

Pineal Gland Cysts

An Evidence Synthesis

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Acknowledgements

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Introduction

This report synthesizes evidence on the effectiveness and safety of treatment options for pineal gland cysts, patient experience with treatment and quality of life with pineal gland cysts and how other countries and other provinces within Canada are treating pineal gland cysts.

Purpose

The purpose of this research is to summarize the current evidence on treatment for pineal gland cysts, including when surgery is a necessary and/or effective treatment option.

Research Objectives

The following research objectives will be addressed in this evidence synthesis:

- To summarize the evidence of the safety and effectiveness for various interventions used in clinical management of patients with pineal gland cysts;
- To summarize existing evidence syntheses, guidelines, and Health Technology Assessments on pineal gland cysts;
- To determine current Canadian practice for the clinical management of patients with pineal gland cysts;
- To determine if clinical practice for the management of pineal gland cysts in Alberta aligns with the evidence.

Background Information

Pineal Gland Cysts

The pineal gland is an endocrine gland located between the mesencephalon and the diencephalon of the brain¹. The primary function of this hormone secreting gland is to secrete melatonin, which is associated with circadian rhythms, endocrine function, immune regulation and aging^{2,3}. Pineal gland cysts are characterized as benign lesions forming on the pineal gland. On imaging, these benign cysts of the pineal gland appear as cystic structures with peripheral calcification⁴. While several theories have been proposed, the pathogenesis of pineal gland cysts remains unknown⁴.

Prevalence

The prevalence of these benign lesions remains a topic of interest. A large 2011 study by Al-Holou et al. examined the medical records of 48,417 patients who had magnetic resonance imaging (MRI) of the head⁵. This study estimated the prevalence of pineal gland cysts to be 1.0% among those who had magnetic resonance imaging, with a peak prevalence occurring between the ages of 19-30 years⁵. In this study, the most common indications for imaging were neurological or mental status change, and headaches. The prevalence of asymptomatic pineal gland cysts is estimated to be between 0.2% and 10.8% in healthy individuals⁶. Smaller studies have estimated this prevalence to be closer to 10%, and in autopsy studies this prevalence has been as high as 40%⁷. The higher prevalence in autopsy studies is mainly due to the ability to diagnose very small cysts that are difficult to detect using MRI⁷. Many studies have shown a significant decrease in the prevalence of pineal gland cysts with advancing age in both sexes⁷. Pineal gland cysts are rare in very young children, and frequency peaks during the ages of 19-30 (2% prevalence), then decreases in older patients⁷. Females have a higher prevalence of symptomatic pineal gland cysts than males⁷.

Symptoms

Pineal gland cysts are generally asymptomatic, so cysts with clinical symptoms are considered rare⁷. Symptoms associated with pineal gland cysts vary but may include gaze paresis (including Parinaud's Syndrome), gait disturbances, headache, vertigo, trouble with co-ordination, memory loss, incontinence, papilledema and obstructive hydrocephalus^{4,6}. Symptoms are often caused by

the cyst compressing nearby structures, such as the quadrigeminal plate, cerebral aqueduct, cerebellum, and fornix^{6,7}.

Some studies have shown that cysts with a diameter greater than one centimeter were more likely to be associated with neurological signs and symptoms⁷, while another by Al-Holou et al. found that 50% of their asymptomatic patients had cysts with diameters greater than one centimeter⁵. Due to these conflicting findings, the relationship between the size of the cyst and symptoms is unclear. It has been suggested that the size of a cyst should not influence treatment⁷.

Diagnosis

Due to their high prevalence and asymptomatic nature, pineal gland cysts are often incidental diagnostic imaging findings⁸. While a computerized tomography (CT scan) is generally the first imaging tool for patients with head injuries, Magnetic Resonance Imaging (MRI) is the gold-standard for pineal gland cyst diagnosis and management⁸. Some researchers have noted that diagnosis of pineal gland cysts using only MRI can be difficult, and certainty can only be achieved using histopathological analysis⁸. Other researchers suggest that in most cases pineal gland cysts have common imaging characteristics, and diagnosis is straightforward⁸. Using MRI, pineal gland cysts are round with a thin wall and are well circumscribed⁷. Along with diagnosis using MRI, one study reported on finding a pineal gland cyst using transcranial ultrasonographic examination that was then confirmed using MRI⁸; this is not usual diagnosis practice.

Clinical Management

In asymptomatic adult patients, it is generally accepted that no surgical management or routine follow-up is required⁷. Routine examination and imaging is often recommended for asymptomatic children, specifically those going through puberty in case the cyst changes or begins to cause symptoms⁷. Surgery is only considered for symptomatic patients, and generally excludes patients with chronic headaches in the absence of associated hydrocephalus⁷.

Symptoms of pineal gland cysts may include: headache, hydrocephalus, oculomotor anomalies, convulsion, deteriorating vision, urinary incontinence, facial numbness, dizziness, loss of consciousness, and gait disturbances⁹⁻¹⁴. Surgery is currently the only known treatment for pineal gland cysts; two types of surgical approaches are utilized⁷. These are open craniotomies and

mini-invasive techniques (including stereotactic aspiration and endoscopic approaches)⁷. Different approaches for open craniotomies have also been reported⁷. There is no comparative evidence concerning which approach may lead to better outcomes. Some short-term risks that have been associated with surgery for pineal gland cysts include transient hemianopia, occipital pseudomeningoceles, disconjugate eye movement, facial droop, homonymous hemianopia, and bleeding⁹⁻¹⁴.

CADTH Report

A report published in 2012 by the Canadian Agency for Drugs and Technologies in Health (CADTH) served as a foundation for this research (Table 1). The CADTH rapid review assesses the literature on diagnosis and treatment of pineal gland cysts¹⁵. The report included twelve citations: eight case reports and case series, two case control studies, one prospective and one retrospective cross sectional study¹⁵. The case control studies included in this report, and cross sectional studies concern diagnosis of pineal gland cysts not treatment. For diagnosis, this CADTH review concludes that both transcranial sonography and true fast imaging with steady state precession methods for cyst diagnosis have high reliability and low variability. In addition, the report concluded that the literature on treatment of pineal gland cysts was too limited to draw conclusions on safety, efficacy and cost¹⁵.

