and blockade of testosterone production in the gonads.[2]

Meningiomas are the most common type of primary intracranial tumor, with a preponderance in females.[3] The estimated age-adjusted incidence of meningiomas is 8.8 per 100,000 population per year.[4] Meningiomas are graded by the World Health Organization (WHO) as grade 1 (nonmalignant), grade 2 (atypical), and grade 3 (malignant); over 80% of meningiomas are WHO grade 1.[5] Meningiomas which are symptomatic, fast growing, or causing raised intracranial pressure are commonly managed by surgical resection when possible.[6]

Historically, transgender women have been prescribed CPA at much higher doses (50–100 mg/day) in comparison to current prescribing practices (10–25 mg/day) or doses utilized for other clinical purposes.[1] There are reports of more conventional CPA doses and an association with meningioma growth,[7,8] but an increasing body of evidence suggests that higher doses are associated with greater risk.[9–11] Therefore, transgender women are potentially at greater risk for developing CPA-associated intracranial meningioma.

Several case reports describing transgender women prescribed CPA as gender-affirming progestogen therapy, who also have an intracranial meningioma, have been published since 2007. However, there is a lack of consensus on how cases such as these should be managed as it is a rare phenomenon.

Therefore, the objectives of this review were to (1) identify the number of individual reported cases of transgender women with intracranial meningioma and exposure to CPA, (2) describe the CPA dose and length of exposure for each transgender person, (3) describe the presentation, radiological details, management strategy, and clinical outcome for each transgender person, and (4) describe histopathological features and WHO grade, including estrogen and/or progesterone receptor status, and surgical details, including Simpson grade of resection.

Methods

Study registration

This systematic review is registered with PROSPERO (CRD42020191965), the prospective international register of systematic reviews. Institutional review board approval was not required for this systematic review.

Scope of review

The subtype of this systematic review is one of etiology and risk.[12] The question format is structured as Population, Exposure, Outcome[13] and summarized in Table 1. The included study type for this systematic review is observational.[13] A previous scoping review suggested that all included studies were likely to be case reports only. We elected to include only articles written in the English language due to the feasibility of translation during the study period and those where the full text was available to allow data extraction necessary for analysis.

The population was defined as transgender women (16 years and above) with radiologically suspected or histologically proven intracranial meningioma, with no restriction on whether gender-affirming surgery had been undertaken. Age 16 was chosen to reflect that the guidelines on gender-dysphoric/gender-incongruent persons recognize that adolescents generally have the capacity to give informed consent for partially reversible treatment at this age.[1] Cases of spinal, radiation-induced, or neurofibromatosis type 2

Table 1. Population, Exposure, Outcome Inclusion Criteria

Population	Transgender women (16 years and above, male-to-female) with intracranial meningioma (any WHO histological grade), with or without history of gender-affirming surgery.
Exposure	CPA use as gender-affirming hormone therapy with no restriction on dose or duration or its use in combination with other gender-affirming hormone therapy.
Primary outcome	Definitive primary management strategy for each transgender person: Surgical resection (with or without drug withdrawal or dose change, and monitoring). Defined as an operation with intent to achieve at least subtotal resection as primary management of meningioma. Drug withdrawal/dose modification and monitoring. Defined as withdrawal of drug or change in dose of drug with subsequent monitoring for stabilization and/or reduction in the size of meningioma.
Secondary outcomes	Presentation (verbatim) and clinical outcome (verbatim). Frequency of meningiomas and anatomical location. CPA daily dose (mg/day) and reported duration (years). For surgical cases, WHO grade (1, 2, 3), meningioma subtype (verbatim), extent of resection (GTR vs. STR), estrogen and/or progesterone receptor status (verbatim).

Definition of population, exposure, primary, and secondary outcomes.
CPA, cyproterone acetate; GTR, gross-total resection; STR, subtotal resection; WHO, World Health Organization.

associated meningioma were excluded as they are considered a different disease entity.

The exposure was defined as CPA used as gender-affirming progestogen therapy. No restriction was placed on CPA dose or duration or whether its use was in combination with other gender-affirming hormone medications.

