UNIVERSITY WISCONSIN-MADISON SCHOOL OF PHARMACY STUDENT WRITING CLUB:

The Frontiers of Cannabidiol: Exploring Future Therapeutic Uses

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When many people think about cannabidiol (CBD), they think about marijuana. They might be surprised to learn that we humans have our own regulatory system related to these chemicals. The endocannabinoid system (ECS) consists of receptors, neurotransmitters called cannabinoids, and enzymes for degradation, all used to regulate homeostasis of the immune system and nervous system within the human body.[1] One thing this system does is to treat inflammatory processes, which helps explain why tetrahydrocannabinol (THC) and CBD might be useful to treat processes like headache, cancer pain, neuropathic pain, and sleep. This article focuses on two main cannabinoids: THC and CBD. THC works as a cannabinoid[1] (CB1) and cannabinoid 2 (CB2) agonist.[2,3] Action on the CB1 receptor leads to the "high" that people can experience when using THC (as in marijuana), and can lead to psychoactive effects. Activation of the CB2 receptor has a major role in the immune system, by mediating cellular immune responses. CBD, in contrast, has less effect on both CB receptors; thus, it has less of an intoxicating effect on the brain.[2,4] Additionally, CBD does not cause euphoric effects in the brain like THC.[5] CBD is an expanding topic in current therapeutic research, as it has the potential to be used in treatment of numerous disease states.

As we learn more about CBD and it has become more available, there has been a recent market boom: CBD is sold at gas stations, grocery stores, convenience stores, and restaurants.[6] The only Food and Drug Administration (FDA) approved cannabinoid substance is Epidiolex. All other forms of CBD and THC are currently unregulated and can vary in strength and content, no matter where they are sold. Given the prevalence of CBD in the marketplace, pharmacists need to know more about it. The objective of this review article is to present current research involving novel CBD/THC use in various disease states.

Antimicrobial

Antimicrobial resistance has become a major threat in healthcare. For example, *Staphylococcus aureus* (*S. aureus*) is the second most frequent hospital-acquired infection and there are a decreasing number of drugs available that are still effective to fight this infection.[7] In addition, there has been a decline in the development and research of new antimicrobials, which makes the new climate of "super bugs" even more dangerous.[8] Cannabis is a common agent for antimicrobials, and is the drug extracted from the cannabis plant that contains both THC and CBD.[2]

Van Klingeren and Ten Ham conducted an in vitro study that tested the effectiveness of THC and CBD at killing bacteria.[9] The results showed that the minimum inhibitory concentration (MIC) was 1-5 µg/mL, meaning fairly low concentrations were required to stop the growth of the tested gram-positive bacteria. However, the cannabinoid's success was greatly reduced in 4% or 5% horse serum. This suggests that THC and CBD might be inactive in horse blood and have no place in therapy regarding systemic antibacterial action, but could be used in a topical formulation. THC and CBD were also investigated against gram-negative bacteria, but they were found to be less effective with a MIC of 20-50 µg/mL. A limitation of this study is that these findings were gathered from crude extracts and not pure samples of THC or CBD. In addition, there was no statistical analysis reported.

Nissen et al. analyzed the effects of essential oils extracted from hemp. Hemp is a form of the cannabis plant that has less than 0.2% THC.[10] The study found that the concentration of different essential oils in each of the hemp varieties is dependent on when the cannabis strains are planted and the plant age. This provides an opportunity to optimize antimicrobial activity of hemp use going forward. The results were promising and showed that hemp from Carmagnola, Fibranova, and Futura plants were able to inhibit bacteria growth in vitro at concentrations ranging from 0.7-2.0 (%v/v). Again, the authors see potential use as an antiseptic topical treatment for wounds and skin scrapes, and as a new treatment agent for antibiotic-resistant strains of bacteria like MRSA and Clostridium difficile.