Table 1: Summary of CADTH Findings

Organization Year Country	Type of Report	Search Dates	Objectives	Evidence	Conclusions
CADTH ¹⁵ , 2012, Canada	Rapid response report	Jan 1, 2002 – Feb 7, 2012	“The purpose of this report is to review the clinical evidence and clinical practice guidelines regarding the diagnosis and treatment of pineal gland cysts.”	<ul style="list-style-type: none"> • 2 case control studies • 1 prospective cross sectional • 1 retrospective cross sectional • 8 case series and case reports 	“Different surgical approaches for pineal gland cyst treatment were identified in case reports, however the limited nature of this evidence limits the ability to draw conclusions regarding their safety, cost, or efficacy. No evidence-based clinical practice guidelines were identified by the literature search. Best practice for the diagnosis and treatment of pineal gland cysts remains to be determined and would benefit from larger comparative clinical studies.”

Methods

Four research methods were used to answer the objectives of this report: a systematic review of the clinical effectiveness/efficacy of treating pineal gland cysts; a systematic review of patient experiences and quality of life living with pineal gland cysts; a review of previously published Health Technology Assessments and guidelines; and an environmental scan. The methodology used is outlined below with a detailed methodology provided in Appendices A, B and D. The Cochrane Collaboration best practice guidelines and the PRISMA reporting guidelines, accepted standards for scientific rigor, were used for both systematic reviews.

A systematic review was completed to gather evidence on the clinical effectiveness and safety of treatment for pineal gland cysts. The 2012 rapid review by CADTH was used to identify relevant literature published between January 2002 and February 2012. A *de novo* literature search of all major literature databases (MEDLINE, EMBASE, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews HTA Database) was conducted to examine literature from 2012 until January 14th, 2016. Literature from these two searches were combined to capture all relevant literature. Following best practice, published systematic reviews were hand-searched to ensure that all relevant papers were captured in the literature search^{7,16,17}. Data were extracted in duplicate using a standardized data extraction form, and quality assessment was completed in duplicate using the Downs and Blacks checklist¹⁸. Results were summarized narratively.

A systematic review on patient experience, patient quality of life and attitudes towards treatment for individuals living with pineal gland cysts was also completed. Major library databases were searched (Cochrane CENTRAL Register of Controlled Trials, PubMed, Cochrane Database of Systematic Reviews, EMBASE, PsychINFO, CINAHL, SocINDEX, Web of Science) from inception until January, 2016. Inclusion and exclusion criteria outlined in Table 2 were used for the clinical and patient experience systematic reviews.

Table 2: Inclusion and Exclusion Criteria for Published literature

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • For safety and effectiveness review, study must assess one of the following: <ul style="list-style-type: none"> ○ Safety of surgical or other treatment for pineal gland cysts ○ Effectiveness or efficacy of surgical or other treatment for pineal gland cysts • For patient perspective review, study must assess one of the following: <ul style="list-style-type: none"> ○ Patient quality of life, attitudes towards surgical treatment of pineal gland cysts or, patient experience living with pineal gland cysts • English or French language • Human studies • Full-text available • Randomized controlled trial, quasi-randomized trial, observational cohort, case control or case series design 	<ul style="list-style-type: none"> • Did not assess one of the required outcomes for inclusion • Not written in English or French • Animal models • Non-original data • Studies reported only in abstract or as poster presentations • Case reports, editorials, opinions, and reviews

A grey literature search for literature not published in academic databases was performed to search for other HTAs, synthesis reports, and guidelines. Grey literature, including four large health technology assessment organizations (the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technology in Health (CADTH), the California Technology Assessment Forum (CTAF), and Blue Cross Blue Shield Technology Evaluation Centre (BCBS TEC)) and Google were searched up until February 2nd, 2016. Any HTAs identified were hand-searched for mention of other HTAs. The findings were summarized narratively.

An environmental scan was completed to understand the current clinical practice in Alberta and other Canadian jurisdictions from the perspective of the providers. On January 11th, 2016, nine neurosurgeons on the Board of Directors of the Canadian Neurosurgical Society, the professional society for neurosurgeons in Canada, were contacted by email. These neurosurgeons were from across Canada: Alberta (n=3), Ontario (n=2), Quebec (n=1), Nova Scotia (n=1), Newfoundland and Labrador (n=1), British Columbia (n=1), Saskatchewan (n=1), and Manitoba (n=1). They were asked the following questions about pineal gland cysts:

- a. Is surgery used as a treatment in your province?

- i. If so, under what conditions?
- b. What other treatment options are available in your province?

Follow-up questions were asked if clarification was required. The results of this survey have been summarized narratively.

Results

Clinical Effectiveness and Safety

One hundred and twenty-three unique citations were identified. One-hundred and six were excluded, and twenty-nine proceeded to full-text review (twelve from the CADTH review and seventeen from the de novo review). After full-text review, twenty-three studies were excluded leaving six studies in the final analysis (Figure 1).

All six studies assess the effectiveness of surgical treatment in reducing symptoms associated with pineal gland cysts. The included studies were conducted in France⁷, India¹⁰, Australia¹¹, Belgium¹², and Germany^{13,14} (Table 3) beginning in 2002¹², and continuing in 2006¹⁰, 2009¹³, 2013⁷, 2014¹⁴, and 2015¹¹. Five of the six studies are case series^{7,10,12-14}, one is a retrospective chart review¹¹. There is no comparative data reported in the literature. In total, these studies reported data on 89 participants; three participants did not have surgery.

A variety of surgical methods were used in the included studies, including suboccipital transtentorial approach^{7,11}, intraventricular endoscopic marsupialization⁷, infratentorial supracerebellar approach^{10,11,13}, interhemispheric posterior parietooccipital approach¹⁰, and occipital interhemispheric approach¹¹. Keyhole, endoscopic and microsurgery were techniques used.

All studies included only symptomatic patients. Prior to surgery, the included participants suffered from a variety of symptoms. Headache was the most frequent (n=52), followed by hydrocephalus (n=22), visual disturbances (n=21), oculomotor anomalies (n=12), gait disturbances (n=6), dizziness (n=5), nausea or vomiting (n=5), and a number of patients had less common symptoms such as convulsion, and facial numbness.

Of the eighty-three participants who underwent surgery, seventy-nine had complete resolution of symptoms, and no recurrence within the follow-up time (Table 3). Four participants had persistent symptoms. One patient had bilateral blindness before and after the procedure, two participants had headaches and visual deficits before and after surgery, and one participant had a partial resection experienced regrowth of the cyst, although six-years after surgery, it remained asymptomatic.

A number of adverse events were reported amongst the six studies, such as occipital pseudo-minigoceles (n=2)⁷, transient hemianopsia (n=4)⁷, transient disconjugate eye movements (n=12)¹¹, facial droop (n=1)¹¹, left homonymous hemianopia (n=1)¹¹, and bleeding (n=1)¹². All surgery-related adverse events resolved either naturally or through further intervention.