The outcomes of interest included study characteristics (type of publication, year of publication, first author, and country of the first author), characteristics for each transgender person (age at presentation, gender-affirming surgery status, CPA dose and duration of exposure, other associated hormonal treatments), and study results (presentation, individual anatomical details for each meningioma, management strategy for each meningioma, and clinical outcome). For surgical cases, additional data points included the following: (WHO grade, histopathological subtype, Simpson grade dichotomized to gross total resection [Simpson 1–3] vs. subtotal resection [Simpson 4–5], and estrogen/progesterone receptor status).

Search strategy

The following electronic bibliographic databases were searched: PubMed, EMBASE, and Web of Science, initially between inception and August 4, 2020. Electronic searches were rerun on December 20, 2020 to identify records published in the interim period. A detailed search strategy was developed to examine each of the three electronic bibliographic databases. The search strategy takes into consideration alternative descriptions for the concept of transgenderism which other authors may have utilized.[14] The search was initially developed for PubMed and modified for the other electronic databases. The full PubMed electronic search strategy is provided (Supplementary Appendix SA1).

Identifying studies

Search results were downloaded from their respective online databases, and a file for each was uploaded to the online platform Rayyan.[15] Following deduplication of articles, two review authors (C.P.M., S.M.K.) independently screened all titles and abstracts retrieved. Screening was performed on the Rayyan platform independently, with each review author blind to the other's screening decisions. Any titles, which did not achieve concordance, were highlighted within the platform and then discussed between the two review authors and resolved.

Assessment of eligibility

Full-text copies of all articles that appeared to meet the inclusion criteria and articles where a decision could not be confidently made based on title and abstract alone were obtained. Two review authors (C.P.M., S.M.K.) assessed all full-text articles against the study eligibility criteria. Any titles which did not achieve concordance were highlighted within the platform and then discussed between the two review authors and resolved. The complete reference lists of full-text articles which met the inclusion criteria were also screened for further titles not previously identified. Reasons for not meeting eligibility criteria were recorded for excluded records and are provided (Supplementary Appendix SA2).

Data extraction

Data were extracted from all eligible articles in duplicate by two review authors independently (C.P.M., S.M.K.) into a custom-designed data extraction spreadsheet in Microsoft Excel (v16.34; Microsoft, Washington, DC). Variations were again discussed between the two review authors and resolved.

Risk of bias assessment

The methodological quality of included studies was assessed using the tool presented by Murad et al., 2018 for assessing case reports and case series.[16] This was considered an appropriate tool to assess the methodological quality of case reports for inclusion in a systematic review. This tool consists of eight questions across four domains, including selection, ascertainment, causality, and reporting. Risk of bias assessment was performed independently by both review authors (C.P.M., S.M.K.) following data extraction. Studies would not be excluded based on the risk of bias assessment for this systematic review, owing to the limited number of cases in the literature. Variations were discussed between the two review authors and resolved.

Results

Study selection

The electronic search of three online databases generated 46 records. Two further records were identified from other sources. Following deduplication, 29 unique records were dual screened by two review authors independently (C.P.M., S.M.K.). Eighteen records were excluded based on title and abstract alone during the screening process. Eleven records underwent full-text

assessment of eligibility. Two further records were excluded at this stage as both were the wrong publication type (conference abstracts). The reasons for the exclusion of records are provided (Supplementary Appendix SA2). Nine studies were included for analysis (Fig. 1).

Study characteristics

The characteristics of the included studies ($n=9$) are summarized (Supplementary Appendix SA3.) The first eligible study was published in 2007,[17] with five of the most recent publications in the last 4 years. Other than one study from Australia,[18] all other included studies were from Europe. As expected, all nine included studies were case reports from a hospital setting. One study reported on two individual patients,[19] while another reported on three individual patients.[20]

Risk of bias within studies

Risk of bias assessment was performed for each individual case report identified ($n=12$). The maximum score achievable was 8. Every case achieved a minimum score of 5, but regardless, no individual patient within this systematic review would have been removed due to the risk of bias assessment. The risk of bias scores are summarized (Supplementary Appendix SA4).

