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Clinical Trials of Cannabinoids in Palliative Medicine

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Tottering behind the breaking wave of cannabis legalization in the United States and other countries is a nascent clinical science. Although recent rigorous reviews[1] conclude that cannabinoids may be useful adjunctive treatments for pain or chemotherapy-associated nausea and vomiting—two symptom domains squarely within the province of palliative medicine—we and our patients would be well served by more and better clinical trial-informed data about dose, specific cannabinoid molecules, duration of effects, coadministration with ''conventional'' symptom management therapies, potential drug interactions, side effects, and related information. Federal drug policy in the United States continues to classify cannabis as a Schedule I compound, maintaining a conflict with state legalization efforts, and adding to the complexity of conducting studies. It is no wonder that much of the world's clinical trials literature on uses of cannabinoids comes from other countries.

In this issue of JPM, a group of Australian palliative care clinicians have taken a novel and creative approach.[2] Capitalizing on a regulatory system that allows for the commercial production, prescription, and sale of small amounts of pure THC (tetrahydrocannabinol) and CBD (cannabidiol) preparations, these investigators undertook what is best described as a feasibility pilot study to investigate whether cannabinoid augmentation of an existing palliative medicine treatment plan for patients with cancer was associated with overall improvement in symptom control, as measured by total Edmonton Symptom Assessment Scale (ESAS) scores and additional secondary measures.

This effort to identify global or overall impacts on symptom measures represents a creative first step. The investigators designed a two-arm open-label trial and enrolled a relatively small group of patients ($n = 21$) who, along with their treating clinicians, chose either THC or CBD based on multiple factors—far from a blinded randomized trial but a pragmatic approach. To qualify, patients with cancer already followed by a palliative care service needed to have an Edmonton (ESAS) total symptom distress score (TSDS) of ≥10, at least one individual ESAS score ≥3, and an Australia-modified Karnofsky score (AKPS) of ≥30. Patients in the CBD arm received 50–300 mg/day of an oral oil-based commercial solution; patients in the THC arm received 2.5–30 mg/day of a similar oral oil-based commercial solution from the same Australian manufacturer. Patients uptitrated every 2 days until day 14 based on a set written schedule, to the end points of either satisfactory symptom relief or dose-limiting side effects. They were then encouraged to ''hold'' until day 14 and, if acceptable, till day 28 (both were follow-up measurement points). Patients also had the option of continuing on medicinal cannabinoids after the trial's completion.

The investigators enrolled 21 of 27 screened subjects for a four-month recruitment period. 18/21 completed the primary outcome measure (TSDSs) at day 14, but only 8/21 made it to day 28. The majority of withdrawals (6/21) were attributed to clinical worsening of the primary disease, followed by noncompliance (2/21) and intolerable side effects (1/21). Only three of the enrollees wished to continue on cannabinoids postcompletion. Median maximum tolerated CBD dose was 300 mg/day, and median maximum tolerated THC dose was 10 mg/day.

Forty-three percent of participants (9/21) met the definition of a beneficial response to cannabinoid augmentation (>6 point reduction in TSDS), but seven patients reported TSDS worsening of varying magnitude. However, when all 14-day completers were analyzed, there was no significant reduction in overall TSDS, and only the emotional subscale showed statistically significant improvement. There was also a signal toward ''overall'' symptom improvement, as measured by PGIC (Patent Global Impression of Change), in 44.4% of completers, and a trend toward reduced depression scores but not decreased anxiety scores on the DASS-21 (Depression, Anxiety, and Stress Scale).

Common adverse events included drowsiness, mood worsening, hypertension, nausea/vomiting, and abdominal pain, all of relatively low magnitude.

Despite the preliminary nature of this study's design and results, Good et al. have significantly advanced our understanding of how cannabinoids might fit into contemporary palliative medicine practice. As a result of their study we begin to get a feel for dosing; we see that overall TSDS scores appear to be a feasible way of measuring impact; we note that the majority of patients tolerate pharmaceutical cannabinoid augmentation; benefits, when achieved, may have more to do with overall ''well-being'' effects than reduction of specific symptoms or clusters; and cannabinoid augmentation seems generally safe and tolerable.

Larger-scale prospective placebo-controlled trials are needed. It will be important to better understand what kind of interindividual differences might account for those patients who report symptom worsening as opposed to improvement, and, if possible, to dissect the overall well-being benefits, if

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they persist in blinded studies. Perhaps we are on the cusp of discovering new basic mechanisms that mediate symptom burden, suffering, and relief?

References

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