Quality Assessment

This literature is of low quality. Using the Down and Blacks Checklist, the six studies had total scores of 10¹³, 12¹⁴, 13¹⁰, 14^{7,12}, 15¹¹, of a possible 27 points. Most studies were clear in their objectives and outcome measures, all clearly described characteristics of included participants, all reported adverse events, and reported patients lost to follow-up. Confounding was not adjusted for in any of the included studies. The poor quality is predominantly due to the weak study designs of the included studies; five of the six studies are case series with no comparative group, and therefore randomization and controlling are not applicable. The full results of the quality assessment can be found in Appendix C.

Figure 1: Flow chart of included and excluded studies

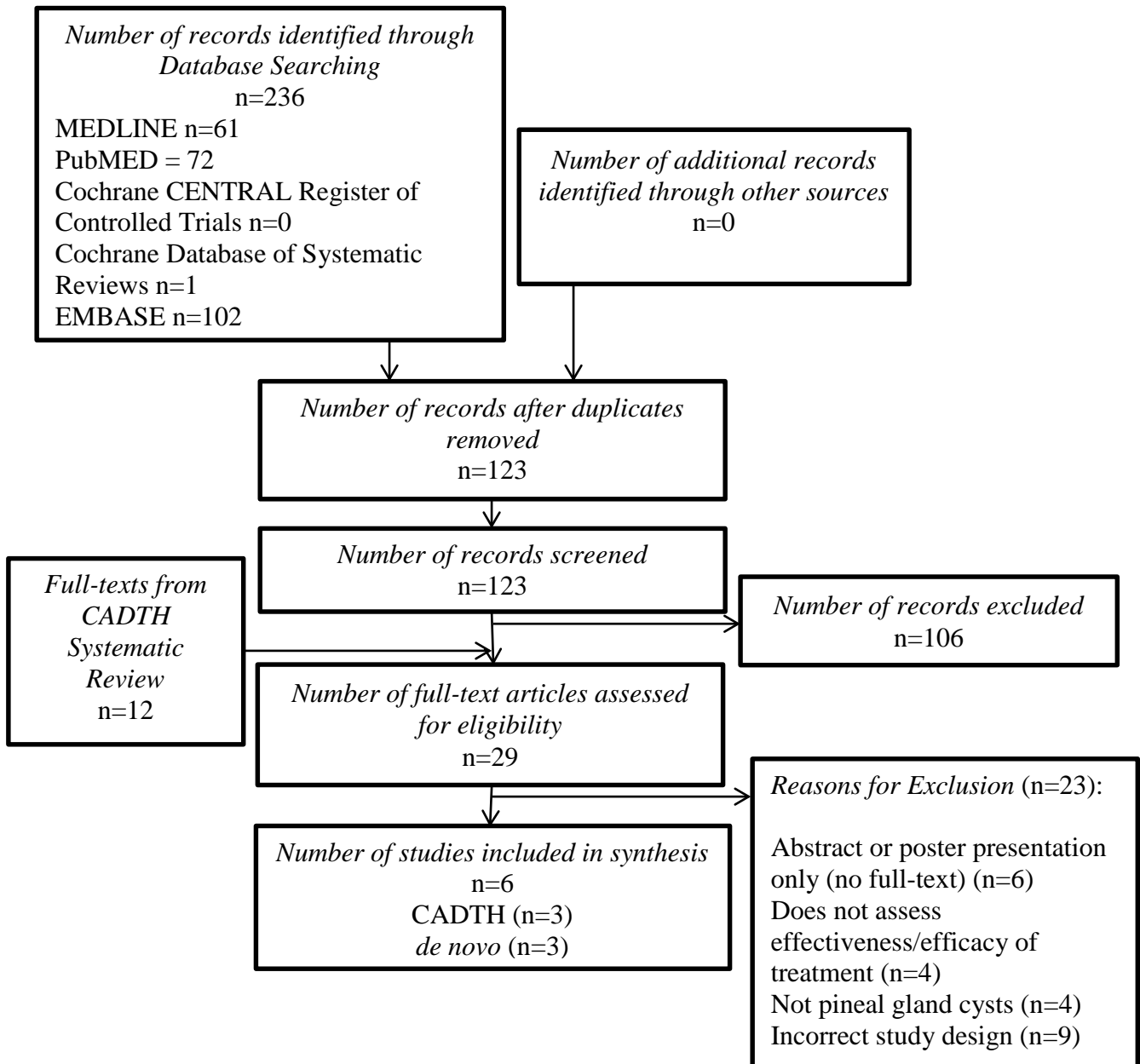


Table 3: Characteristics of Included Studies

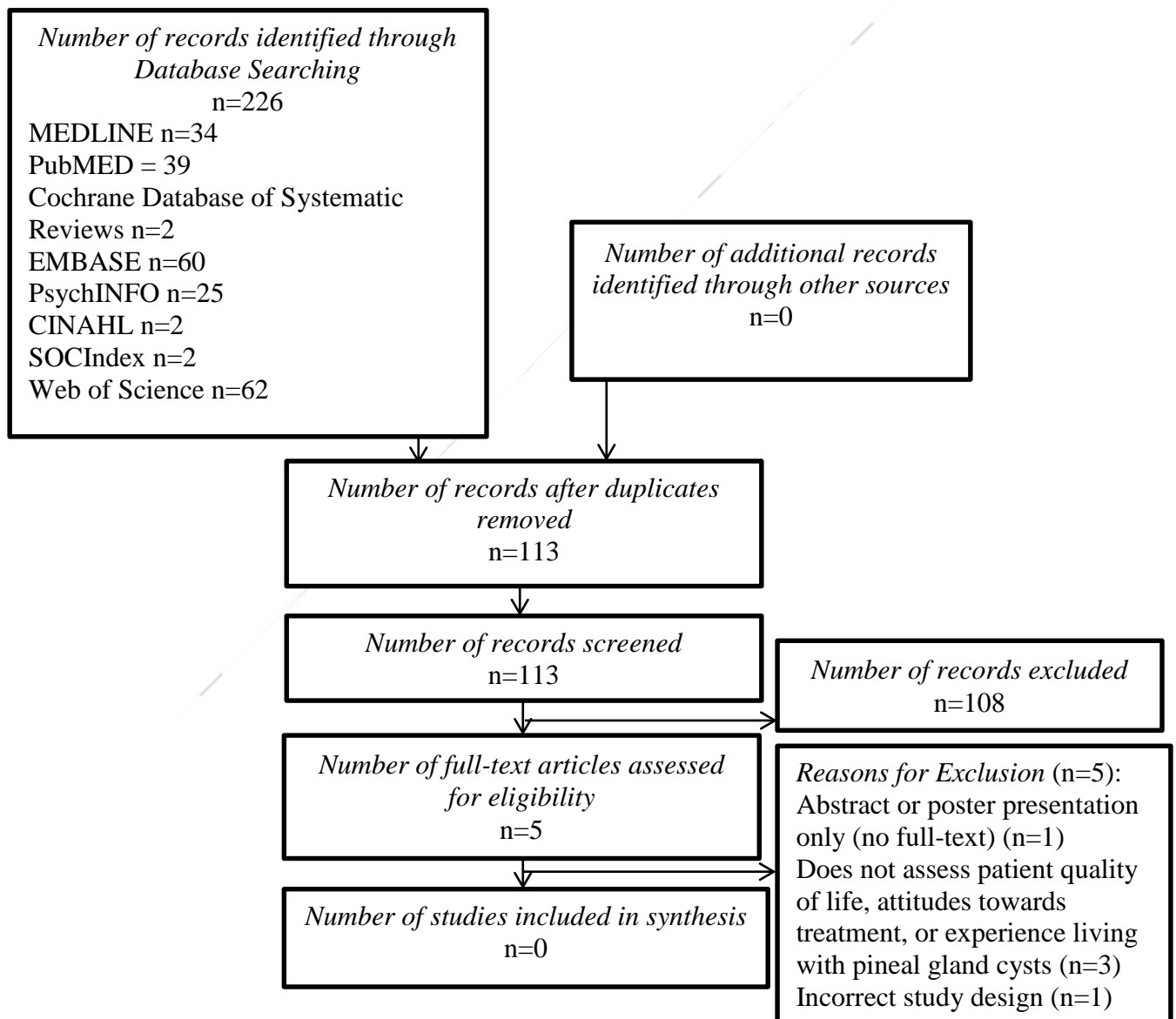
<i>Author, Reference, Year of Publication, Country</i>	<i>Patient Selection</i>	<i>Research methods</i>	<i>Key findings</i>	<i>Safety</i>
Berhouma ⁷ , 2013, France	<p>Total number of patients: 26</p> <p>Patient Selection: Consecutive patients admitted to the Department of Neurosurgery of Pierre-Wertheimer University hospital</p> <p>Inclusion Criteria: Diagnosis of pineal gland cyst</p> <p>Exclusion Criteria: None reported</p> <p>Patient Characteristics: 26 participants (16 females and 10 males) with a mean age of 23.5 years (range 7-49) were included.</p> <p>Symptoms prior to treatment: Intracranial hypertension with obstructive hydrocephalus (n=18), oculomotor anomalies (n=12), parinaud's syndrome (n=2), non-specific headaches (n=2)</p>	<p>Study Design: Case series</p> <p>Intervention(s): Suboccipital transtentorial approach (n=20), intraventricular endoscopic marsupialization associating third ventriculostomy (n=4)</p> <p>Comparator: None</p> <p>No surgery: n=2</p>	<ul style="list-style-type: none"> • Total removal of cyst was successful in 70% of participants. • During a mean follow-up time of 144 months, there were no recurrences 	<p>Adverse events from intervention:</p> <ul style="list-style-type: none"> • Two patients had occipital pseudo-meningoceles which required depletive spinal taps • Four patients experienced transient hemianopia
Desai ¹⁰ , 2006, India	<p>Total number of patients: 24</p> <p>Patient Selection: Patients with pineal region epidermoids who were treated at the Department of Neurosurgery in the King Edward Memorial Hospital between 1992 and 2003</p> <p>Inclusion Criteria: None reported</p> <p>Exclusion Criteria: None reported</p> <p>Patient Characteristics: 24 participants (9 females and 15 males) with a mean age of 29.2 years (range 13-51 years) were included. Patients