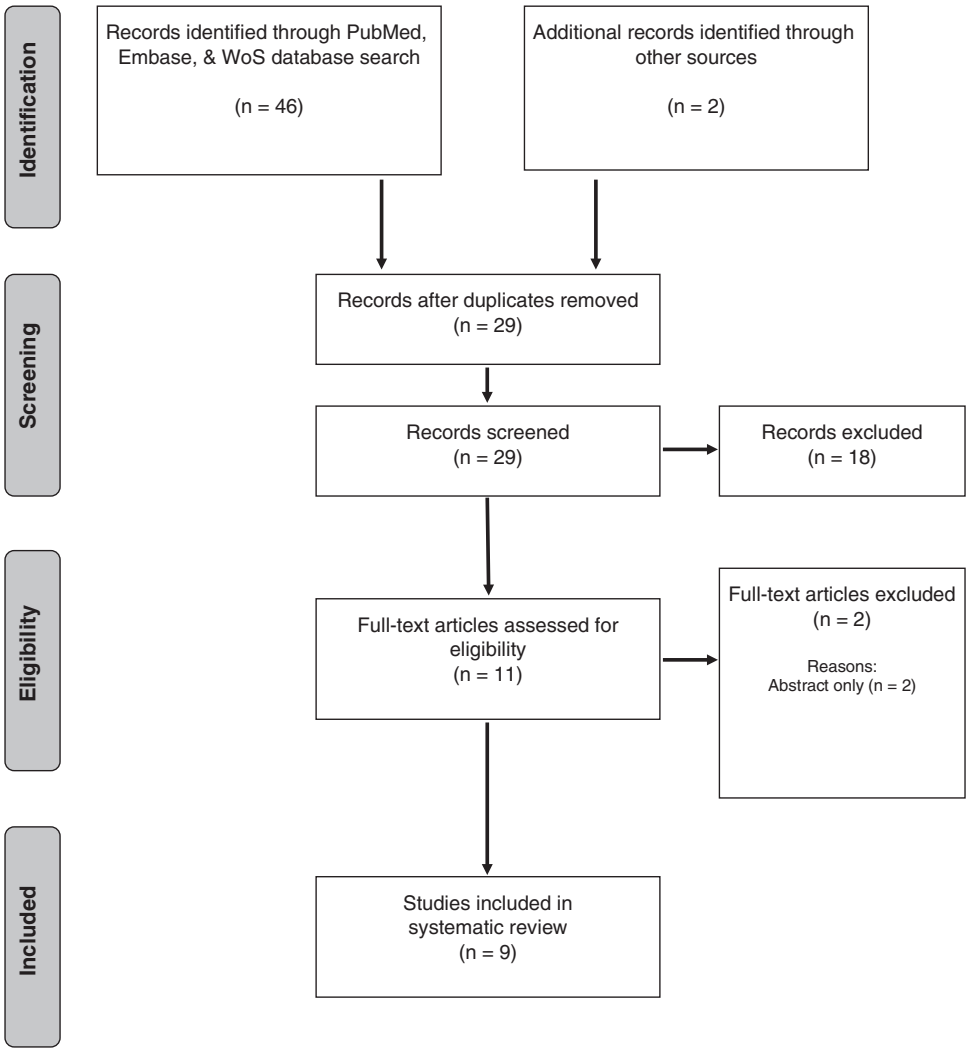

FIG. 1. Study selection flow chart.

Results of individual case reports and associated meningioma

From the 9 included articles, 12 case reports were identified, and information on all individual meningiomas ($n=35$) described in these case reports was collated. Table 2 summarizes the characteristics of each transgender person, while Table 3 summarizes the clinical characteristics of each meningioma (and associated surgical and pathological characteristics where applicable).

Synthesis of individual case reports

Table 4 summarizes each case report included within this systematic review. In summary, the median age was 48 years (interquartile range [IQR], 43–55 years). Eight transgender persons had undergone gender-affirming surgery. Reported doses of CPA were 10, 50, 100, or 200 mg/day. The most commonly prescribed dose was either 50 or 100 mg/day ($n=10$). The median duration of CPA treatment was 9.5 years (IQR, 6.5–17.5 years), but for some transgender persons, treatment with CPA was likely to have been longer than the reported length of exposure. Five transgender persons had a single meningioma, and seven had multiple meningiomas. The majority ($n=10$) were managed upfront with surgical intervention, and most also had CPA stopped at the same time ($n=8$), except for one who had the dose tapered.[19] Two transgender persons were managed by cessation of CPA only without surgical intervention.[21,22]

Synthesis of individual meningioma associated with included case reports

Table 4 summarizes the individual meningioma ($n=35$) described within the case reports included within this systematic review. In summary, 15 meningiomas were managed with surgical resection. The histological assessment showed that the majority ($n=13$) were WHO grade 1, but two were WHO grade 2. One transgender person who required reoperation for recurrence was found to have evidence of transformation to WHO grade 2.[18] Estrogen and progesterone receptor status were inconsistently reported (Table 3).