Furthermore, Appendino et al. confirmed the results that both THC and CBD show potent antimicrobial activity in vitro (MIC values in the 0.5-2 µg/

mL range).[11] The results were impressive and showed that there was antimicrobial activity against SA-1199B, EMRSA-15 and EMRSA-16. This could lead to major breakthroughs in drug resistance, because EMRSA-15 and EMRSA-16 are currently the top methicillin-resistant S. aureus strains spreading through U.K. hospitals. The antimicrobial mechanism of cannabinoids is not fully known; however, Appendino et al. suggest that these compounds are not substrates for the leading resistance mechanism in bacteria. Another avenue of research is on the topical use of cannabinoids against MRSA skin colonization, which is starting to become resistant to mupirocin, the standard of care for this condition. This study did not address the activity of cannabinoids in any kind of serum or blood, which would give further insight into cannabinoid effectiveness as systemic antibiotics. Once again no statistical analysis was reported.

Overall, there is some evidence supporting the use of cannabis as an antimicrobial agent. However, there is limited high-quality research available into its effectiveness in systemic circulation. It seems as if CBD and THC may be useful as a topical antimicrobial. Going forward, more studies will be needed to confirm CBD's effectiveness as an antibiotic. We will want to investigate further as resistant microorganisms become a bigger problem in hospitals around the world.

Autism Spectrum Disorder

According to the United States Centers for Disease Control (CDC), Autism Spectrum Disorder (ASD) occurred in 1 of every 59 children in 2014.[12] The prevalence of ASD and lack of treatment has made it a prime candidate for possible treatment with CBD. Research into CBD use in this patient population is young and hasn't made strong conclusions yet, but the possibilities are exciting.

Previous studies on ASD have suggested that an imbalance of the neurotransmitters glutamate and gamma-Aminobutyric acid (GABA) in certain areas of the brain could result in symptoms of ASD.[13] Glutamate normally serves as an excitatory neurotransmitter in the brain, and GABA is normally inhibitory, with imbalances in the two resulting in neurological conditions. The locations of these imbalances in the brains of ASD patients are specific and have been studied to find potential therapeutic agents.

In a 2017 study, Ajram et al. set out to determine whether the drug riluzole, a glutamate blocker, could be a pharmacologic agent that could help to balance glutamate and GABA.[14] In a placebo-controlled, double-blind, randomized study of 37 men (17 with ASD, 20 control), a significant difference ($p < 0.05$) in neurotransmitter balance was found in patients with ASD. More specifically, riluzole increased the proportion of GABA in patients with ASD in specific brain regions. In the control patient group, riluzole decreased the proportion of GABA, indicating an opposing effect in patients with ASD versus control patients.

Ajram et al.'s study proved that pharmacologic agents could be used to help this neurotransmitter difference in patients with ASD, and paved the way for exploring other options, such as CBD. In a similar test to explore the efficacy of CBD to restore neurotransmitter balance, Pretzsch et al. conducted a placebo-controlled, randomized, double-blind crossover study of 34 men (17 with ASD and 17 control) looking for effects on glutamate and GABA balance.[15] While limited, preliminary results suggested that CBD helped balance the neurotransmitters in patients with ASD (puncorr= 0.001 when measuring GABA+ in both the basal ganglia and the dorsomedial prefrontal cortex).

Neurotransmitter balance is an area of focus in treating ASD but is not the only frontier where CBD is being explored. In another double-blind, placebo-controlled study conducted by Pretzsch et al., 30 male patients (13 with ASD and 17 control) were randomized and dosed with CBD or placebo and then administered a functional magnetic resonance imaging (fMRI) test.[16] The results of this study showed that patients with ASD showed a significant shift (pFWE=0.045) in the fractional amplitude of low-frequency fluctuations (fALFF), especially in key ASD-related areas, when administered effective doses of CBD. The fALFF test is a similar measure to the Amplitude of Low-Frequency Fluctuation (ALFF) test, both of which measure and quantify slow fluctuations of brain activity that are seen in the resting brain.[17,18] By administering CBD to patients with ASD, brain activity in these key areas was increased, which could correlate with benefit in ASD.

Symptomatic treatment for ASD is also a growing area of research with CBD. Symptoms of ASD include hyperactivity, aggression, sleep disturbances, anxiety, and self-injury.[19] These symptoms were observed in an open-label 2019 study performed by Barchel et al. on the effects of a premade oral CBD solution, containing some THC at a 1:20 ratio with CBD, on symptoms and co-morbidities of children with ASD.[20] The study asked parents of 53 children with ASD (45 male, 8 female; ages 4-22) to subjectively measure improvement in symptoms following the administration of the CBD premade solution for 30 days. Although the study was subjective and relatively small, the results pointed towards the improvement of symptoms (established non-inferiority compared to standard of care in all studied symptoms, and an overall improvement in 74.5% of participants) following the 30-day course of CBD solution.