had experienced symptoms for between 2 months and 4 years (an average of 7 months)</p> <p>Symptoms prior to treatment: Headache (24), ataxia (n=10), deteriorating vision (n=9), giddiness (n=8), apathy and listlessness (n=2), altered sensorium (n=2), impaired memory (n=2), convulsion (n=3), urinary incontinence (n=1), diplopia (n=2), upward gaze restriction (n=1), restricted neck movement (n=1), hemiparesis (n=1), facial numbness (n=1), facial nerve paresis (n=2)</p>	<p>Study Design: Case series</p> <p>Intervention(s): infratentorial-supracerebellar (n=20) and interhemispheric posterior parietooccipital approaches (n=3), both approaches – first and second stage surgery (n=1)</p> <p>Comparator: None</p>	<ul style="list-style-type: none"> • Total resection was successful in 6 participants, in 13 participants, a part of the cyst exterior was left due to neural structures and veins • 23 of the participants did not experience any growth or recurrence. After six years, one participant experienced non-symptomatic growth in a cyst which had been partially resected. • All symptoms were alleviated in 23 participants. One patient had bilateral blindness which remained unchanged. 	<p>Adverse events from intervention:</p> <ul style="list-style-type: none"> • No complications
Kalani ¹¹ , 2015, Australia	<p>Total number of patients: 18</p> <p>Patient Selection: Medical records from Adults who had presented with a pineal gland cyst at the Center for Minimally Invasive Neurosurgery in Australia from 2001-2004.</p> <p>Inclusion Criteria: Diagnosis of pineal Gland Cyst, surgical candidate</p> <p>Exclusion Criteria: Radiographic perioperative complications, or parinaud's syndrome, symptomatic pineal gland cyst non-surgical candidate</p> <p>Patient Characteristics: 18 participants (3.5 females per 1 male) with a mean age of 24 years (range 4-47 years) were included.</p> <p>Symptoms prior to treatment: headaches (n=17), visual disturbances (n=10), gait disturbance (n=5), dizziness (n=5), episodic loss of consciousness (n=2), and hypersomnolence (n=1)</p>	<p>Study Design: Retrospective chart review</p> <p>Intervention(s): supracerebellar, infratentorial or occipital, interhemispheric, transtentorial approach</p> <p>Comparator: None</p>	<ul style="list-style-type: none"> • 19.1 months on average post-operatively, 17 patients showed complete resolution or improvement of symptoms. • No participants experienced worsening symptoms 	<p>Adverse events from intervention:</p> <ul style="list-style-type: none"> • Twelve patients had transient disconjugate eye movements post-operatively • One patient had a temporary facial droop • One patient had left homonymous hemianopia, which resolved within 2 weeks. <p>All symptoms had</p>

