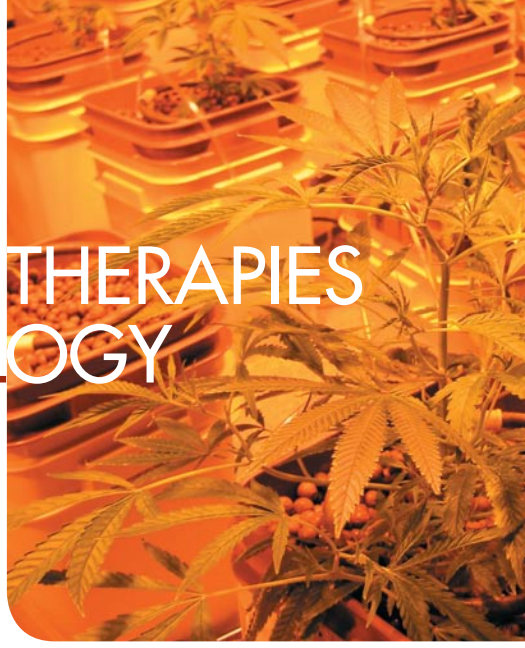

CANNABINOID-BASED THERAPIES IN SUPPORTIVE ONCOLOGY

Growing evidence for a broad role in symptom management

Vincent Maida, BSc, MD, CCFP, ABHPM

Top-line summary

The term "cannabinoid" collectively refers to a class of chemical compounds that are ligands of cannabinoid receptors. Delta-9-tetrahydrocannabinol, commonly known as THC, is the most abundant and clinically relevant cannabinoid derived from the cannabis plant. Extracts from the cannabis plant have been employed by ancient cultures for a variety of medical maladies, including pain, tremors and spasms. The discovery of cannabinoid receptors (CB1 and CB2) and the characterization of the endogenous cannabinoid system in the past 15 to 20 years have given legitimacy to the use of cannabinoids in a number of medical settings. Agonism of CB1 leads to neuromodulatory effects, while agonism of CB2 leads to immunomodulatory effects. The range of effects in the setting of ubiquitous distribution of the receptors provides opportunity for multiple clinical benefits. This is especially advantageous in the management of malignant disorders where patients suffer from a constellation of disease-related symptoms and side effects from treatments.

Patients suffering from malignant disorders experience multiple symptoms related to disease and side effects from treatments. Even with the use of current first-line agents for symptom management, a large proportion of patients continue to experience less than optimal pain and symptom contol.[1-6]

Suboptimal symptom management translates into decreased quality of life, reduced adherence to disease-modulating therapies, increased healthcare costs, and potentially to shorter life expectancy.[1,7,8] In clinical practice and research settings, the search is ongoing to identify effective modalities to optimize pain and symptom management in cancer patients.

The cannabinoids are a novel class of drugs that target cannabinoid receptors both centrally (CB1) and peripherally (CB2). They are emerging as valuable adjunctive agents for optimizing the management of multiple symptoms of disease and treatment-related side effects in cancer patients.[9] Cannabinoid receptors and their endogenous ligands have survived 500 million years of human evolution. The endogenous ligands (anandamide, palmitoyl-ethanolamide [PEA], and 2-arachidonoylglycerol [2-AG]), exogenous cannabinoids (e.g. derived from botanical cannabis) and pharmaceutical cannabinoids essentially mimic the action of endocannabinoids and may also potentiate endocannabinoid signalling.[10,11] While much about the pathophysiologic mechanisms of the endocannabinoid system remains unknown, emerging data support a broad spectrum of clinical actions, ranging from effects on nausea, vomiting and appetite, to pain and even cancer itself.[9,12-17]

A colourful history and folklore are associated with the use of cannabis-derived products. They have been employed for food, fibre and medicinal purposes for over 5000 years.[18] Marihuana was typically used in the form of a tea or edible extract, and was recommended for over 100 different ailments in ancient Chinese medicine. It was not until the early 19th century, however, that the medicinal use of cannabis was employed in the West. William O'Shaughnessy, an Irishman,

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used cannabis preparations to treat pain, spasms and the often deadly nausea and vomiting occurring with cholera. Progress in understanding the medicinal properties of cannabis-derived products slowed during the 20th century due to concerns regarding safety. In the latter part of the century, scientists cloned the first cannabinoid receptors and identified ligands, spurring interest in the beneficial effects of cannabinoids.

