Smoke gets in your tics

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Many (though not all) of my patients who have tried marijuana have felt that their tics improved after using it. Such self-treatment is not rare (poster P94 here), and other doctors report similar results (see for example poster P6 here). Pharmacological benefits from cannabis products are plausible, since cannabinoid receptors in the brain's basal ganglia are well positioned to affect movement (Kluger et al., 2015).

Of course, in addition to any real benefit from marijuana, there could be expectation effects, or one could simply care less about tics when high. Random allocation clinical trials with blind rating of benefit (RCTs) are essential to demonstrating whether marijuana has any true benefit for tics. Müller-Vahl and colleagues carried out two RCTs about 15 years ago in Tourette syndrome (TS) using THC (tetrahydrocannabinol), the main intoxicating ingredient in cannabis (Müller-Vahl et al., 2002, 2003). Both trials showed benefit, but the trials were relatively small. Two to 3 years ago, the Tourette Association of America funded two pilot studies in this field, but results have not yet been reported. One trial, at Yale, was to study the FAAH (fatty acid amide hydrolase) inhibitor PF-04457845 in TS (Ahn et al., 2011), but the trial was placed on clinical hold pending results from a different trial. Investigators at Toronto Western Hospital were funded for a trial in TS of medical cannabis products with varying concentrations of THC and cannabidiol (of America). Cannabidiol is being studied in several brain disorders, including epilepsy, with hopes that it may provide benefit without the psychological side effects of THC.

Not surprisingly, the paucity of data has led to different viewpoints. Müller-Vahl has argued that THC may be appropriate in some TS patients (Müller-Vahl, 2013), whereas an American Academy of Neurology review and a Cochrane-style review in JAMA concluded that the evidence was insufficient to recommend THC for tic disorders (Koppel et al., 2014; Whiting et al., 2015). The clinical utility of cannabinoids in TS was one of two clinical controversies debated at the 2015 First World Congress on Tourette Syndrome and Tic Disorders (Mathews and Stern, 2016).

In this setting, several recent announcements demonstrate hope for answering whether, for cannabinoids in TS, "where there's smoke, there's fire." At the beginning of 2017, an Israeli company announced enrollment of the first subject in a phase IIa clinical trial of THX-TS01. Notably, this study is enrolling in the USA. THX-TS01 is a combination product, containing both THC and palmitoylethanolamide (PEA), another "endocannabinoid-like" compound. Based on some preclinical studies, the company hopes the combination may prove more effective than either ingredient alone.

In mid-April, 2017, the first patient was enrolled in a Phase 1b study of the monoacylglycerol lipase (MGLL) inhibitor ABX-1431. Inhibition of MGLL in mice increases the concentration of the endogenous cannabinoid receptor ligand 2-arachidonoylglycerol (2AG) in brain, with consequent activation of cannabinoid CB1 receptors (Savinainen et al., 2012).

Müller-Vahl and her colleagues are about to start a much more definitive RCT of cannabinoids in TS. This multicenter study aims to enroll almost 100 subjects in a study of nabiximols, a combination product containing THC and cannabidiol in nearly a 1:1 ratio. This product is available by prescription in some European countries for spasticity in multiple sclerosis.

At this time, there is insufficient evidence of anti-tic efficacy to recommend any of the products discussed above for treatment of tics. This is especially true given medical, practical and legal drawbacks to marijuana smoking (Svrakic et al., 2012) and substantial recent changes in the pharmacology of cannabis and related products available on the street (Cascini et al., 2012; Ford et al., 2017; Monte et al., 2017). On the other hand, there is good reason to expect that some of these products—perhaps cannabidiol or the small molecule modifiers of endocannabinoid metabolism—may prove to be safe and effective, and the appropriate studies are finally underway. An update on this topic likely will look very different in a few years.

Addendum 26 April 2017: A nice review of cannabinoid safety appeared recently in Lancet Psychiatry (Englund et al., 2017).

Addendum 03 May 2017: Abi-Jaoude and colleagues published today a retrospective case series of cannabis in 19 adults with TS who were using cannabis in various forms (smoked, inhaled vapor, ingested) (Abi-Jaoude et al., 2017). Nearly all of their 19 adult patients were rated as having substantially lower tic burden when using compared to when not using. Many patients reported side effects, but overall they were relatively mild.

Addendum 23 Aug 2017: A case report describes a previously treatment-resistant man with TS who responded well to nabiximols (Kanaan et al., 2017).

Addendum 05 Dec 2017:
1. The draft TS treatment guidelines from AAN discuss cannabinoids. 2. (Levine et al., 2017) review the strong evidence associating "early, frequent, and heavy adolescent cannabis exposure and poor cognitive and psychiatric outcomes in adulthood," with the appropriate caveat that most of this evidence does not allow a conclusion as to whether the cannabis use *caused* the poor outcomes.

Addendum 27 Sep 2018: The US FDA approved Epidiolex® (CBD) for certain seizure syndromes in June, 2018, and today the DEA rescheduled it as a Schedule V controlled substance (the least restrictive). This will greatly facilitate clinical use and clinical trials of CBD in the U.S.

Addendum 18 Jan 2018:
A review of the National Academy report summarizes: "The evidence supporting improvement in ... Tourette syndrome ... and a variety of neurodegenerative disorders was described as limited, insufficient or absent" (Abrams, 2018).

Addendum 16 Jul 2018:
Abide Therapeutics reports promising early results from a Phase 1 study of ABX-1431 in TS at the AAN meeting a couple of months ago (Therapeutics, 2018).

Addendum 12 Nov 2018:
Phone interviews of Israeli patients treated with (open-label) medical cannabis revealed that many reported benefits, but about a quarter of patients who had taken it for a year or more had discontinued it for several reasons, including side effects (Thaler et al., in press).