				resolved by last follow-up
Michielsen ¹² , 2002, Belgium	<p>Total number of patients: 7</p> <p>Patient Selection: Consecutive adults or children who presented with symptoms of pineal gland cysts at one hospital between 1991 and 2000</p> <p>Inclusion Criteria: Pineal gland cyst, symptoms from pineal gland cyst, any age</p> <p>Exclusion Criteria: None reported</p> <p>Patient Characteristics: 7 participants (6 females and 1 male) with a mean age of 21.6 (range 4-33) were included. Patients had experienced symptoms for between 1 week and 6 years.</p> <p>Symptoms prior to treatment: Headache (n=6), vomiting (n=4), lethargy (n=4), visual deficit (n=2), diplopia (n=1), gait disturbances (n=1), spastic paresis (n=1), anorexia (n=1), springing pupil (n=1), papilledema (n=1); hydrocephalus (n=4)</p>	<p>Study Design: Case series</p> <p>Diagnostic method: CT-scan</p> <p>Intervention(s): Open microsurgery (n=2): Patient is in sitting position, a burr hole is made, a y-shaped incision is made in the dura and the cerebellum is retracted. Cyst is resected.</p> <p>Comparator: Endoscopic technique (n=4): Patient is in supine position, a burr hole is made. Endoscope is inserted and cyst is aspirated and removed.</p> <p>No surgery: n=1</p>	<ul style="list-style-type: none"> • <i>Open microsurgery:</i> surgery took 4-5.5 hours, and patients stayed in hospital for an average of 19 days. Complete resection was successful in one patient. In the other patient, only a subtotal cyst resection was possible due to bleeding. Both patients had symptoms following surgery, including headache, visual deficit, and cervicalgia. • <i>Endoscopy:</i> surgery took a maximum of 30 minutes, and patients stayed in hospital for 3 days. All patients were symptom free following surgery, and there were no recurrences within follow-up (12 to 108 months). 	<p>Adverse events from intervention:</p> <ul style="list-style-type: none"> • No complications reported for endoscopy • Total cyst resection not possible in one open microsurgery patient due to bleeding
Sarikaya-Seiwert ¹³ , 2009, Germany	<p>Total number of patients: 3</p> <p>Patient Selection: Not reported</p> <p>Inclusion Criteria: Pineal gland cyst</p> <p>Exclusion Criteria: Not reported</p> <p>Patient Characteristics: 3 participants who were 16, 16 and 38 years old (all females) were included in this study.</p> <p>Symptoms prior to treatment: headache (3), intermittent diplopia (1), papilledema (1), nausea (1)</p>	<p>Study Design: Case series</p> <p>Intervention(s): Infratentorial/supracerebellar approach</p> <p>Comparator: none</p>	<ul style="list-style-type: none"> • Total resection was successful in all three participants • All three participants were symptom free following surgery 	<p>Adverse events from intervention:</p> <ul style="list-style-type: none"> • No complications
Thaheer ¹⁴ , 2014, Germany	<p>Total number of patients: 11 total (4 with pineal gland cysts)</p> <p>Patient Selection: Not reported</p> <p>Inclusion Criteria: Diagnosis of pineal region tumor (only results for those with pineal gland cysts are included here)</p> <p>Exclusion Criteria: None reported</p> <p>Patient Characteristics: 4 participants with a mean age of 22 (range 14-35) who had pineal gland cysts were included in this study.</p> <p>Symptoms prior to treatment: Not reported</p>	<p>Study Design: Case series</p> <p>Intervention(s): Endoscope assisted infratentorial supracerebellar keyhole approach in the prone position</p> <p>Comparator: None</p>	<ul style="list-style-type: none"> • Total resection of pineal gland cyst was possible in all four participants • All four patients were symptom free after intervention 	<p>Adverse events from intervention:</p> <ul style="list-style-type: none"> • No complications

Systematic Review of Patient Experience

One hundred and thirteen unique citations were identified (Figure 2). One-hundred and eight citations were excluded during abstract review, and five proceeded to full-text review. All five of the reviewed studies were excluded, and therefore, no articles were included in this systematic review. Both reviewers agreed on the inclusion and exclusion of all articles (kappa statistic = 1.0). There is no evidence reporting on the patient experience, quality of life or attitudes with pineal gland cysts.

Figure 2: Flow Chart of Studies Included and Excluded in Review



Grey literature search and other evidence synthesis or guidelines

No additional Health Technology Assessments, guidelines or synthesis reports were found.

Environmental Scan

Of the nine neurosurgeons, three responded with comments. One participant forwarded the survey to seven additional neurosurgeons, none of whom provided responses about pineal gland cysts. Another respondent forwarded the survey to a colleague, but no response was received. The participants who replied were from Alberta, Nova Scotia, and Quebec.

Out of Province

Both the Nova Scotian and Quebecois respondents indicated that surgical procedures for pineal gland cysts are done in their province, but that they are rare; one respondent said that the majority of pineal gland cysts do not require surgical intervention. One of the respondents listed that pineal gland cysts are surgically removed when there is: a) obstructive hydrocephalus, b) progressive symptoms with evidence of an enlarging cyst, c) visual or oculomotor disturbances or d) larger than 7-10mm in size. This neurosurgeon explained that surgery is generally not offered if a cyst is less than 7mm and a headache is reported as the only symptom. Similarly, the other neurosurgeon replied that the conditions under which they would surgically remove a pineal gland cyst include: a) obstructive hydrocephalus, or b) clear symptoms of brainstem compression. Neither neurosurgeon identified any other treatment options available in their province for pineal gland cysts.

Alberta

The respondent from Alberta replied that an estimated two people per year have surgery for pineal gland cysts in the province. The indications for surgery include: an enlarging cyst on MRI; a cyst that is causing aqueductal obstruction and leading to hydrocephalus; or a contrast enhancing solid component on MRI. There are no non-surgical treatment options for pineal gland cysts being used in Alberta. The surgical options available in Alberta are endoscopic trans-ventricular fenestration (neuro-endoscope) or open craniotomy for fenestration/biopsy of the cyst. Since hydrocephaly is almost always present, most operations are done endoscopically. Based on the three responses received, the indications for surgery are consistent in Alberta, Nova Scotia and Quebec.