Discussion

This systematic review identified 9 articles describing 12 individual case reports of high-dose CPA (most frequent doses were 50 mg/day [$n=5$] and 100 mg/day [$n=5$]) and intracranial meningioma development and/or growth in transgender women. Thirty-five individual meningioma were described, and hence, multiple meningiomas were common ($n=7$). For most cases ($n=10$), surgical resection was the initial preferred management strategy. However, two cases were successfully managed by CPA cessation, suggesting that this strategy may alleviate the need for surgical intervention for meningioma under these conditions.

CPA and growth of meningioma in the context of clinical guidelines

Of particular concern is the higher doses of CPA prescribed in the transgender female population. There are reports of more conventional CPA doses and an association with meningioma growth,[7,8] but an increasing body of evidence suggests that higher doses are associated with greater risk.[9–11] A recent French cohort study demonstrated a dose-dependent increase in relative risk of meningioma development.[23] Following this, the European Medicines Agency released an update regarding the risk of meningioma with the use of CPA in February 2020. The recommendations suggest that CPA with daily doses over 10 mg should only be used for androgen-dependent conditions, and only once lower doses have been tried and have failed to show efficacy. CPA should be titrated to the lowest effective dose. Should a meningioma be diagnosed, all medicines containing CPA should be stopped.[24]

More recently, a cohort study of 253,777 females aged 7–70 reported a strong dose-effect relationship between CPA and risk of intracranial meningioma, with a noticeable risk reduction on discontinuation. In addition, subgroup analysis of 10,876 transgender persons identified an incidence of 20.7 per 100,000 person-years versus 0 in the control group of transgender women not exposed.[11] Therefore, transgender women are potentially at greater risk for developing CPA-associated intracranial meningioma, especially if the administered dose is high. However, it is important to note that meningioma remains a rare disease, even when considering the increased risk associated with the use of CPA.

Despite these observations, *de novo* or accelerated growth of meningioma is not yet listed as an increased risk by the Endocrine Society clinical practice guidelines, updated in 2017.[1] The guidelines currently suggest a CPA dose in the range of 25–50 mg/day with hormone level monitoring to avoid overtreatment.[1] However, prescription of CPA at doses greater than 25 mg/day for transgender people is no longer common in most European countries.

Table 2. Individual Case Report Characteristics

Author	No.	Age (years)	GAS	Dose (mg/day)	Duration (years)	Presentation	Meningioma (*n*)	Surgery	CPA (change)	Outcome
Millward et al.[36]	1	69	Y	200	7[a]	Incidental	4	Y	N	Clinically well but mild cognitive difficulties. No recurrence at follow-up, further size decreases in nonoperated meningiomas.
Boer et al.[21]	2	53	Y	50	17	H/A	7	N	Y	Clinically well. Size decrease in three of six meningiomas (one dramatically).
Raj et al.[19]	3	43	Y	50	7[b]	V/L	5	Y	N	Light perception only in R eye. Transgender person wished to continue hormonal therapy. Growth of operated and nonoperated meningiomas at follow-up. Further surgery is scheduled.
Raj et al.[19]	4	48	N	50	21	V/L	4	Y	Tapered	Clinically well, vision improved. Hormones tapered but not stopped. Follow-up not reported.
Mancini et al.[43]	5	41	N	50	9	Incidental	1	Y	Y	No report of clinical condition. No recurrence at 2 years.
Ter Wengel et al.[20]	6	46	Y	100[c]	2[d]	V/L	1	Y	Y	Clinically well. Switched to estradiol. No recurrence at 2 years.
Ter Wengel et al.[20]	7	51	Y	100	25[e]	Delusional	2	Y	Y	Clinically well, improved following surgery. No recurrence at 5 years.
Ter Wengel et al.[20]	8	65	Y	10	19	V/L	6	Y	Y	No report of clinical condition. No regrowth of residual at 3 years, size reduction in some other meningiomas.
Knight and McDonald[18]	9	60	Y	50	10	H/A	1	Y	N	Early recurrence after first surgery, further surgery performed, and hormones then stopped. WHO grade 2, commencing radiotherapy.
Bergoglio et al.[44]	10	35	N	100	4	H/A	1	Y	Y	Clinically well. No recurrence at 1 year.
Cebula et al.[22]	11	48	N	100	10	H/A	2	N	Y	Follow-up demonstrated new tumor growth, after which CPA was stopped. One meningioma radiologically disappeared, larger meningioma shrunk after CPA stopped.
Gazzeri et al.[17]	12	28	Y	100	5	H/A, V/L, P/C	1	Y	Y	Clinical improvement in behavior and vision. No recurrence at 1 year.