Addendum 31 Jan 2019: European clinicians report a single boy whose parents treated him with vaporized cannabis and oral THC, who reported marked if incomplete improvement. This report is interesting, but the authors go too far in concluding that "from this single case study, it is suggested that cannabis-based medicines ... are effective and safe in the treatment of severe tics in minors with TS" (Szejko et al., 2019). They go on to warn that even they view "cannabis-based medicine in children ... as a last-line treatment, when well-established treatments have failed to improve tics."

Addendum 28 Mar 2019: Clinical trial in Australia

Addendum 18 Apr 2019: Artukoglu and Bloch give a nice summary of the available clinical trials information about cannabinoids for TS (Artukoglu and Bloch, 2019)

Addendum 30 Aug 2019 TAA statement on medical marijuana for TS, and their excellent review of the literature

Addendum 29 Oct 2019 Meta-analysis concludes no significant benefit from THC for TS, but notes this result could owe to inadequate size and numbers of studies (Black et al., 2019).

Addendum 03 Mar 2020:

Results from an open-label clinical trial of dronabinol (THC) given with PEA (palmitoylethanolamide) were recently reported (Bloch, 2019; Biosciences, 2018). The study enrolled 17 medication-refractory adults with relatively severe TS (baseline YGTSS total tic score [TTS] of 38.4 ± 8.3), 16 of whom completed the study. There was significant improvement overall in tics, compared to the beginning of the study, with a mean improvement in TTS of 7.6 (95% CI = 2.5-12.8, p=.002), or 21%, and 6 of the 16 responding with a TTS reduction of more than 25%. No serious adverse events were reported, but every participant reported feeling "high" and drowsiness or fatigue. Other possible side effects were common, including difficulty concentrating (81%), ataxia (62%) and nausea (50%). This study marks an important advance, though without a comparison group one cannot conclude that the improvement is due to the treatment itself, as opposed to *e.g.* expectation effects.

Abide Therapeutics's drug ABX-1431 is now Lundbeck's Lu AG06466 (Lundbeck, 2020, 2019). Results have not yet been posted on ClinicalTrials.gov for the study mentioned above (Therapeutics, 2017), but the 2018 AAN abstract reported that this was a single-dose crossover study with 40 mg ABX-1431 or placebo (Mueller-Vahl et al., 2018). Tics improved significantly more at 8 hours after drug than with placebo (p<.04), with improvements vs. baseline seen at 4 and 8 hours by TTS and by the ATQ, a self-report measure of tic severity. Transient headache, somnolence and fatigue were the most common side effects.

An 8-week European controlled trial of ABX-1431 that began in late 2018 is currently marked as "Active, not recruiting" on ClinicalTrials.gov (Therapeutics, 2019).

Addendum 30 Mar 2020:

Lundbeck announced that the multisite, European, phase IIa trial of the MAG lipase inhibitor LuAG06466 (previously ABX-1431) completed, but did not meet its primary endpoint of statistically significantly better YGTSS Total Tic Score reduction compared to placebo (A/S), 2020). While disappointing, phase 2 trials are generally not powered for efficacy, and the company points out that the lack of serious adverse events supports further development either for other indications if not for TS.

Addendum 16 June 2021:

Full results on the Lu AG06466 appeared in Movement Disorders (Müller-Vahl et al., 2021).

Addendum 19 July 2021:

Hassamal and Hassamal (2021) review "spice," "bath salts," and other synthetic marijuana substitutes.

Addendum 19 March 2022:

Here's an open-label study of cannabis in 18 people with TS (Anis et al., 2022).

Addendum 29 Mar 2023:

A few months ago, a report appeared on a survey of people with TS before and 6 months after starting cannabis for tics (Barchel et al., in press). The mean daily dose was 123 mg (THC) and 50.5mg (CBD). Survey responders reported significant improvements in quality of life, employment status and number of (other) medications. Those with OCD (67%) and anxiety (89%) were especially likely to improve. However, tic improvement was not statistically significant: "motor tics (p=0.375), vocal tics (p>0.999), tics frequency (p=0.062)." "General mood" also did not improve significantly. The results suggest that, while cannabis may help people with tics, it does not primarily improve tics per se.

Szejko et al. (2022) provided a reasonable review of the literature published to date.

The biggest news yet on this page comes from the CANNA-TICS study, whose results were published last month (Müller-Vahl et al., 2023). The authors performed a randomized, controlled trial of nabiximols in 97 adults with TS or chronic motor or verbal tic disorder. Befitting the study investigators' view of the literature, people were randomized to drug or placebo in a 2:1 ratio. The primary, predefined efficacy endpoint was a tic reduction of at least 25% on the YGTSS total tic score after 13 weeks of treatment, a magnitude of change recognized as clinically meaningful improvement by an expert panel. The study did not show significant improvement by this measure. However, there were some indications of improvement, including a higher response rate (22% vs 9%) in the nabiximols group, a significantly greater reduction in self-reported tic severity on the Adult Tic Questionnaire, a numerically greater improvement of tics on a standardized video rating scale, and trends for improvement in quality of life and in impairment due to tics. There were no serious safety issues, with side effects of similar severity in 95% of those in the active drug group versus 79% of those in the placebo group (p=.03). Patients with ADHD or with worse general health were most likely to improve. Thirteen percent of patients at the site that enrolled over half the participants reported intentional or accidental unblinding on an end-of-study interview. Of course, other participants likely suspected their drug assignment; a forced-choice blindedness assessment is not reported. In sum, a reasonably large RCT showed hints of superiority for nabiximols over placebo, but the study did not meet the pre-specified treatment target.

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