Discussion

Six studies on the treatment of pineal gland cysts were found. These six studies included eighty-three participants who underwent surgery. Seventy-eight had complete resolution of symptoms, and no recurrence within the follow-up time; four continued to have symptoms and one experienced symptom-free regrowth of the cyst. No studies were found that assessed patient quality of life, attitudes towards treatment, or experience living with pineal gland cysts. Three Canadian neurosurgeons, from each of Nova Scotia, Quebec and Alberta, mentioned similar indications for surgery.

The systematic review on clinical effectiveness retrieved three additional studies that were not included in the CADTH report. However, the literature base on treatment of pineal gland cysts remains weak. There are no studies in the published literature that compare different treatment options or treatment versus no treatment, and no studies assessed the impact of treatment on asymptomatic individuals. The included studies are level three evidence in the hierarchy of research evidence, which is the lowest level of evidence¹⁹.

Despite the weak evidence base, the limited literature is broadly in consensus. The evidence demonstrates that surgical resection of pineal gland cysts relieves all symptoms in 95% of individuals, and that recurrence after surgery is unlikely. Ninety-five percent of the participants in the included studies experienced complete relief of symptoms, and although adverse events were reported post-operation, all were temporary. No significant long-term safety concerns were reported. Broadly, the published literature shows that surgical treatment of symptomatic pineal gland cysts successfully relieves symptoms in nearly all cases and is safe.

Randomized controlled trials are the highest quality evidence. This study design establishes whether a specific treatment is responsible for the outcome achieved as participants are randomly allocated to receive the treatment or the alternative and there are no other differences between treatment groups. However, for treatment of pineal gland cysts, it is unlikely that studies of this type will be conducted. Given that surgery in symptomatic patients can relieve symptoms, it may be perceived as unethical to withhold treatment within the context of a research study. Thus, although case series are low quality evidence, it is unlikely that higher quality evidence will

become available. It is more likely that additional case series, including greater numbers of patients, will be published. These additional case series would be helpful to continue to develop the current evidence base on pineal gland cysts although they will not increase the level of evidence as categorized within the evidentiary hierarchy.

There are no published studies which assess patient quality of life, attitudes towards treatment or experiences living with pineal gland cysts. Future research on patient experiences and quality of life for those with pineal gland cysts would be useful, particularly given the number and variety of symptoms often associated with pineal gland cysts and the invasive nature of surgical treatment.

Conclusions

- The evidence published on treatment of pineal gland cysts is weak; however, the literature is in agreement that surgery for symptomatic pineal gland cysts is effective at relieving symptoms.
- There is no comparative evidence concerning which surgical approach may lead to better outcomes.
- Surgery does not cause significant long-term side-effects
- There is no evidence on patient quality of life, attitudes towards treatment of experiences living with pineal gland cysts.
- Neurosurgeons report that surgery for pineal gland cysts is rare because symptomatic pineal gland cysts are rare. In Nova Scotia, Quebec and Alberta additional fluid in the brain, an enlarging cyst, and signs that the cyst is compressing nearby structures are indications for surgery. Indications for surgery are similar across these three provinces.

Appendices

Appendix A: Survey of National Treatment Practices

Methods

An environmental scan was completed. On January 11th, 2016, nine neurosurgeons on the Board of Directors of the Canadian Neurosurgical Society were contacted by email. These neurosurgeons are from across Canada: Alberta (n=1), Ontario (n=2), Quebec (n=1), Nova Scotia (n=1), Newfoundland and Labrador (n=1), British Columbia (n=1), Saskatchewan (n=1), and Manitoba (n=1). They were asked the following questions about pineal gland cysts:

- a. Is surgery used as a treatment in your province?
 - i. If so, under what conditions?
- b. What other treatment options are available in your province?

Those emailed were invited to forward the survey on to others who may be knowledgeable about the treatment of pineal gland cysts in their province. On January 20th, 2016, a reminder email was sent to all previously contacted participants who had not yet responded. A response was requested by January 25th, 2016.

Appendix B: Detailed Methodology for Systematic Review of Effectiveness and Safety

Methods

A systematic review was completed to gather evidence on the clinical effectiveness and safety of treatment for pineal gland cysts. A previous review conducted in 2012 by CADTH was used to identify relevant literature published prior to 2012. Given the quality of the CADTH report, it was judged that any evidence relating to the current review's objective would have been identified in the CADTH review for the dates covered by that search. Full-texts included in the CADTH review proceeded directly to full-text review. A *de novo* literature search was conducted to examine literature from 2012 to the current date. Literature from these two searches were combined to form a comprehensive understanding of the literature published on treatment of pineal gland cysts. Details of each literature search are provided in the following sections.

CADTH Literature Search

PubMed, EMBASE, the Cochrane Library, and the University of York Centre for Reviews and Dissemination Databases were searched from January 2002 until February 7th, 2012. Search terms such as “pineal gland,” “epiphysis cerebri,” “pineal body,” and “pineal bodies” were combined using the Boolean Operator “or.” Results were limited to English language studies. No other limitations or filters were applied. Details of this search can be found below.

De Novo Literature Search

MEDLINE, EMBASE, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews HTA Database were searched from 2012 until January 14th, 2016. Terms aimed at capturing the clinical condition such as “pineal gland,” “pineal,” “pineal body,” and “pineal glands” were combined using the Boolean Operator “or.” Results were limited to English and French language studies, and animal-model studies were filtered out. A date limit was applied to capture results from 2012 to current, and to exclude studies published prior to 2012. No other limitations or filters were applied. Details of this search can be found below.

Literature Selection

All abstracts from the *de novo* review were screened in duplicate. Abstracts proceeded to full-text review if they assessed at least one of the following criteria: a) safety of surgical or other

treatment for pineal gland cysts b) effectiveness or efficacy of surgical or other treatment for pineal gland cysts. Abstracts were excluded if they did not meet the above criteria, or if they were not written in English or French, presented non-original data, or if they were an editorial, case report, opinion piece, or review. Abstracts selected by either reviewer proceeded to full-text review. This initial screen was intentionally broad to ensure that all relevant literature was captured.

Any abstracts identified by the *de novo* review, and all studies included in the CADTH review were reviewed in full-text by two reviewers. Studies were included if they met all inclusion criteria and failed to meet any of the exclusion criteria presented in Table 4. Any inclusion or exclusion discrepancy between reviewers was resolved through discussion and consensus. A Kappa Statistic for agreement was calculated. Published systematic reviews were hand-searched to ensure that all relevant papers were captured in the literature search^{7,16,17}.