Age in years at time of diagnosis. GAS status denoted by (Y) for yes and (N) for no. The dose of CPA is given in milligrams (mg) per day. Duration of CPA use is given in whole years as reported in individual case reports. Presentation is described (H/A) headache, (V/L) visual loss, (P/C) personality change. The number of meningiomas per case report is stated. Surgery as management is denoted by (Y), and stopping/changing CPA as management is denoted by (Y). Outcome is described with reference to clinical outcome and follow-up where possible.

[a]HRT since 1998 but records could only confirm CPA since 2012; hence 7-year duration confirmed but likely 21 years of exposure.

[b]Transgender person had been prescribed HRT for "several years" before GAS, after which CPA dose and duration are confirmed.

[c]Switched to CPA dose of 10 mg/day after 2 years which continued for 3 years.

[d]Total duration was 5 years but with 3 years at a much lower dose.

[e]GAS was documented 35 years prior, with confirmation of CPA use for at least 25 years, but likely much longer.

GAS, gender-affirming surgery; HRT, hormone replacement therapy.

Findings from this systematic review of case reports

This systematic review of 3 online electronic databases identified only 12 individual case reports of transgender women across 9 publications, with evidence of documented exposure to CPA of varying doses and durations and subsequent discovery of intracranial meningioma. This is therefore a rare event. Other than one patient who received 10 mg/day and another who received 200 mg/day, most transgender persons within this cohort received doses of 50 or 100 mg/day, both of which can be considered high doses. The median

Table 3. Individual Meningioma Radiological and Surgical/Pathological Characteristics (Where Applicable)

