## Appendix 2. Evidence Map

### CLINICAL CONSENSUS NUMBER 7

The Use of Cannabis Products for the Management of Pain Associated with Gynecologic Conditions

<table>
<thead>
<tr>
<th>RECOMMENDATION STATEMENTS</th>
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<tr>
<td>• Better quality data on the use of cannabis products are needed. There are insufficient data to make a recommendation regarding the use of these products for management of pain associated with gynecologic conditions.</td>
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<td>• Clinicians should be aware of the possibility of patients' use of cannabis products for pain management and be prepared to counsel them about the theoretical benefits based on the endocannabinoid pathway, potential adverse effects, and the limitations of the data on the use of the cannabis products for the management of gynecologic pain.</td>
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<td>• Limited, low-quality survey data show that cannabis use may lead to decreased use of opioids. However, more data are needed before cannabis products can be substituted for other pain medications.</td>
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### SUPPORTING EVIDENCE

<table>
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<tr>
<th>Category I</th>
<th>Category II</th>
<th>Category III</th>
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<tbody>
<tr>
<td><strong>Systematic Reviews</strong></td>
<td><strong>Observational studies</strong></td>
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<td>Liang 2022: Survey data showed that most women reported that cannabis improved pain from numerous gynecologic conditions. Cohort studies and an RCT using PEA-combination medications reported pain reduction. However, interpretation of the studies is limited due to varying cannabis formulations, delivery methods, and dosages that preclude a definitive statement about cannabis for gynecologic pain relief.</td>
<td>Allam 2022: Expression of CB1 and CB2 were determined by immunohistochemistry, immunoblotting, and gene expression studies. Intense expression for CB1 and CB2 was detected in the epithelial cells in ovarian endometriotic lesions. Compared with stroma in ovaries with endometriotic lesions, the expression of CB1 and CB2 was significantly higher in the epithelial cells in endometriotic lesions in the ovary (P&lt; 0.0001 and P&lt; 0.05, respectively). Immunoblotting and gene expression assays showed similar patterns for CB1 and CB2 protein andCNR1 (gene encoding CB1) andCNR2 (gene encoding CB2) gene expression. These results suggest that ovarian endometriotic lesions express CB1 and CB2 receptors, and these lesions may respond to cannabinoids as pain medication.</td>
<td>Wadsworth 2022: Between 14–33% of cannabis consumers in Canada and the US reported using cannabis to manage headaches or pain. Of these consumers, 79% and 78%</td>
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respondents in Canada; 80% and 83% in US illegal states; and 83% and 84% in US legal states, respectively, reported cannabis use for pain relief instead of opioids or prescription pain medication. There was little evidence of an association between the legal status of recreational cannabis and cannabis use for pain relief instead of opioids or prescription pain medication, among Canadian (AOR=0.98, 95%CI: 0.78, 1.22) and US respondents (AOR=1.11, 95% CI: 0.96, 1.28).

Armour 2021: This was a cross-sectional online survey of those using cannabis for health-related conditions, with a subset of those reporting a diagnosis of endometriosis and/or polycystic ovary syndrome. Two hundred thirteen valid responses were analyzed. Mean age of respondents was 32 years and 79.8% were current cannabis users. The most common outcomes that cannabis was used for were to improve pain relief (95.5%) and to improve sleep (95.5%). Respondents reported that their symptom was “much better” for pain (81%), sleep (79%), and nausea or vomiting (61%). Over three-quarters (81.4%) indicated cannabis had reduced their normal medication usage. Over half (59%) were able to completely stop a medication, most commonly (66%) analgesics. Opioids (40%) were the most common class of analgesic stopped.

Carrubba 2021: A cross-sectional survey of women with pelvic and perineal pain, dyspareunia, or endometriosis was performed. A total of 240 patients were approached, with 113 responses (47.1% response rate). There were 26 patients who used cannabis (23%). The majority used at least once per week (n=18, 72%). Most users (n=24, 96%) reported improvement in symptoms, including pain, cramping, muscle spasms, anxiety, depression, sleep disturbances, libido, and irritability. Over one-third (35%) stated that cannabis use decreased the number of phone calls or messages sent to their provider, and 39% reported decreased number of clinical visits. Side effects, including dry mouth, sleepiness, and feeling “high,” were reported by 84% (n=21).

