Introduction

It is sobering to reflect, given the current controversy surrounding cannabis (the herbal drug derived from the plant Cannabis sativa), that the drug boasts an impressive historical pedigree of supporters, including Linnaeus,1 Descartes2 and Osler.3 It was firmly entrenched in the American pharmacopoeia in the 19th century as an effective analgesic agent4 and it was only in the 1920s that it was deemed illegal in Canada,5 with the US following a decade later;6 however, the pendulum may now be swinging back in the opposite direction, notwithstanding justifiable concerns over psychosis, most notably in the developing, and therefore vulnerable, adolescent brain.7,8 This resurgence of interest in the therapeutic properties of the drug reflects advances in pharmacology over the last 25 years, which have revealed an endogenous cannabinoid system (ligands; signaling pathways; and CB1 and CB2 receptors in the brain/spinal cord and immune tissue, respectively) modulating an array of physiological effects, including: analgesia, muscle relaxation, immune suppression and appetite stimulation, amongst others.

When trying to tease out the relationship between cannabis and cognition in people with multiple sclerosis (MS), it is helpful to divide cannabis into two broad categories, namely: smoked, vaporized or ingested varieties on the one hand; and pharmaceutically engineered medications on the other. The former may be legally or illegally obtained, depending on geographical location. The cognitive literature relating to both categories is small at present, but this should not obscure the importance of the subject, given the high prevalence rate of cognitive dysfunction in MS and the frequency with which the drug is used. Whether these two observations are causally related forms the focus of this topical review. In keeping tightly to this aim, we will not review the psychiatric sequelae of cannabis use.

MS, cognition and cannabis

Concerns that cannabis may adversely affect cognition in people with MS should be viewed in the context of high rates of cognitive dysfunction associated with the disease. Approximately 40% of people with
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relapsing–remitting MS (RRMS) are impaired, with the figure rising to 60–70% in secondary progressive MS (SPMS). Even benign MS is associated with 40% impairment; and people with radiologically isolated syndromes can show deficits, too.

Cannabis-101

A few words clarifying terminology and briefly summarizing its pharmacokinetics are needed, to begin with. Cannabis (marijuana is the herbal variety and hashish, the resin) contains over 60 pharmacologically active cannabinoids, the most important being Δ⁹-tetrahydracannabinol (Δ⁹-THC), isolated in 1964, which is psychoactive; and cannabidiol (CBD), isolated in 1963, which is not. When inhaled, Δ⁹-THC concentrations peak within minutes, and maximum psychotropic effects are reached between 15–30 minutes and decline after approximately 3 hours. The timeline following ingestion is slower and more variable. The Δ⁹-THC is fat soluble and is stored in adipose tissue after repeated use, with slow release into the blood stream. Therefore, the Δ⁹-THC metabolites may be detected in the urine for up to 46 days, in the case of regular users. This pharmacokinetic timeline should be kept in mind, when interpreting the smoked cannabis-cognition literature.

Cannabis and cognition in MS

Approximately 40% of people with MS have used cannabis at some point, with 14–18% reporting regular use mainly for symptom relief. Of those who have never used cannabis, three-quarters would do so if the drug were legal. Users are more often male and have higher self-ratings of disability. People with MS who report finding the drug helpful may use it 2–3 times/day for 5–6 days/week, entailing a significant financial outlay.

There is only one randomized controlled trial (RCT); which is a placebo-controlled, cross-over design of smoked cannabis that also contains cognitive data, albeit as a secondary outcome measure. In a study focusing on spasticity, 37 people with MS smoked cannabis under supervision, using the Foltin puff procedure, thereby receiving uniform dosages. The cognitive assessment was confined to a single test, the Paced Auditory Serial Addition Task (PASAT), which was administered serially after each of eight treatment sessions, i.e. while the cannabis group was acutely intoxicated. At each session, the cannabis group was more cognitively impaired than the placebo group. Three studies focus specifically on the effects of smoked cannabis on cognition. The earliest of these was retrospective; and it found that cannabis users did not differ from non-users in verbal nor visual memory, information processing speed (based on the PASAT) nor verbal fluency/semantic memory, but they performed 50% slower on a computerized version of the Symbol-Digit Modalities Test (SDMT). These preliminary data came with numerous limitations that included the small sample size, the absence of laboratory testing confirming the presence of cannabis metabolites, and a limited cognitive battery.

A subsequent study by the same researchers addresses all these concerns. In addition, to avoid testing subjects who were acutely intoxicated, cannabis users were instructed not to smoke the drug for at least 12 hours prior to testing. The results showed that cannabis smokers, whose frequency of use was four or more times per week, had greater cognitive impairments with respect to information processing speed (SDMT and PASAT), visual-spatial abilities and executive function. Global cognitive impairment was present in 32% of the cannabis-free group and 64% of the cannabis users.