Author	No.	Location	Surgery	WHO	Subtype	GTR/STR	O/R	P/R
Millward et al.[36]	1.1	L ant clinoid	y	1	Meningothelial	STR	−ve	90% +ve
Millward et al.[36]	1.2	R petrous	n					
Millward et al.[36]	1.3	Olfactory groove	y	2	Chordoid[a]	GTR	15–60% +ve	90% +ve
Millward et al.[36]	1.4	L greater sphenoid wing	n					
Boer et al.[21]	2.1	R sphenoid	n					
Boer et al.[21]	2.2	R cavernous sinus	n					
Boer et al.[21]	2.3	Unknown (small)	n					
Boer et al.[21]	2.4	Unknown (small)	n					
Boer et al.[21]	2.5	Unknown (small)	n					
Boer et al.[21]	2.6	Unknown (small)	n					
Boer et al.[21]	2.7	Unknown (small)	n					
Raj et al.[19]	3.1	Suprasellar	y	1	Not stated	GTR	Lower	High
Raj et al.[19]	3.2	Cribriform plate	y	1	Not stated	GTR	Lower	High
Raj et al.[19]	3.3	R frontal convexity (small)	n					
Raj et al.[19]	3.4	R frontal convexity (large)	y	1	Not stated	GTR	Lower	High
Raj et al.[19]	3.5	Suprasellar	n					
Raj et al.[19]	4.1	L cavernous sinus	y	1	Not stated	STR	−ve	+ve
Raj et al.[19]	4.2	L frontal convexity	y	1	Not stated	GTR	−ve	+ve
Raj et al.[19]	4.3	L temporal convexity	y	1	Not stated	GTR	−ve	+ve
Raj et al.[19]	4.4	R tentorial	n					
Mancini et al.[43]	5.1	L occipital convexity	y	1	Meningothelial	GTR	20% +ve	90% +ve
Ter Wengel et al.[20]	6.1	L ant clinoid	y	2	Not stated	GTR	−ve	Strongly +ve
Ter Wengel et al.[20]	7.1	R tentorial	y	1	Not stated	GTR	Weakly +ve	+ve
Ter Wengel et al.[20]	7.2	Unknown (small)	n					
Ter Wengel et al.[20]	8.1	L sphenoid	y	1	Not stated	STR	+ve	−ve
Ter Wengel et al.[20]	8.2	R frontal convexity	n					
Ter Wengel et al.[20]	8.3	R frontal convexity	n					
Ter Wengel et al.[20]	8.4	L frontal convexity	n					
Ter Wengel et al.[20]	8.5	R parafalcine frontoparietal	n					
Ter Wengel et al.[20]	8.6	R frontoparietal	n					
Knight and McDonald[18]	9.1	L frontal convexity	y	1[a]	Transitional	GTR	1–5% +ve	Weakly +ve
Bergoglio et al.[44]	10.1	Tuberculum sellae	y	1	Meningothelial	GTR	−ve	Strongly +ve
Cebula et al.[22]	11.1	L temporal convexity	n					
Cebula et al.[22]	11.2	L temporal pole	n					
Gazzeri et al.[17]	12.1	Olfactory groove	y	1	Meningothelial	GTR	−ve	Not reported

For each case report, an individual row is ascribed for each meningioma along with a meningioma number. Location is described verbatim. Surgery at the individual meningioma level is denoted by (y) for yes. For surgically managed meningioma, surgical and pathological characteristics are described where possible. WHO grade is stated as 1 or 2 (no grade 3 meningiomas were included in this study).

[a]WHO grade 2 on recurrence. When provided, meningioma histopathological subtype is stated. Resection status is described, dichotomized as GTR equivalent to Simpson grade 1, 2, or 3, and STR equivalent to Simpson grade 4 or 5. When provided, estrogen and progesterone receptor status are described verbatim.

duration of exposure was 9.5 years, but we identified four patients who likely received CPA for longer than stated. Similarly, this can be considered a long exposure time. Fortunately, this prescribing practice is somewhat outdated, and so this cohort likely reflects the consequences of historical practice.

There was a much higher rate of multiple meningiomas in this cohort at 58%, compared to typically between 1% and 10% in the wider meningioma literature.[25] While we cannot be certain of the reason for this, one explanation would be that CPA may exert a global effect on potential meningiomata, encouraging development and growth which may never have occurred, or would not have resulted in the extent of multiplicity seen if not for CPA exposure. Given the observation that CPA cessation results in significant growth reversal,[20,22] we can assume at least that CPA is a growth promoter, but we cannot conclude if CPA is causal for meningioma development.

Furthermore, all 12 transgender persons identified in this systematic review were prescribed estrogen of some preparation. It is unclear whether estrogen exerted independent effects to stimulate meningioma development and/or growth or whether its action is synergistic to CPA. Estradiol has been identified as an enhancer of meningioma cell proliferation *in vivo*,[26] although conflicting results exist as to whether there are increased meningioma growth rates for patients.[27,28]

Reports in the literature also describe a preponderance of CPA-associated meningioma to the skull base, possibly explained by the differing embryonal origin of the skull base meninges, which raises the

Table 4. Summary of Case Report and Meningioma Characteristics and Management

Case report variables	Total ($n = 12$)
Age in years (median, IQR)	48 (43–55)
Gender-affirming surgery, *n* (%)	8 (67)
Dose 10 mg/day, *n* (%)	1 (8)
Dose 50 mg/day, *n* (%)	5 (42)
Dose 100 mg/day, *n* (%)	5 (42)
Dose 200 mg/day, *n* (%)	1 (8)
Duration in years, median (IQR)	9.5 (6.5–17.5)
Single meningioma, *n* (%)	5 (42)
Multiple meningioma, *n* (%)	7 (58)
Managed by surgery, *n* (%)	10 (83)
Managed by CPA cessation only, *n* (%)	2 (17)
Meningioma variables	**Total ($n = 35$)**
Surgically resected, *n* (%)	15 (43)
WHO grade 1, *n* (%)	13 of 15 (87)[a]
WHO grade 2, *n* (%)	2 of 15 (13)
Estrogen receptor positivity, *n* (%)	8 of 15 (53)
Progesterone receptor positivity, *n* (%)	13 of 14 (93)[b]