Table 4: Inclusion and Exclusion Criteria for Clinical Effectiveness and Safety

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Assesses at least one of the following <ul style="list-style-type: none"> ○ Safety of surgical or other treatment for pineal gland cysts ○ Effectiveness or efficacy of surgical or other treatment for Pineal Cysts • English or French language • Human studies • Full-text available • Randomized controlled trial, quasi-randomized trial, observational cohort, case control or case series design 	<ul style="list-style-type: none"> • Does not look at safety or effectiveness/efficacy of surgical treatment for pineal gland cysts • Not written in English or French • Animal models • Non-original data • Studies reported only in abstract or as poster presentations • Case reports, editorials, opinions, reviews and qualitative studies

Data extraction and Quality Assessment

For all studies, year of publication, country, study design, intervention, patient selection, inclusion and exclusion criteria, patient characteristics, symptoms prior to treatment, key findings, and safety were extracted in duplicate using standardized data extraction forms. Discrepancies between reviewers during data extraction were resolved through consensus.

During data extraction, quality assessment using the Downs and Blacks checklist¹⁸ was completed in duplicate. Using this checklist, each study was assessed based on 27 criteria, widely covering areas reporting quality, external and internal validity, and power. Studies are assigned a value of “1” if they meet the question criteria, “0” if they do not or if it is not possible to determine whether they meet the criteria; with one exception where one question may be given “2” points. In some cases, a question may not be applicable, due to study design, and in this case not applicable (NA) is used. Any discrepancy between reviewers on quality assessment was resolved through discussion and consensus.

PRISMA guidelines and reporting standards were used.

CADTH Clinical Effectiveness and Safety Search Strategy

PubMed strategy

Set #1: Pineal gland cysts

(Pineal gland[MeSH] OR “Epiphysis Cerebri”[tiab] OR “pineal body”[tiab] OR “pineal bodies”[tiab] OR “pineal gland”[tiab] OR “pineal glands”[tiab])

AND (Cysts[MeSH] OR cyst[tiab] OR cysts[tiab])

EMBASE strategy

Set #1: Pineal gland cysts

Pineal body/

(pineal gland OR pineal glands OR epiphysis cerebri OR pineal bodies OR pineal organ OR glandula pinealis OR corpus pineale).ti,ab

AND

Cyst/

OR

(cyst OR cysts).ti,ab

De Novo Pineal Cysts Clinical Effectiveness and Safety Search Strategy (January 2016)

MEDLINE

1. Pineal Gland/

2. (epiphysis cerebri or corpus pineale or glandula pinealis or pineal body or pineal bodies or pineal gland or pineal glands or pineal organ*).tw.
3. pineal.tw.
4. 1 or 2
5. Cysts/
6. (cyst or cysts).tw.
7. 5 or 6
8. 4 and 7
9. 3 and 7
10. 8 or 9
11. limit 10 to (english or french)
12. limit 11 to animals
13. limit 11 to (animals and humans)
14. 12 not 13
15. 11 not 14
16. limit 15 to yr="2012 -Current"

PubMed

1. pineal gland[MeSH Terms]) OR (epiphysis cerebri[Title/Abstract] OR corpus pineale[Title/Abstract] OR glandula pinealis[Title/Abstract] OR pineal[Title/Abstract] OR pineal body[Title/Abstract] OR pineal bodies[Title/Abstract] OR pineal gland[Title/Abstract] OR pineal glands[Title/Abstract] OR pineal organ*[Title/Abstract])
2. (cysts[MeSH Terms]) OR (cyst or cysts)
3. 1 and 2
4. Limit 3 to Publication date from 2012/01/01 to 2016/12/31; English; French

EMBASE

1. pineal body tumor/
2. pineal body/
3. (epiphysis cerebri or corpus pineale or glandula pinealis or pineal body or pineal bodies or pineal gland or pineal glands or pineal organ*).tw.
4. pineal.tw.
5. 1 or 2 or 3 or 4
6. cyst/ or brain cyst/
7. (cyst or cysts).tw.
8. 6 or 7
9. 5 and 8
10. limit 9 to (english or french)
11. limit 10 to animal studies
12. limit 10 to (human and animal studies)
13. 11 not 12
14. 10 not 13
15. limit 14 to yr="2012 -Current"

Cochrane CENTRAL

1. Pineal Gland/
2. (epiphysis cerebri or corpus pineale or glandula pinealis or pineal body or pineal bodies or pineal gland or pineal glands or pineal organ*).tw.
3. pineal.tw.
4. 1 or 2
5. Cysts/
6. (cyst or cysts).tw.
7. 5 or 6
8. 4 and 7
9. 3 and 7
10. 8 or 9
11. limit 10 to (english or french)
12. limit 11 to animals
13. limit 11 to (animals and humans)
14. 12 not 13
15. 11 not 14
16. limit 15 to yr="2012 -Current"

Cochrane Database of Systematic Reviews

HTA Database

1. (epiphysis cerebri or corpus pineale or glandula pinealis or pineal body or pineal bodies or pineal gland or pineal glands or pineal organ*).tw.
2. pineal.tw.
3. 1 or 2
4. (cyst or cysts).tw.
5. 3 and 4
6. limit 5 to yr="2012 -Current"

Appendix C: Quality Assessment of Clinical Effectiveness and Safety Studies using the Downs and Blacks Checklist

Question:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
Berhouma ⁷	1	1	1	1	0	1	0	1	1	0	1	UTD	1	0	0	1	NA	1	1	1	1	NA	0	0	0	UTD
Kalani ¹¹	1	1	1	1	0	1	1	1	1	0	1	UTD	1	0	0	1	NA	1	1	1	1	NA	0	0	0	UTD
Thaher ¹⁴	0	0	1	1	0	1	0	1	1	0	0	UTD	1	0	0	1	NA	1	1	1	1	NA	0	0	0	1
Desai ¹⁰	0	1	1	1	0	1	0	1	1	0	1	UTD	1	0	0	1	NA	1	1	1	1	NA	0	0	0	UTD
Michielsen ¹²	1	1	1	1	0	1	0	1	1	0	1	UTD	1	0	0	1	NA	1	1	1	1	NA	0	0	0	UTD
Sarikaya-Seiwert ¹³	1	0	1	0	0	0	0	1	1	0	0	UTD	1	0	0	1	NA	1	1	1	1	NA	0	0	0	UTD

UTD: Unable to Determine

Appendix D: Pineal Gland Cysts Patient Experiences Detailed Methods and Search Strategy

Methods

A systematic review was completed. Cochrane CENTRAL Register of Controlled Trials, PubMed, Cochrane Database of Systematic Reviews, EMBASE, PsychINFO, CINAHL, SocINDEX, Web of Science were searched from inception until January, 2016. Terms describing the clinical condition, such as “pineal gland,” “pineal cysts,” “pineal cyst,” and “pineal body” were combined using the Boolean operator “or.” These terms were then combined using the Boolean Operator “and” with terms such as “quality of life,” “experience,” “perspective,” “grounded theory,” “focus groups,” and “qualitative research.” Results were limited to French and English language, and non-animal studies.