While none of these current studies claim to prove CBD's efficacy in treating ASD, they pave the way forward. These studies are all within the last decade, and as understanding of both ASD and of CBD grows, these areas could continue to expand.

Smoking Cessation

Worldwide, 1.1 billion people smoke; in the United States, 17% of adults smoke. With that large population, CBD might provide helpful therapy for smoking cessation.[21,22] There is currently limited evidence for using CBD for smoking cessation, but it is an area of growing research. Hindocha and colleagues used CBD and measured the patient's desire to smoke when they saw cigarettes (also known as "attentional bias to cigarette cues").[21] This was done by showing the patient different stimuli and measuring their desire to smoke a cigarette after each cue. The major mechanism that CBD is thought to affect for smoking cessation is the inhibition of fatty acid amide hydrolase (FAAH), which is

involved in the breakdown of endogenous cannabinoids.[21,23] Patients took an 800 mg oral dose of CBD, and it was found that the attentional bias was similar to that of a patient who had recently smoked a cigarette or no longer desired one. When comparing CBD to placebo, the researchers found CBD reduced attentional bias by a statistically significant level for both a patient who had recently smoked (p-value 0.007) or did not smoke before testing (p-value 0.004).[21] Levels of cravings and withdrawals were also not impacted by the use of CBD. However, CBD might be beneficial in reducing the pleasant feelings of cigarettes.

Another study done by Morgan et al. found that CBD reduced cigarette consumption.[23] Here, a CBD inhaler was used at 400 micrograms/dose, and patients used the inhaler any time they had the urge to smoke a cigarette. Over a two-week period, patients saw reduced total cigarette consumption. The results were found to be statistically significant with a p-value of 0.002. Patient anxiety was also lowered (p-value 0.04), which could play a role in helping with the cravings of cigarette smoking. People who smoked more cigarettes going into the study saw the greatest reductions in usage while using the CBD inhaler. Furthermore, there was a correlation between increased benefit and more uses of the inhaler; however, no statistical significance was found with the correlation.

Overall, CBD might be useful in the future as an adjunct therapy for smoking cessation. There is a growing body of evidence being gathered that will help to clarify CBD's potential use in smoking cessation. Current research is focused mainly in the UK and is currently working to establish whether CBD is a valid option for smoking cessation, along with its optimal route of administration. Researchers propose that CBD disturbs memory consolidation, which is one way it might work with smoking cessation. This could mean that CBD may be beneficial in other addictive drug treatment in the future, but more evidence is needed.

Parkinson's Disease

Over 10 million people worldwide live with Parkinson's disease (PD).[24] It is a central nervous system disorder characterized by the loss of dopaminergic neurons.[25] Reduced levels of dopamine cause various motor and non-motor complications in the human body. Motor impairments include resting tremors, bradykinesia, muscle rigidity, and postural disturbances; non-motor symptoms present as cognitive deficits; sleep disturbances; and psychiatric disorders such as anxiety, psychosis, and depression. The most common drug therapy for managing PD is carbidopa/levodopa, yet this medication only improves motor function.[25,26] Therefore, current pharmacologic intervention for PD is limited, due to side effects and lack of efficacy for long-term use of these medications. There is a need for better treatment options, and that potential could be found in CBD. CBD is found to provide anti-inflammatory, neuroprotective, anxiolytic, and antipsychotic effects—all of which could help in the treatment for PD.

One of the very first human studies comes from Zuardi and colleagues, wherein they analyzed the effects of CBD on psychotic symptoms of PD patients.[27] This was an open-label pilot study where both the researchers and participants knew the treatment that the participant was receiving. Here, 6 PD patients (2 women and 4 men) who all had psychosis for at least 3 months received flexible oral dosing of 150mg/day of CBD for 4 weeks. Doses increased weekly from 150mg to 400mg depending on the tolerability of each subject. CBD was given in adjunct with their regular therapy. Different scales were used to evaluate psychotic symptoms: the Brief Psychiatric Rating Scale (BPRS); the Parkinson Psychosis Questionnaire (PPQ); and the Unified Parkinson's Disease Rating Scale (UPDRS). Use of CBD was correlated with a decrease in frequency and severity of sleep disturbances, in addition to hallucinations and delusions, evidenced by a significant decrease in all test scores listed above. Furthermore, motor and cognitive functions were not affected by CBD. No adverse reactions were observed during the course of treatment.