Age and duration of treatment, both in years are given as median values with associated interquartile range. Frequency of transgender person being prescribed CPA at doses of 10, 50, 100, and 200 mg/day is calculated. Total number of transgender persons to undergo gender-affirming surgery is calculated. Number of transgender persons with single versus multiple meningioma is stated. Number of transgender persons managed by surgery versus CPA withdrawal only is stated. Total number of meningioma surgically resected is calculated. WHO grade of each meningioma is also calculated. Any level of estrogen or progesterone receptor positivity contributed to the frequency count.

[a]One meningioma was Grade 2 on recurrence.

[b]For progesterone receptor positivity, status was not reported for one transgender person, and therefore, the total was ($n = 11$) which was used to calculate percentage for this variable.

IQR, interquartile range.

question of whether the effect of CPA is specific to meningiomata in this region.[29,30] Anatomical location was extracted within this systematic review, but was not reported in all cases; among the 29 reported, 14 (48.3%) were found at the skull base, slightly higher than the expected proportion ($\sim$40%).[31]

In the wider meningioma literature, the recurrence of grade 1 meningiomas is 7–25% and grade 2 is 29–52%.[5] While case reports are limited and follow-up was short, only one case of a WHO grade 1 meningioma recurrence was observed in this systematic review.[18] Of interest, at reoperation, the meningioma demonstrated transformation to WHO grade 2, a phenomenon observed in only 2 out of 100 reoperated cases.[32] This person did not stop taking CPA following surgical resection. To what extent the continued use of CPA had on recurrence and/or WHO grade transformation cannot be concluded. Again, while we cannot be certain, cessation of CPA may have contributed to the lack of recurrence observed in the other operated cases.

Management of CPA associated meningioma growth

An important outcome of this systematic review was to summarize the management option selected for presumed CPA-associated meningioma development and growth in transgender women. Large and/or symptomatic meningioma are usually managed by surgical resection; however, reports have detailed halted growth and even regression of growth when associated with CPA exposure.[7,33–35] This strategy would only seem sensible should there be no concerns regarding critically raised intracranial pressure, risk of clinical deterioration, or permanent neurological disability secondary to delayed surgical management. Ten of the 12 transgender women we identified underwent upfront surgical resection, and only 2 were managed by CPA cessation and monitoring. Seven of the 10 who did undergo surgical resection also had CPA stopped or tapered, but 3 did not. The reasons for not stopping CPA after surgical resection were (1) lack of awareness of the potential implications of continuing CPA (Patient No. 1),[36] (2) patient preference (Patient No. 3),[19] and (3) unspecified hormones continued after surgery, and recurrence after 13 months with only subtotal resection at second operation, after which hormones were stopped (Patient No. 9).[18] In the two largest cohort studies on the association of CPA and meningioma,[11,30] the most frequent management strategy was surgery or radiotherapy.

No studies have described conservative management of this group with CPA cessation or dose reduction. This is of growing importance, with evidence demonstrating considerable limitations in health-related quality of life after treatment for intracranial meningioma.[37] Given the importance of gender-affirming hormone therapy for transgender persons, a suitable alternative to CPA should be offered.

Alternative gender-affirming hormone therapy

Alternatives to CPA have been discussed within the literature, such as Nomegestrol acetate (NOMAC), a progesterone agonist with moderate antiandrogenic effects.[38,39] When NOMAC was used as an alternative to CPA in a reported case of CPA-associated intracranial meningioma, further tumor growth was observed.[40] Interestingly, in three patients receiving NOMAC with meningioma, cessation of NOMAC resulted in 70% tumor volume reduction in the first year of follow-up, suggesting a similar mechanistic effect on tumor growth.[41] Finally, a report of meningioma regression following discontinuation of another progestin, chlormadinone, has

also been described.[42] It would seem convincing that progestin drugs such as NOMAC and chlormadinone are not suitable alternatives to CPA.