Medicinal marihuana has been legalized in Canada since 1999. Health Canada operates the Medical Marihuana access program.[19] At present, 12 American states have similar provisions for providing access to medical marihuana. Although available to qualifying patients, a number of Canadian regulatory bodies do not support the use of medicinal marihuana, such as the Canadian Medical Protective Association (CMPA), College of Physicians and Surgeons of Ontario (CPSO), and Canadian Medical Association (CMA).

Three pharmaceutical agents, differing in structure and hence in some pharmacokinetic aspects, are currently available for use in cancer and multiple sclerosis (MS) patients (**Table 1**).[20-22] Nabilone is an oral synthetic delta-9-tetrahydrocannabinol (D9-THC) analog and dronabinol is an oral synthetic formulation of D9-THC. A combination of the standardized cannabis extracts D9-THC and cannabidiol (CBD) formulated as a buccal spray is in use in Europe and Canada. This THC:CBD spray received approval for conditional use as adjunctive treatment for the symptomatic relief of neuropathic pain in adults with MS in Canada in 2005. All 3 medications are CB receptor agonists, producing neuromodulatory and immunomodulatory effects (**Table 2**, page 24).[18,23] THC:CBD spray is composed of 2 main cannabinoid extracts: THC (27 mg/mL) and CBD (25 mg/mL).[21] CBD is unlike conventional cannabinoids as it does not directly bind to CB receptors. Although the mechanism of action has not yet been fully elucidated, CBD is thought to exert activity through the inhibition of endocannabinoid uptake and hydrolysis. Moreover, it exhibits antioxidant properties, and holds significant promise in view of antipsychotic, antiseizure and anti-inflammatory properties observed in preclinical studies.[24-26]

ESTABLISHED ROLE — CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Control of nausea and vomiting takes place in a number of anatomic sites in the central nervous system (CNS) and gastrointestinal (GI) tract and is mediated by a host of neurochemicals. Therefore, it is not surprising that no single pharmaceutical agent is capable of exerting complete control of chemotherapy-induced nausea and vomiting (CINV). The introduction of the 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists represented a revolution in the management of CINV.[27] Yet, while these agents are effective in preventing and managing acute CINV, they offer limited benefit to patients suffering from delayed nausea and vomiting. Aprepitant, marketed in the United States and not yet available in Canada, antagonizes substance P/neurokinin-1 receptors and is indicated for the prevention of delayed CINV in patients receiving highly or moderately emetogenic chemotherapy.[5,6] Aprepitant augments the antiemetic effects of dexamethasone and 5-HT3 receptor antagonists. Although the addition of aprepitant is more effective in achieving complete control, defined as no emesis or need for rescue medication, up to one-third of patients continue to experience persistent delayed nausea.[4]

The cannabinoids nabilone and dronabinol have been shown to reduce the frequency of vomiting and lessen the severity of nausea in cancer patients with persistent CINV.[28] A systematic review of 16 studies of nabilone, 11 of dronabinol, and 1 of intravenously administered levonantradol (a synthetic cannabinoid analog of dronabinol) found the cannabinoids to be superior to placebo, as well as to active controls (prochlorperazine, metoclopramide, chlorpromazine, haloperidol, domperidone and alizapride) in reducing the frequency of vomiting and lessening the severity of nausea.[28] Complete

TABLE 1. Properties of currently available exogenous cannabinoids vs marihuana[20-22]

	marihuana	THC:CBD spray	dronabinol	nabilone
active agents	THC + > 60 other cannabinoids	THC + CBD	synthetic THC	synthetic analog of THC
route of administration	inhaled	oral mucosal	oral	oral
number of metabolites	> 60	not determined	> 21	2
distribution volume	lipid soluble (very large)	lipid soluble (very large)	lipid soluble (very large)	lipid soluble (very large)
anset of action (minutes)	6–20	30–150	30–60	60–90
T_{max} (hours)	0.5–2.0	1.5–4.0	1–4	2
duration of action (hours)	3–4	6–8	4–6	8–12
plasma $T_{1/2}$ (hours)	28–57	1.5	19–56	2
plasma $T_{1/2}$ (metabolites; hours)	44–59	not determined	49–53	35
urine THC drug testing	yes	yes	yes	no