All abstracts were screened in duplicate. Abstracts proceeded to full-text review if they met at least one of the following criteria: a) patient quality of life b) attitudes towards surgical treatment of pineal cysts or c) patient experience living with pineal gland cysts. Abstracts were excluded if they did not meet the above criteria, or if they were not written in English or French, presented non-original data, or if they were an editorial, case report, opinion piece, or review. Abstracts selected by either reviewer proceeded to full-text review. This initial screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after abstract review proceeded to full-text review by two reviewers. Studies were included if they met all inclusion criteria and failed to meet any of the exclusion criteria presented in Table 5. Any inclusion or exclusion discrepancy between reviewers was resolved through discussion and consensus. A Kappa Statistic for agreement was calculated.

Table 5: Inclusion and Exclusion Criteria for Patient Perspectives Systematic Review

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none">• Assesses at least one of the following:<ul style="list-style-type: none">○ Patient quality of life, attitudes towards surgical treatment of pineal gland cysts or, patient experience living with pineal gland cysts• English or French language• Human studies• Full-text available	<ul style="list-style-type: none">• Does not look at patient quality of life, attitudes towards treatment of pineal gland cysts, or patient experiences living with pineal gland cysts• Not written in English or French• Animal models• Non-original data• Studies reported only in abstract or as poster presentations• Editorials, case reports, opinions and reviews

MEDLINE

Cochrane CENTRAL Register of Controlled Trials

1. Pineal Gland/
2. (epiphysis cerebri or corpus pineale or glandula pinealis or pineal body or pineal bodies or pineal gland or pineal glands or pineal organ*).tw.
3. pineal.tw.
4. 1 or 2
5. Cysts/
6. (cyst or cysts).tw.
7. 5 or 6
8. 4 and 7
9. 3 and 7
10. 8 or 9
11. limit 10 to (english or french)
12. limit 11 to animals
13. limit 11 to (animals and humans)
14. 12 not 13
15. 11 not 14

16. "Quality of Life"/
17. (experience* or perception* or perspective* or preference* or "quality of life" or satisfaction).tw.
18. exp qualitative research/
19. grounded theory/
20. focus groups/ or interviews as topic/
21. (qualitative or focus group* or interview*).tw.
22. 16 or 17 or 18 or 19 or 20 or 21
23. 15 and 22

PubMed

1. Pineal Gland[MeSH]
2. (epiphysis cerebri or corpus pineale or glandula pinealis or pineal body or pineal bodies or pineal gland or pineal glands or pineal organ*)[tiab]
3. pineal[tiab]
4. 1 or 2
5. Cysts[MeSH]
6. (cyst or cysts)[tiab]
7. 5 or 6
8. 4 and 7
9. 3 and 7
10. 8 or 9
11. limit 10 to (english or french)
12. limit 11 to animals
13. limit 11 to (animals and humans)
14. 12 not 13
15. 11 not 14
16. "Quality of Life"[MeSH]
17. (experience* or perception* or perspective* or preference* or "quality of life" or satisfaction)[tiab]
18. exp qualitative research[MeSH]

19. grounded theory[MeSH]
20. focus groups[MeSH] or interviews as topic[MeSH]
21. (qualitative or focus group* or interview*)[tiab]
22. 16 or 17 or 18 or 19 or 20 or 21
23. 15 and 22

Cochrane Database of Systematic Reviews

HTA Database

1. (epiphysis cerebri or corpus pineale or glandula pinealis or pineal body or pineal bodies or pineal gland or pineal glands or pineal organ*).tw.
2. pineal.tw.
3. 1 or 2
4. (cyst or cysts).tw.
5. 3 and 4
6. (experience* or perception* or perspective* or preference* or "quality of life" or satisfaction).tw.
7. (qualitative or focus group* or interview*²).tw.
8. 6 or 7
9. 5 and 8

EMBASE

1. pineal body tumor/
2. pineal body/
3. (epiphysis cerebri or corpus pineale or glandula pinealis or pineal body or pineal bodies or pineal gland or pineal glands or pineal organ*).tw.
4. pineal.tw.
5. 1 or 2 or 3 or 4
6. cyst/ or brain cyst/
7. (cyst or cysts).tw.
8. 6 or 7
9. 5 and 8

10. limit 9 to (english or french)
11. limit 10 to animal studies
12. limit 10 to (human and animal studies)
13. 11 not 12
14. 10 not 13
15. patient satisfaction/ or patient attitude/
16. psychological aspect/
17. exp "quality of life"/
18. patient preference/
19. exp qualitative analysis/ or exp qualitative research/
20. grounded theory/ or naturalistic inquiry/
21. exp interview/
22. (experience* or perception* or perspective* or preference* or "quality of life" or satisfaction).tw.
23. (qualitative or focus group* or interview*).tw.
24. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 14 and 24

PsycINFO

1. Pineal body/
2. (epiphysis cerebri or corpus pineale or glandula pinealis or pineal).tw.
3. 1 or 2
4. (cyst or cysts).tw.
5. 3 and 4
6. limit 5 to (english or french)

CINAHL

1. (MH "Pineal Gland") OR TI (epiphysis cerebri or corpus pineale or glandula pinealis or pineal) OR AB (epiphysis cerebri or corpus pineale or glandula pinealis or pineal)
2. MH "Cysts") OR TI (cyst or cysts) OR AB (cyst or cysts)
3. 1 and 2

SocINDEX

1. epiphysis cerebri or corpus pineale or glandula pinealis or pineal[All Fields]
2. cyst or cysts[All Fields]
3. 1 and 2

Web of Science

1. (epiphysis cerebri or corpus pineale or glandula pinealis or pineal)[Topic/Title]
2. (cyst or cysts)[Topic/Title]
3. 1 and 2
4. (experience* or perception* or perspective* or preference* or "quality of life" or satisfaction)[Topic/Title]
5. (qualitative or focus group* or interview*)[Topic/Title]
6. 4 or 5
7. 3 and 6

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