Later, in a double-blind clinical trial, Chagas and colleagues treated 21 PD patients (6 women and 15 men).[28] Patients were free from dementia and psychiatric disorders. They were divided evenly into three groups who received placebo, CBD 75 mg/day, or CBD 300 mg/day for a duration of 6 weeks. Measurements were performed at baseline and in the last week of the trial. Rating scales (UPDRS, Parkinson's Disease Questionnaire–39, and Udvalg for kliniske undersogelser-UKU) were used to assess the overall quality of life. Results showed no differences between motor scores on the UPDRS (p=0.544). Additionally, no significant adverse effects were reported when assessed with the UKU. However, the Parkinson's Disease Questionnaire–39 provided a more hopeful conclusion with statistically significant differences between the placebo group and the CBD 300 mg/day group (p=0.034). Greater improvements were identified in emotional well-being, mobility, cognition, communication, and body discomfort of PD patients in the CBD group.

A further case series from Chagas and colleagues revealed that CBD was helpful in the treatment of rapid eye movement sleep behavior disorder (RBD) in PD patients.[29] This disorder usually presents early on in PD, occurring years before motor symptoms. Patients who have RBD tend to act out their dreams due to loss of muscle tone. Dreams can be vivid, intense, or violent and cause harm to the patient or their bed partner. In this study, the four patients (all men) were administered 75 mg/day (three patients) or 300 mg/day (one patient) of CBD taken orally.[30] Patients reported a significant reduction in the frequency of RBD events with minimal side effects.

Generally, findings conclude that CBD seems to be well tolerated and provides therapeutic effects in non-motor symptoms. However, there are many limitations with these studies. The sample sizes were very small, and the duration of treatment was short, making it difficult to correlate the possible effectiveness involved in CBD's therapeutic properties. Moreover, neuroprotective effects are not easily measured in humans. One last aspect that was not touched upon was CBD's possible interactions with PD medications. There is a need for large-scale randomized controlled trials, ones to mimic and assess the long-term efficacy of CBD. Although there are few human studies out there, results from these early CBD trials offer a

FIGURE 1. Current CBD/THC Research Studies and the Disease States Used in Creating this Article