Mancini et al., describe switching to a different class of drug following CPA cessation, such as the GnRH analog leuprorelin acetate, which in combination with estradiol did not result in recurrence of the meningioma.[43] Alternatively, micronized progesterone or medroxyprogesterone acetate, more commonly prescribed in North America, do not appear to be associated with meningioma development and/or growth. Dependence for antiandrogens is removed after gonad-removing procedures, so this may be an alternative strategy to eliminate the need for drugs such as CPA.

Risk of bias and limitations

The level of evidence that can be ascertained from case reports only is low. However, in combination with the wider literature, high-quality case reports can allow meaningful conclusions to be drawn. We assessed all 12 case reports individually using a tool specifically designed to assess case reports and case series.[16] Overall, our risk of bias assessments provides reasonable confidence in the association between high-dose CPA in transgender women and meningioma growth, but not causality for meningioma development.

Limitations

The included case reports within this systematic review are limited to those that have been published at the individual person level with sufficient detail to meet the objectives and are therefore more likely representative of transgender females that are symptomatic and subsequently managed in a hospital setting. A specific limitation observed within this systematic review included challenges in defining the exact length of exposure and dose of CPA and a likely underestimation of both. However, the literature does already support a dose-effect response, and the main objective of this systematic review was to summarize management decisions. A final limitation of this systematic review relates to an inability to separate the contribution of CPA-associated growth from potentially independent or synergistic effects associated with estrogen-based gender-affirming hormone therapy that is often prescribed concomitantly. While significant attention has been given to the association between CPA and meningioma, the literature does support an increased risk of meningioma in women who have ever received hormone replacement therapy compared to never (Odds Ratio 1.29, 95% confidence interval 1.03–1.60). Therefore, even estradiol-based preparations may not be without risk.[28]

Recommendations

- A dose-effect association between CPA and intracranial meningioma exists although this remains a rare disease. A thorough medication review should be undertaken to ensure that CPA is always prescribed appropriately or stopped on detection of intracranial meningioma.
- If not immediately indicated, surgery and/or radiotherapy may be reserved for transgender persons who continue to demonstrate meningioma-related symptoms or growth on interval monitoring after CPA cessation or dose reduction.
- Given the importance of gender-affirming hormone therapy to transgender women, if CPA is to be stopped, alternative replacement therapy should be considered.
- While the use of CPA in high doses and for prolonged periods is now somewhat outdated, practice guidelines informing care of the transgender women should be updated to reflect the risk that may exist based on historical prescribing practice.
- If CPA is required, there may be a role for screening before initiating high dose or expected long-term treatment with CPA.
- Wider education of the association between CPA and intracranial meningioma is warranted due to the use of this drug without prescription.

Conclusions

An increasing body of evidence demonstrates an increased risk of intracranial meningioma when higher doses of CPA are prescribed (>25 mg/day). Transgender women have historically been prescribed high doses of CPA, and we present 12 case reports of CPA-associated meningioma development and growth.[17–22,36,43,44] Cessation of CPA when safe to do so may avoid surgical intervention, but this review demonstrates that surgical resection was the mainstay of treatment. Clinicians should be aware of the risk of high-dose CPA and intracranial meningioma in this patient cohort even though this remains a rare disease. If necessary, alternative

gender-affirming hormone therapy should be offered, given the critical importance of these medications to transgender women.

Authors' Contributions

Conception and design C.P.M., S.M.K., A.I.I., A.F.A., C.E.G., Acquisition of data C.P.M., S.M.K., Analysis and interpretation of data C.P.M., S.M.K., Drafting or revising the article C.P.M., S.M.K., A.I.I., M.D.J., A.F.A., C.E.G.

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Supplementary Material

Supplementary Appendix SA1
Supplementary Appendix SA2
Supplementary Appendix SA3
Supplementary Appendix SA4

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Abbreviations Used

CPA = cyproterone acetate
IQR = interquartile range
NOMAC = nomegestrol acetate
WHO = World Health Organization