A third neuropsychological study included a magnetic resonance imaging (fMRI) component, the latter in the context of a test of working memory, the n-back. In this test, memory is challenged sequentially with a series of tasks (0-back → 1-back → 2-back) of increasing difficulty. Once more, greater cognitive impairment on the indices of information processing speed (using PASAT) and visual memory was seen in the 20 cannabis users whom were not acutely intoxicated, versus 19 non-users. The pattern of cerebral activation also differed between the groups in two ways. First, more intense activation was observed in the cannabis users in the neural circuits underpinning the n-back, particularly in the anterior cingulate and posterior parietal regions. Second, the cannabis group showed activation in additional brain regions that were not linked to the n-back paradigm. These differences were associated with more errors on the most challenging of the three N-back tasks, namely the 2-back.

A fourth study explored the degree to which smoking cannabis influenced performance on the SDMT. A block design method was employed for the imaging component. While no overall error differences were observed between the cannabis and non-cannabis groups, the former was slower on 9 of the 11 blocks, a statistically significant result. Both groups activated frontal-parietal regions linked to this task in healthy,
drug-naive subjects, but the cannabis group showed excessive activation in the paralimbic regions and reduced activation in the thalami, bilaterally. This dysfunctional pattern of activation matched that reported previously in a RCT cannabis positron emission tomography (PET) imaging study of healthy controls given a test of attention.23

The unequivocal functional brain differences between people with MS who smoke or abstain from cannabis are supported by structural differences, although here the findings are more nuanced.24 A detailed structural analysis, incorporating diffusion tensor imaging of the 39 subjects whose n-back and SDMT are described above, failed to find absolute differences in lesion volume, total normal appearing grey and white matter volumes, and fractional and mean diffusivity indices; however, of note is that a Partial Least Squares analysis incorporating both cannabis users and non-users found that gray matter volume in the thalamus, basal ganglia, medial temporal and medial prefrontal regions; and white matter volume in the fornix, were correlated with cognitive deficits. Crucially, these brain volume reductions were associated with more extensive cognitive impairment in the cannabis MS group. Put another way, cannabis appears to further compromise the brain’s structural integrity, as it pertains to cognitive abilities.

Summary
The findings from the six studies presented here should be viewed with caution, given that few of the many factors that can influence neuropsychological performance in cannabis users were controlled for. These factors include the potency of the cannabis (∆9-THC concentrations), duration, amount, route and frequency of use, the timing of the assessment (Stage 1: Acute ⩽ 4 hours after use; Stage 2: During the withdrawal stage when symptoms like reduced concentration and irritability may be prominent25,26; and Stage 3: Post-withdrawal, but with cannabinoids still present), and the presence of other drugs. In addition, the reliability of the findings needs bolstering, as five of the six studies come from the same research group. With these limitations in mind, cannabis appears to be associated with more cognitive impairment across an array of indices, including: information processing speed, working memory, executive functions and visual-spatial abilities. Deficits are linked to alterations in neural circuit activation, which are either excessive or reduced, depending on the task. Moreover, reductions in regional brain volumes are more robustly associated with cognitive dysfunction in the presence of cannabis.

Cannabis and cognition in healthy subjects
There is a large volume of literature devoted to this subject, a summary of which helps frame the MS data presented above. In the acute phase of intoxication, i.e. up to 4 hours after inhalation, the memory deficits for any new material presented while intoxicated are present. Abnormalities are typically more discernible with immediate and delayed recall, rather than recognition measures.27 When it comes to the non-acute cognitive effects of cannabis, the findings are more equivocal and influenced by a host of factors described earlier.

In an often-quoted study, Pope et al.28 studied three groups of subjects; former heavy users, current users and non-user controls, during a period of supervised abstinence. Detailed neuropsychological assessments were completed at Day 0, 1, 7 and 28. Only current heavy users were more impaired than controls, and only on a measure of verbal memory, which disappeared after day 7. A meta-analysis has confirmed the residual effects of cannabis on memory, but with a small effect size and of transient duration, following abstinence.29

The most robust data demonstrating the deleterious effects of cannabis comes from a prospective birth cohort study of 1037 subjects. An index neuropsychological assessment was completed at 13 years of age. Thereafter, cannabis assessments were undertaken at 18, 21, 26, 32 and 38 years of age; with a follow-up cognitive assessment 25 years after the index assessment. If cannabis use began in adolescence and was followed by regular use, defined as ⩾ 4 times per week, then many cognitive deficits were present at follow-up; and these persisted even with abstinence in adulthood.30

Pharmaceutically engineered cannabis
Two cannabis preparations in pill form, namely dronabinol (Marinol) which contains ∆9-THC; and nabilone (Cessamet, which comprises CBD, have been approved for the treatment of nausea and vomiting linked to chemotherapy. Dronabinol is also used for treating weight loss associated with human immunodeficiency virus (HIV) infection. Oral Cannabis Extracts (OCE) in pill form have also been developed: These may contain either CBD alone, or CBD in combination with THC, with the latter in varying concentrations.