Geoffrion 2021: This was a retrospective analysis of women with moderate-to-severe pelvic pain. After cannabis legalization, prevalence of current cannabis use increased from 13.3% (366/2,760) to 21.5% (143/666) (P<.001). Compared with pre-legalization, post legalization users were associated with higher levels of education (P<.001), worse anxiety (P=.036), and worse pain catastrophizing (P<.001) scores. They were taking fewer antiinflammatories (P<.001), neuroleptics (P=.027) and daily opioids or narcotics(P=.026), but more herbal medications (P=.010).

Sinclair 2020: An online survey was conducted between October and December 2017. Women aged 18-45 living in Australia with
surgically confirmed endometriosis were eligible to participate. 484 responses were included for analysis with 76% of women reporting the use of general self-management strategies within the last 6 months. Of those using self-management, 13 reported cannabis use for symptom management. Self-reported effectiveness in pain reduction was high (7.6 of 10), with 56% also able to reduce pharmaceutical medications by at least half. Women reported the greatest improvements in sleep and in nausea and vomiting. Adverse effects were infrequent (10%) and minor.
APPENDIX 2. The Use of Cannabis Products for the Management of Pain Associated with Gynecologic Conditions

**Palmitoylethanolamid (PEA)-Transpolydatin**

**PROPOSED RECOMMENDATION STATEMENT**

- There are limited randomized controlled trial data demonstrating the efficacy of PEA-transpolydatin for pain relief for primary dysmenorrhea, endometriosis, and chronic pelvic pain. However, more and stronger data are needed before making a definitive recommendation.

**SUPPORTING EVIDENCE**

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<td><strong>Indraccolo 2022</strong>: Only cases treated with palmitoylethanolamide comircized with polydatin for a short period can be assessed. Good responders are more than 50%. In chronic pelvic pain, there is a 19.0% conditional probability to find good responders among patients with pain score at enrolment of 6 to 8 and of 6.8% to find poor responders among patients with a pain score at enrolment of 6 to 8. Painful disease does not matter on responders’ rates.</td>
<td><strong>De Leo 2019</strong>: 60 women aged between 20 and 39 with endometriosis and chronic pelvic pain were given a nutraceutical product based on 400 mg alpha-lipoic acid, 300 mg palmitoletanolamide (PEA) and 100 mg myrrh, at a dose of 2 tablets per day for 6 months. With regard to pain symptoms and in particular chronic pelvic pain, patients reported a significant improvement at 3 months, and this was again significantly reduced after 6 months of treatment from VAS values of 5±2.11 at time 0 to 3.75±1.8after 3 months to reach 3.28±1.37 after 6 months of therapy.</td>
<td><strong>Observational studies</strong></td>
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<td><strong>Liang 2022</strong>: Survey data showed that most women reported that cannabis improved pain from numerous gynecologic conditions. Cohort studies and an RCT using PEA-combination medications reported pain reduction. However, interpretation of the studies is limited due to varying cannabis formulations, delivery methods, and dosages that preclude a definitive statement about cannabis for gynecologic pain relief.</td>
<td><strong>Stochino Loi 2019</strong>: 30 symptomatic women with laparoscopic diagnosis of endometriosis and pregnancy desire were enrolled. Patients were treated with um-PEA twice daily for 10 days followed by m(PEA/PLD) twice daily for 80 days. At the end of treatment, all patients showed a significant improvement in chronic pelvic pain, deep dyspareunia, dysmenorrhea, dyschezia, as well as in quality of life and psychological well-being.</td>
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<td><strong>Randomized Controlled Trials</strong></td>
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<td><strong>Tartaglia 2015</strong>: women aged 16-24 years with primary dysmenorrhea were randomized to receive treatment or placebo, 1 tablet a day for 10 days from the 24th day of cycle. Treatment included the oral combination of PEA-transpolydatin: 400mg + 40mg. Improvement in pelvic pain was seen in 98.18% (95% CI 97.64-98.60%) of cases in the treatment group vs 56.36% (95% CI 48.62-63.81%) in the placebo group (p&lt;.001).</td>
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<td><strong>Caruso 2015</strong>: Fifty-six women constituted the study group and were given PEA 300 mg and LA 300mg twice daily. To define the endometriosis-associated pelvic pain, the visual ana-logic scale (VAS) was used. The Short Form-36 (SF-36), the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS) were used to assess the QoL, the sexual function and the sexual distress, respectively. The study included three follow-ups at 3, 6 and 9 months. No changes were observed in</td>
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pain, QoL and sexual function at the 3rd month follow-up (P=NS). By the 6th and 9th month, pain symptoms (P<0.001) and all categories of the QoL (P<0.001) improved. The FSFI and the FSDS scores did not change at the 3rd month follow-up (P=ns). On the contrary, at the 3rd and 9th months follow-ups they improved with respect to the baseline (P<0.001).