	Citations	Type of Study	Number of Participants	Control	Intervention	# evidence with confidence interval
Antimicrobial	Van Klingeren B, Ten Ham M. 1976	In vitro studies	N/A	N/A	THC 2mg/mL or CBD 2mg/mL	MIC for S. aureus: CBD: 1-5 µg/mL in agar broth and CBD: 20-50 µg/mL
	Nissen L, Zatta A, Stefanini I, Grandi S, Sgorbati B. 2010	In vitro studies	N/A	N/A	Hemp varieties: 0.7-2.0 (%v/v)	MIC for Clostridium difermentas: Futura hemp: 1.41 µg/mL (P<0.05)
	Appendino G, et al. 2008	In vitro studies	N/A	DMSO (3.125%)	CBD 125 µL or erythromycin 125 µL or tetracycline 125 µL	MIC for S. aureus (SA-1199B): CBD: 1 µg/mL, Erythromycin: 0.25 µg/mL, and tetracycline 0.25 µg/mL
Autism Spectrum Disorder	Ajram, et al. 2017	Double-blind RCT	37 subjects (17 w/ASD, 20 Control)	Placebo (n=20)	Riluzole 50 mg	Riluzole increased the proportion of GABA in the prefrontal cortex of the ASD group but decreased the proportion of GABA in controls (group × drug interaction; F(1, 24)=4.288, P<0.05)
	Pretzsch, et al. 2019	Double-blind RCT	34 subjects (17 w/ASD, 17 Control)	Placebo (n=17)	CBD 600 mg/day	CBD decreased GABA levels in patients with ASD, while decreasing levels in Control patients when looking at the basal ganglia and dorsomedial prefrontal cortex ($F(1,22) = 13.506$, puncorr = 0.001, $\eta 2 = 0.380$)
	Pretzsch, et al. 2019	Double-blind RCT	30 subjects (13 w/ASD, 17 Control)	Placebo (n=17)	CBD 600 mg/day	CBD showed a significant change in patient fALFF scores for patients with ASD, but not in neurotypical control patients (vermis VI: TFCE, pFWE = 0.045, k = 7, CoG: x = 21.1, y = −55.7, z = −14; fusiform: TFCE, pFWE = 0.029, k = 19, CoG: x = 28.3, y = −51.8, z = −9.58)
	Barchel, et al. 2019	Open label cohort study	53 subjects	Symptoms prior to CBD therapy	CBD 16mg/kg, max 600 mg and THC 0.8mg/kg, max 40mg	74.5% of participants had improved symptoms (p values reported for individual symptoms, with no symptom showing a p value of <0.05).
Smoking Cessation	Hindocha C, et al. 2018	Randomized, double-blind crossover RCT	30 subjects	Placebo	CBD 800 mg capsule	Reduced attention bias if recently smoked (p=0.007)
	Morgan CJA, Das RK, Joye A, Curran HV, Kamboj SK. 2013	Double-blind RCT	24 subjects	Placebo	CBD 400 mcg/dose inhaler	Reduced cigarette consumption (p=0.002), reduced anxiety levels (p=0.04), no statistically significant reduction in cravings
Parkinson's Disease	Zuardi, et al. 2009	Open-label pilot study	6 subjects	N/A	CBD 150mg/day, increased weekly to max dose 400 mg/day	BPRS total scores improved (p<0.001), PPQ scores decreased (p=0.001), UPDRS decreased (p=0.046), CGI-I improved (p=0.001), MMSE and FAB scores no statistically significant change
	Chagas, et al. 2014	Double-blind RCT	21 subjects	Placebo (n=7)	CBD 75mg/day (N=7) or CBD 300mg/day (N=7)	UPDRS, BDNF levels, and H1-MRS no statistically significant change, PDQ-39 total score differences (p=0.034)
	Chagas, et al. 2014	Case series	4 subjects	N/A	CBD 75mg/day pr CBD 300mg/day	Case 1, 2, 3: no episodes of agitation, aggressive behavior or nightmares, Case 4: behavior and dream improvement, reduction in episodes of complex movement (laughing, kicking, pushing, punching)
Multiple Sclerosis	Novotna A, et al. 2011	Double-blind parallel group study	241 subjects	Placebo	Nabiximols: THC 2.7mg and CBD 2.5mg (max 12 sprays per day)	Highly significant difference in favor of nabiximols (P = 0.0002).
	Koehler J, et al. 2014	Medical Chart Review	166 subjects	N/A	1:1 ratio THC: CBD spray (mean dose 4 sprays)	Response rate of 72%, mean NRS score decreased by 57% in the first 10 days of treatment
	Paolicelli D, et al. 2016	Observational study	102 subjects	N/A	Nabiximols: THC 2.7mg and CBD 2.5mg (mean 6.5 sprays/day)	Mean reduction to the NRS spasticity score was 2.5 ± 1.2 points (P < .0001)
	Akgün K, .Akgün K, Essner U, Seydel C, Ziemssen T. 2019	Systemic Review	14 studies (n=7440)	N/A	Nabiximols: THC 2.7mg and CBD 2.5mg	Percentage of patients that reached MCID with at least a 20% reduction in NRS ranged from 41.9% to 82.9%.

ASD: ; CBD: ; GABA: ; MIC: ; RCT: ;

promising view of treatment for the future of Parkinson's disease patients.

Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) that was reported to affect 2.3 million individuals around the globe in 2018.[31] It is one of the most common causes of neurological disability in younger adults that leads to symptoms of pain, muscle spasticity, spasms, and bladder dysfunction.[32,33] As treatment of MS continues to be studied and developed, the management of the associated symptoms is important for patient compliance. Spasticity associated with the disease is present in 80% of patients and often leads to the symptoms of pain, spasms, and decreased function.[34] Current research has shown the effectiveness and safety of THC/CBD for this disease state, and might signal advancements in therapy in the United States.