Finally, an oromucosal spray, nabiximols (Sativex) containing a ratio of ∆9-THC 2.7 mg; CDB 2.5 mg is on the market in Europe and Canada. The clinical
efficacy of these preparations for people with MS having symptoms of pain, spasticity, bladder dysfunction and tremor has recently been reviewed systematically by the Guideline Development Subcommittee of the American Academy of Neurology. 31

**Pharmaceutically engineered cannabis and cognition in MS**

Five studies of pharmaceutically engineered cannabis have been identified, in which cognitive data appear. In only one of these was cognition reported as the primary outcome measure; although even here, cognition was part of a larger MRI and electrophysiological study investigating the effects of cannabis on spasticity. 32 In this 8-week double-blind RCT (parallel group crossover), 17 cannabis-naïve people with MS were given either Sativex or placebo for 3 weeks, followed by a 2-week washout period before the crossover. The MS Functional Composite (MSFC), which contains a single cognitive measure, namely the 3-second PASAT, was administered at baseline and at the end of the Sativex or placebo treatment. No between-group differences on the PASAT nor any other index of the MSFC were found.

A more comprehensive assessment of cognition, namely the Brief Repeatable Neuropsychological Battery (BRNB), was used as a secondary outcome measure in a 5-week RCT of 66 people treated with combined Δ9-THC and CBD, administered in an oromucosal spray for the treatment of central pain. 33 The BRNB contains tests of verbal and visual memory, information processing speed and verbal fluency/semantic memory. While the cannabis group reported less pain and better sleep, improvement in the long-term component of the Selective Reminding Test was found in the placebo group only, suggesting that the cannabis group may have failed to benefit from a practice effect.

A third RCT (placebo-crossover, 14 days of active treatment) investigated the effects of Δ9-THC (2.5 mg) and CBD (0.9 mg) in a capsule form, in 57 people with MS-related spasticity. 34 As a secondary outcome measure, cognition was assessed with the PASAT, as part of the MSFC, and augmented with a digit span test. No group differences were found on either measure.

A fourth RCT (placebo-parallel group) of 160 people with MS investigated the effects of Sativex over 6 weeks on an array of MS-related symptoms that included spasticity, bladder dysfunction, tremor and pain. The primary outcome was a subjective visual analog scale (VAS) rating of each person’s most problematic symptom. VAS ratings were also obtained for cognition, mood, sleep and fatigue. Statistically significant improvements were reported for spasticity only, with no adverse effects on cognition. Another study from the same group followed 137 subjects for a year, using an open-label design. Once more, visual analogue scales were used and no subjective reports of cognitive difficulties emerged.

A different methodology was followed in a study of 24 people (18 with MS) whom had neurogenic symptoms that included pain, impaired bladder control and spasticity. Comparisons were undertaken between Δ9-THC, CBD, Δ9-THC and CBD (ratio 1:1), and placebo over a 2-week period; using a consecutive series of double-blind, randomized, placebo-controlled, single-patient crossover trials. 35 In addition to using visual analogue scales, an objective measure of cognition was obtained, namely the Short Orientation-Memory-Concentration (SOMC) test. A statistically significant fall-off in performance on the SOMS relative to baseline was found with the Δ9-THC group only.

Finally, there is a miscellaneous group of studies investigating the effect of Sativex (2 studies) on spasticity; and of Δ9-THC in capsule form (1 study) on tremor. All three studies list cognitive dysfunction as an adverse event, but do not provide statistical analyses of their significance. 36–38

**Summary.** The results from the five studies presented are equivocal, with respect to cognitive dysfunction; however, no firm conclusions are possible, given the paucity of cognitive data.

**Conclusions**

As this topical review reveals, there is much that remains unknown about the cognitive effects of cannabis across the spectrum of use. What little data there are, particularly relating to inhaled rather than the pharmaceutically manufactured drugs, do raise some concerns; but in the absence of a methodologically robust clinical trial, answers will remain elusive. That the time is right for such trials is indisputable. Societal attitudes towards the drug are rapidly moving towards acceptance and in favor of legalization. 39 Governments are in tune to this. The medical profession must retain a place at the discussion table, but until such time as health care providers have a better understanding of the benefits and cognitive risks of treatment, their views will continue to reflect no more than personal opinion; and potentially biased ones, at that. In an era of evidence-based medicine, buffeted as it is by some
pungent winds emanating from the grow-ops, the time has come to replace dogma with facts.

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