CBD = cannabidiol; THC = delta-9-tetrahydrocannabinol

control of nausea was attained in 70% of patients receiving cannabinoid therapy vs 57% of those receiving placebo, and complete resolution of nausea in 59% in the cannabinoid groups vs 43% in active control groups. Importantly, a substantial proportion of subjects in the cannabinoid groups were experiencing refractory and/or severe CINV. Nabilone has also been shown to exert greater effects against nausea than the commonly used antiemetic prochlorperazine.[29] Similarly, a comparative study between dronabinol and the 5-HT3 receptor antagonist ondansetron found the cannabinoid to be more effective in resolving nausea.[30] On days 2 through 5, 71% of subjects receiving dronabinol experienced complete resolution of nausea, in contrast to 64% of those receiving ondansetron and 15% of those in the placebo group.

Anticipatory CINV (occurring before administration of a chemotherapy cycle) remains a significant issue as it affects 10% to 29% of patients,[31,32] and the introduction of the 5-HT3 receptor antagonists has not significantly impacted its prevalence. A recent animal model of anticipatory CINV has demonstrated that THC is effective, while 5-HT3 receptor antagonists are ineffective for its prevention.[33]

The mechanisms by which the cannabinoid agonists induce their antiemetic effects are incompletely defined. Agonism of CB1 receptors in the CNS and GI tract appears to be the primary mechanism.[11,34] The cannabinoids also exert some antagonism against 5-HT3 and dopamine receptors, recognized neurotransmitters involved in the pathophysiology of CINV.[35,36] Clinical trial results, along with the inclusion of nabilone and dronabinol in the 2007 National Comprehensive Cancer Network recommendations for the management of breakthrough CINV,[6] establish the cannabinoids as valuable adjunctive medications in cancer patients suffering from refractory CINV.

TABLE 2. Localisation and characteristics of CB1 and CB2 receptors[19,23]

	neuronal	non-neuronal
G-protein-coupled receptor	CB1	CB2
location	CNS >> periphery basal ganglia hippocampus cerebral cortex cerebellum spinal cord afferent nociceptors	periphery >> CNS spleen tonsils mast cells macrophages lymphocytes microglia
function	neuromodulatory	immunomodulatory
endogenous agonist	anandamide 2-arachidonoylglycerol (2-AG)	palmitoyl-ethanolamide (PEA)
exogenous agonist	THC	THC, CBD
antagonist	SR141716 (rimonabant)	SR144528

CBD = cannabidiol; THC = delta-9-tetrahydrocannabinol

EMERGING ROLES

Analgesia

Pain is one of the most prevalent symptoms experienced by people with cancer, affecting over 70% of patients, with up to 50% having less than acceptable pain control.[2] Although opioids remain first-line agents, they are associated with a significant side effect burden that includes sedation, nausea and constipation. Recent evidence suggests that high-dose, long-term opioid therapy may have proneoplastic effects and the ability to predispose to infection through demonstrated immunosuppressive effects.[37]

Another promising attribute of the cannabinoids relates to their intrinsic analgesic properties. A significant body of preclinical evidence clearly demonstrates analgesia mediated through antinociceptive, antihyperalgesic, anti-allodynia and anti-inflammatory mechanisms (**Table 3**).[12] Further, a number of preclinical studies have demonstrated synergistic sensory analgesia when opioids and cannabinoids are combined.[38,39] This is important because such combination therapy may permit prescribing opioids at lower doses, translating into reduced risk for opioid-related side effects. Sensory synergy has yet to be demonstrated in clinical trials although synergistic affective analgesia in humans has been demonstrated in an experimental thermal pain model.[40]

Data from a meta-analysis examining the use of cannabis-derived treatments for neuropathic and MS pain support the use of cannabinoids in this setting.[41] The cannabinoids significantly reduced pain ($p = 0.03$) compared with placebo. Findings from another study not included parallel those of the meta-analysis.[14] Patients with chronic upper motor neuron syndrome (due to traumatic spinal injury, ischemic infarction, intracerebral hemorrhage or MS) in whom conventional therapy had not provided adequate pain relief experienced significantly decreased spasticity-related pain ($p < 0.05$) with the use of the cannabinoid nabilone.[14]