Giugliano 2013: Participants were divided into 2 groups according to endometriosis site (A: recto-vaginal septum; B: ovary). One tablet containing 400mg of micronized N-palmitoylethanolamine plus 40mg transpolydatin, was administered twice daily on a full stomach for 90 days. The intensity of endometriotic pain decreased significantly for both groups (p<0.0001). The efficacy of drug treatment was significant after 30 days. Pain intensity decreased equally in the two groups except for dysmenorrhea, which was reduced more rapidly in group B.
Adolescents and Use of Cannabis

PROPOSED RECOMMENDATION STATEMENT

- Adolescents using recreational cannabis products are at increased risk of detrimental cognitive effects and psychotic disorders when compared with adults. Data on short- and long-term effects on adolescent brain development are needed before medical cannabis products can be recommended for adolescents for the management of gynecologic pain.

SUPPORTING EVIDENCE

Ryan 2017 (AAP): Counseling Parents and Teens About Marijuana Use in the Era of Legalization of Marijuana

- Adolescents and preteens may be screened for substance use and brief intervention, as recommended in the Screening, Brief Intervention, and Referral for Treatment (SBIRT) policy statement. The effectiveness of the SBIRT technique has been documented in adults with alcohol use problems; because of the lack of information in the adolescent population, the US Preventive Services Task Force recently gave SBIRT an “I” rating, stating that there was insufficient evidence to recommend either for or against this technique. However, on the basis of the limited evidence available and the low cost of this brief intervention, the AAP and the National Institute on Alcohol Abuse and Alcoholism both recommend that this technique be used in pediatric practices as part of routine care.
  - For adolescents who do not use marijuana, motivational techniques may be helpful in eliciting reasons for abstaining from use and resisting peer pressure in a manner that supports their decision to abstain.
  - Adolescents who use marijuana regularly or heavily are more likely to meet criteria for a substance use disorder. For these teenagers, a brief motivational intervention may be used to target: (1) reducing use and (2) continuing the conversation either with the pediatrician or a mental health or behavioral counselor.

Category I

Systematic Reviews

Godin 2022: Both high- and low-frequency marijuana usage were associated with a significantly increased risk of schizophrenia. The frequency of use among high- and low-frequency users is similar in both, demonstrating statistically significant increased risk in developing schizophrenia.

Lichenstein 2021: Based on a systematic review, we identified 90 studies including 9441 adolescents and emerging adults (n=3924 CU, n=5517 non-CU), which provide preliminary evidence for functional and structural alterations in frontoparietal, frontolimbic, frontostriatal, and cerebellar regions among adolescent cannabis users. Larger, more rigorous studies are essential to reconcile divergent results, assess potential moderators of cannabis effects on the developing brain, disentangle risk factors for use from consequences of exposure, and elucidate the extent to which cannabis effects are reversible with abstinence.