Current medications being used for the indication of spasticity related to MS are baclofen, tizanidine, gabapentin, and dantrolene, but many patients fail to respond to these treatments or might suffer intolerable side effects with continuous usage.[35] Along with these more traditional treatments, nabiximols (Sativex®), a cannabis-based medication, has been approved for the same indication in Canada and some European countries, but has not yet been approved in the United States. It consists of a 1:1 ratio of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). It has been approved in other countries as an add-on therapy for symptom improvement in MS or as an alternative therapy in adults who have tried and failed other therapies.[35] Many of the studies on CBD use in MS address this medication's safety and efficacy in specific trials and a collective review.

In 2011, Novotna et al. created a randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy of nabiximols.[33] This was a 51-site study conducted throughout Europe for subjects who had MS and spasticity not relieved by another current antispastic drug. Nabiximols is formulated as an oromucosal spray. A spray containing 2.7 mg THC and 2.5 mg CBD was used in the study, where patients could administer 12 sprays in any 24-hour period. After four weeks of treatment in a single-blind preliminary study, only individuals who saw an improvement were continued on to a 12-week double-blind, randomized study. The primary end points evaluated were the

Numerical Rating Scale (NRS) for efficacy and safety and tolerability, while secondary end points included spasm frequency, sleep disruption, and Barthel Activities of Daily Living scores. The study showed nabiximols to improve spasticity in patients, but only among patients who had a successful four-week trial of therapy in the first phase of the study. Again, there appears to be efficacy of the medication, but further trials need to be conducted.

Similarly, in a 2014 study by Koehler et al., results showed benefits in spasticity in MS patients, but this time also demonstrated nabiximols being effective as monotherapy rather than as an add-on therapy.[36] Data was collected through medical charts at an MS clinic in Germany, which followed 166 patients over a 15-month timeframe who were initiated on the THC/CBD oromucosal spray. The study also included data on patients who had different forms of MS that included relapse-remitting, secondary progressive, and primary progressive forms. In all, 120 patients remained on the treatment and overall spasticity scores decreased with a mean dosage of 4 sprays per day. Those who discontinued use cited adverse effects of dizziness, fatigue, and oral discomfort.

In a 2015 study, Paolicelli et al. provided data regarding the post-marketing efficacy and safety of the THC/CBD medication in 102 MS patients.[37] They conducted a 40-week study where patients were assessed through the Expanded Disability Status Scale (EDSS), the NRS for spasticity, the Ambulation Index (AI), and a Timed 25-Foot Walk (T25-FW) at the beginning of treatment and then every 3 months after. The average dose in this cohort was 6.5 sprays per day, which reduced NRS spasticity scores by 2.5±1.2 points ($p<0.0001$). Yet, this data excluded patients who did not show significant improvement in spasticity scores after the first 4 weeks of the study. Researchers were able to determine the efficacy and safety of this medication but still needed additional structural evidence supporting the use due to data being self-reported by patients and excluding patients.

A recent meta-analysis in 2019 by Akgün et al. compiled 14 publications, including observational studies and treatment registries, that assessed patient characteristics, effectiveness, and safety outcomes.[35] They chose to look at studies outside of randomized controlled studies (RCTs) in order to confirm that what was reported in practice matched the results of RCTs. The mean dosage in the 14 publications reviewed was 5 to 6 sprays per day, and no new adverse events or reactions were noticed in practice. The selected reviews in this meta-analysis supported long-term THC:CBD spray use and noted the benefit of this medication as responders can be recognized within the first 4 weeks of treatment. The review provided evidence for the efficacy and safety of THC:CBD in clinical practice.

While some of the studies had limitations proving objective data, due to patients providing their own feedback and results, there does appear to be effective management of MS symptoms of spasticity with the combination medication. The safety and efficacy is continuously shown as similar to those of other medications with the same indication approved in the United States, which might signal another way to manage MS symptoms in the future.

Conclusion

Cannabidiol provides a frontier that still requires more research. Epidiolex® is the only form of CBD with FDA approval, but with more research, other cannabidiol forms could be approved in the future. As of October 2020, clinicaltrials.gov shows trials centered around conditions not mentioned in this article, like pain, epilepsy, alcohol use, PTSD, and heart failure.[38] Some of the current evidence, or lack thereof, should be considered when pharmacists and consumers approach these novel treatment options.

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