Data are emerging that indicate efficacy of cannabinoids in chronic pain as well.[15] In one investigation in 30 patients with treatment-refractory chronic pain, nabilone was significantly more effective ($p = 0.006$) than placebo (intent-to-treat analysis) in reducing spinal pain intensity when added to standard analgesic therapy.[15] Interestingly, these patients suffered from a wide range of ailments, including cervical syndrome, lower back pain, thoracic syndrome and others. GW Pharmaceuticals directed a European Phase III study in patients with cancer pain not responsive to opioids. Those receiving THC:CBD spray experienced significant pain reduction, measured by a numeric rating scale, compared to those receiving placebo ($p = 0.014$).[42] Further, 43% of subjects demonstrated more than 30% reduction in pain.

Ongoing and planned studies may provide further evidence for the use of cannabinoids to manage pain. In addition to planned U.S. studies with nabilone in patients with chemotherapy-induced neuropathic pain, diabetic neuropathy and MS neuropathic pain, there are ongoing trials with THC:CBD in Europe and Canada in diabetic neuropathy and neuropathic pain characterized by allodynia. A U.S. Phase III clinical trial in patients with cancer pain is in the planning stage.

Antispasmodic effects

Although not one of the most prevalent symptoms in cancer care, treatment of muscle spasms remains challenging. They occur mostly in patients who have developed CNS metastases with resulting malignant spinal cord compression, plexopathy or radiculopathy. A Cochrane meta-analysis revealed that none of the commonly used oral spasmolytics exert significant activity.[43] Cannabinoids have long been known to possess spasmolytic properties with respect to both skeletal and visceral muscle.[44,45] Clinical evidence for their antispasmodic effects is derived primarily from studies conducted in patients with MS.[46,47] Preliminary investigation revealed relief of muscle spasms and spasticity following administration of THC:CBD spray in 24 patients with MS (n = 18), spinal cord injury (n = 4), brachial plexus damage (n = 1) and limb amputation secondary to neurofibromatosis (n = 1).[46] Another randomized, double-blind, placebo-controlled, crossover trial in 57 patients with MS confirmed these preliminary findings: in 37 of the patients, all of whom received at least 90% of the prescribed dose of a different combination of cannabinoids (2.5 mg THC and 0.9 mg CBD in a gelatine capsule taken orally), spasm frequency declined significantly (p = 0.013).[47] In view of the aforementioned trials, cannabinoids are evolving into premier drugs in the management of spasticity-related disorders.

TABLE 3. Preclinical evidence for cannabinoid-induced analgesia[12]

effects showed in preclinical studies	type of pain			
	acute	visceral	chronic	neuropathic
antinociceptive	significant evidence		significant evidence	significant evidence
antihyperalgesic	significant evidence		significant evidence	due to upregulation of CB1 receptors data from animal studies support a role for CB2 receptors
anti-inflammatory		significant evidence	CB2 receptors play important role	CB2 receptors play important role
anti-allodynic			due to upregulation of CB1 receptors	
comparison with opioids	comparable in potency and efficacy		greater potency and efficacy in both inflammatory and neuropathic pain	

Source: Lynch ME. *Pain Res Manage* 2005;10(suppl A):7A-14A.

Orexigenic effects

Cancer-related anorexia and associated cachexia are prevalent manifestations of disease in people with malignancies. From 15% to 40% of all cancer patients experience anorexia, and up to 80% of those with advanced disease are affected.[48] The cancer anorexia-cachexia syndrome (CACS) is a major cause of morbidity and mortality in people with cancer. The cannabinoids may be a valuable treatment option in these patients. Their orexigenic effects occur through the inhibition of leptin at a hypothalamic level.[49] Further, preclinical studies have observed a potential anticachectic effect of THC, perhaps due to mediation of cytokines.[18]

The synthetic cannabinoid dronabinol is indicated for the treatment of anorexia in AIDS patients. Long-term use in this population has been shown to be effective and safe.[50] Clinical evidence for the use of cannabinoids in cancer and palliative care patients with CACS is limited. An early investigation showed that dronabinol increases appetite, resulting in significant weight gain when compared to placebo in patients with advanced cancer.[51] In a Phase II study, 19 patients with various malignancies received dronabinol for 4 weeks.[52] Data from the 18 evaluable patients demonstrated improved appetite in 13, 3 experienced weight gain and 3 withdrew from the study due to emergence of side effects. Recently, Walsh et al reported a case series of patients with cancer-related anorexia who were given dronabinol for 7 weeks.[16] Five of the 7 patients gained a median of 1 kg over 7 weeks of therapy, and 3 maintained improved appetite despite disease progression.