Category II

Observational studies

Ellingson 2021: After correcting for multiple testing, a greater frequency and earlier onset of regular cannabis use were associated with poorer cognitive performance, specifically on tests of verbal memory. Further, after accounting for familial factors shared by siblings and alcohol use, poorer verbal memory performance was still associated with greater lifetime frequency of cannabis use at Wave 1 (b=-0.007 [-0.002, -0.012], adjusted-p=.036); earlier cannabis use at Wave 2 (b=-0.12 [-0.05, -0.19], adjusted-p=.006; b=-0.14 [-0.06, -0.23], adjusted-p=.006); and greater frequency of past-six-months use at Wave 2 (b=0.02 [-0.01, -0.03], adjusted-p=.002; b=0.02 [-0.01, -0.03], adjusted-p=.008).

Hjorthoj 2021a: The polygenic risk scores for schizophrenia was not associated with cannabis use disorder in controls or patients with other psychiatric disorders than schizophrenia. This speaks against the hypothesis that shared genetic vulnerability would explain the association between cannabis and schizophrenia.
Power 2021: This review found 7 cohort studies including 808 cases and 5308 controls. We found a significant effect for the association between frequent or dependent cannabis use in youth and IQ change. Cohen's $d = -0.132$ (95% CI = $0.198$ to $-0.066$) $p < 0.001$. Study quality was moderate to high. This translates to an average decline of approximately 2 IQ points following exposure to cannabis in youth.

Hjorthoj 2021b: A total of 7 186 834 individuals were included in the analysis, including 3 595 910 women (50.0%) and 3 590 924 men (50.0%). The adjusted hazard ratio for schizophrenia fluctuated at approximately 4 (with 95% CIs ranging from approximately 3 to 6) throughout most of the study period when people diagnosed with cannabis use disorder were compared with those without cannabis use disorder. The PARF of cannabis use disorder in schizophrenia also fluctuated, but with clear evidence of an increase from 1995 (when the PARF was relatively stable around 2.0%, with a 95% CI of approximately 0.3% to either side) until reaching some stability around 6.0% to 8.0% (with a 95% CI of approximately 0.5% to either side) since 2010.

Mahedy 2021: There was some evidence to suggest that adolescent tobacco and cannabis use were associated with deficits in working memory, response inhibition and emotion recognition.

Paul 2021: Participants who reported higher frequency of cannabis use tended to have lower number of correct responses in the list-sorting working memory task and lower bilateral hippocampal volumes. Association between severity of cannabis exposure as indexed by frequency of cannabis use and impairment in working memory was mediated by lower left hippocampal volume in cannabis users.

Petker 2021: Covarying alcohol use, tobacco use, age, sex, income, and education, daily cannabis users exhibited significantly more impulsive delay discounting and hyperactive-impulsive ADHD symptoms compared to both other groups. However, cannabis use was not associated with inattentive ADHD symptoms, verbal intelligence, working memory, probability discounting, short-term verbal memory, or behavioral inhibition. Age of initiation of cannabis use exhibited neither main effects nor interactions in relation to any domains of cognitive performance or ADHD symptomatology.

Schaefer 2021: Twins reporting greater cumulative cannabis use in adolescence reported higher levels of psychopathology as well as poorer socioeconomic outcomes in young adulthood. However, cannabis use remained associated only with socioeconomic outcomes (i.e., educational attainment, occupational status, and income) in monozygotic-cotwin control analyses, which account fully for shared genetic and environmental confounding. Follow-up analyses examining associations between twin differences in adolescent cannabis use and longitudinal change in academic functioning during the middle- and high-school years provided a possible mechanism for these associations, indicating that greater cannabis use during this period was associated with decreases in grade point average and academic motivation as well as increases in...
academic problem behavior and school disciplinary problems. Our findings thus suggest that cannabis use in adolescence has potentially causal, deleterious effects on adolescent academic functioning and young-adult socioeconomic outcomes despite little evidence suggesting a strong, causal influence on adult mental health or cognitive ability.
References


APPENDIX 2. The Use of Cannabis Products for the Management of Pain Associated with Gynecologic Conditions