Few effective therapies are available for the management of CACS. Megestrol acetate increases appetite, but its long-term use is limited by the development of potentially serious side effects. Benefits of cannabinoid therapy include the potential to use them long-term and their effects on other symptoms experienced by cancer patients.

Antineoplastic effects

It has been known for at least 2 decades that cannabinoids inhibit tumour growth in certain animal models, thereby prolonging survival.[17] Over the past few years a number of human in vitro models have begun to demonstrate antineoplastic effects of these novel agents. The responsible mechanisms are thought to include induction of apoptosis via CB2,[53] modulation of angiogenesis[54,55] and modulation of cell migration.[56,57] Expression of CB1 and CB2 receptors is increased in a number of human cancer cell types. Using prostate cancer cells, Sarfaraz et al demonstrated induction of apoptosis, a reduction in protein expression of proliferating cell nuclear antigen and vascular endothelial growth factor, and reduced growth of tumour cells after treatment with a CB agonist.[58] The researchers propose that cannabinoids might offer effective treatment against prostate cancer. Cannabinoids have also been shown to exert antiproliferative activity against melanoma cells and breast cancer tumours.[59,60]

While findings from preclinical trials regarding the antineoplastic effects of cannabinoids are intriguing, clinical

studies are needed to demonstrate efficacy in humans. One study examined the prognosis of patients with hepatocellular carcinoma based on density of CB1 and CB2 receptors.[61] Those with high CB1 and CB2 receptor expression had significantly better disease-free survival compared to those with low receptor expression ($p = 0.010$ for CB1 and $p = 0.037$ for CB2 receptors). The next step, exploring the effects of cannabinoid administration in patients with various malignancies, may define a role for these medications in the treatment of cancer, in addition to their usefulness for managing symptoms and side effects.

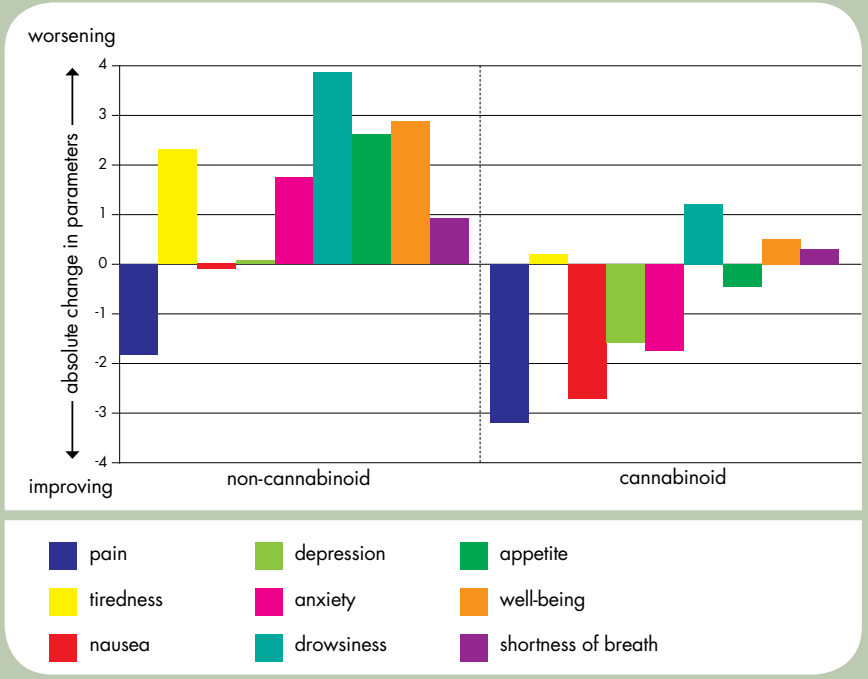
KEYS TO CLINICAL APPLICATION

Cannabinoids have a favourable safety profile. No deaths from overdose have been reported. This is likely explained by the relative lack of cannabinoid receptors in the medulla of the brain. The most commonly reported side effects of cannabinoid therapy are dizziness, drowsiness, dry mouth, ataxia and euphoria.[20-22] Side effects are generally mild to moderate in intensity and are of short duration. Despite the increased prevalence of side effects associated with cannabinoid therapy in comparative trials, patient preference favours cannabinoids.[28] In 18 cannabinoid trials, patients were asked to indicate which therapy they preferred. Between 38% and 90% indicated cannabinoid therapy over placebo and active control. Tolerance to side effects, but not to the beneficial effects of the cannabinoids, typically occurs within a few weeks of treatment initiation.

While the THC:CBD product is administered as a buccal spray, nabilone and dronabinol are given orally.[20-22] The buccal spray route of administration for THC:CBD provides a pathway that can significantly bypass the "first-pass" effect that cannabinoids are known to undergo when taken orally. The duration of action of nabilone is longer than that of dronabinol, which translates into less frequent dosing. Nabilone is typically given once or twice daily, while dronabinol may be given as many as 6 times daily.[20,21] In contrast, the dosing regimen for buccal spray THC:CBD is self-titrating, allowing individualized dosing.[42] The cannabinoids are metabolized principally via the cytochrome P450 (CYP450) 2C9 isoenzyme.[61,62] Neither nabilone, dronabinol nor the THC component of THC:CBD spray induces CYP450 isoenzymes; however, dronabinol and the CBD component of THC:CBD spray inhibit the CYP450 3A4 isoenzyme. The lack of inhibition associated with nabilone suggests a low potential for drug-drug interactions, particularly with those medications metabolized via the CYP450 3A4 pathway.[62,63] This is important as cancer patients are often receiving several different medications, many of which are metabolized via the CYP450 3A4 isoenzyme.

Similar to many other medications, judicious dosing enables the practitioner to attain maximum benefit of cannabinoids while avoiding intolerable side effects. The starting dose of either nabilone or dronabinol should be the lowest recommended, that is, 0.5 mg for nabilone and 2.5 mg for dronabinol.[20,21] The dosage can then be gradually increased, with patient monitoring during titration, to a maximum daily dosage of 6 mg for nabilone and 20 mg for dronabinol. Beginning nabilone or dronabinol therapy at the lowest dose at bedtime may reduce the emergence of unwanted side effects and improve sleep. With THC:CBD spray, treatment for neuropathic pain management should be started at a maximum rate of 1 spray every 4 hours up to a maximum of 4 sprays, on the first day. On subsequent days the patient may gradually increase the total number of sprays as needed and tolerated. The majority of patients require ≤ 12 sprays, however, some may require and tolerate a higher number of sprays.[41] For all agents, once the point at which benefits are maximized and side effects are minimized has been reached, the patient usually can be maintained on that dose.

FIGURE 1. The cannabinoid nabilone significantly reduces multiple symptoms in cancer patients[64]



Source: Maida V et al. San Antonio Breast Cancer Symposium 2006, Abstract 3145.

A "BROAD-SPECTRUM OPTIMIZER"

A retrospective analysis of a consultative palliative medicine outpatient program has demonstrated the potential of adjunctive therapy with nabilone to improve the pain and polysymptom management needs of advanced cancer patients.[64]

Sixty-five cancer patients were prescribed nabilone in the setting of severe pain and polysymptom burden (**Figure 1**). The nabilone-treated group, who were prescribed an average daily dose of 1.8 mg, demonstrated significant improvements in pain, nausea, appetite, anxiety and depression as reflected through serial Edmonton Symptom Assessment System (ESAS) evaluations. In addition, this group demonstrated lower utilization of other drugs, such as opioids, corticosteroids and tricyclic antidepressants.

Management of pain and multiple symptoms in cancer patients remains a significant challenge for healthcare professionals. Cannabinoids are an exciting area in medical therapeutics, albeit often stigmatized and controversial. A growing scientific and clinical evidence base supports the prescribing of cannabinoids for pain and symptom management in cancer patients. Although unlikely to evolve into first-line agents, their broad spectrum of activity, mediated through unique and complementary mechanisms of action, allows for treatment of a variety of pain and polysymptom issues together with "established" first-line agents. CE

Disclosure

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