Expanding Capabilities for Unapproved Cannabis-Derived Product Surveillance in the United States, TriNetX, July 1, 2018 – June 30, 2022

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Background

In June 2018, the US Food and Drug Administration (FDA) approved the first cannabis-derived cannabidiol (CBD) human drug product (Epidiolex®), currently indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients ages ≥1 year [1]. In December 2018, the U.S. Agriculture Improvement Act of 2018, also known as the 2018 Farm Bill, legalized hemp, defined as cannabis (Cannabis sativa L.) and derivatives of cannabis with low concentrations of the psychoactive compound delta-9-tetrahydrocannabinol (THC) (no more than 0.3 percent THC on a dry weight basis), and removed hemp from the definition of marijuana in the Controlled Substances Act (CSA). Since then, the emerging cannabis-derived products (CDPs) market—spanning thousands of non-FDA approved products marketed as drugs, foods, cosmetics, and dietary supplements—has generated unique regulatory and surveillance challenges [2].

[1] US Food and Drug Administration. Package insert. Epidiolex®; GW Research, Ltd. 2022 [updated February 24, 2022].

[2] US Food and Drug Administration. Cannabis Derived Products Data Acceleration Plan. Exploring Novel Data Sources to Help Inform Cannabis Derived Product Safety and Quality Gaps 2021 [updated October 16, 2021]

Objective

To explore the use of electronic health records (EHR) to identify exposures to unapproved CDPs, including cannabidiol (CBD), as part of active safety surveillance efforts in the United States.

We conducted descriptive analyses of CDP exposures using the TriNetX Live™ data network within the FDA's Sentinel System, which provided EHR data from 76 healthcare organizations (HCOs) across 31 states; 15 of these HCOs had the ability to extract information from clinical notes and map it to RxNorm terms using a proprietary natural language processing (NLP)-based algorithm. We required patients to have at least one encounter in the two years prior to a CDP exposure (day 0) recorded between July 1, 2018, through June 30, 2022, to define three exposure-based cohorts identified using relevant RxNorm terms: (1) CDP [excluding Epidiolex® or CBD 100 mg/mL]; (2) CBD [excluding Epidiolex® or CBD 100 mg/mL]; and (3) Epidiolex® or CBD 100 mg/mL. We assessed demographics, clinical characteristics (days [-365, 0]), and co-exposures (days [-30, 0]).

Results

Figure 1. Demographics, Cannabis-Derived Products Cohort

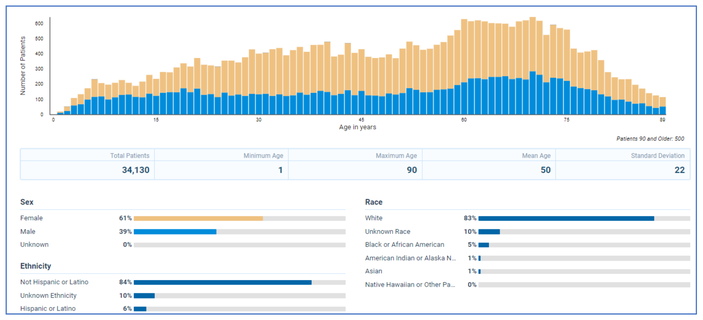


Figure 2. Demographics, Cannabidiol Cohort

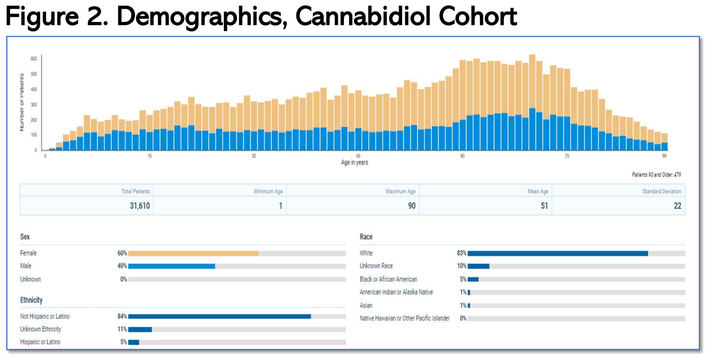
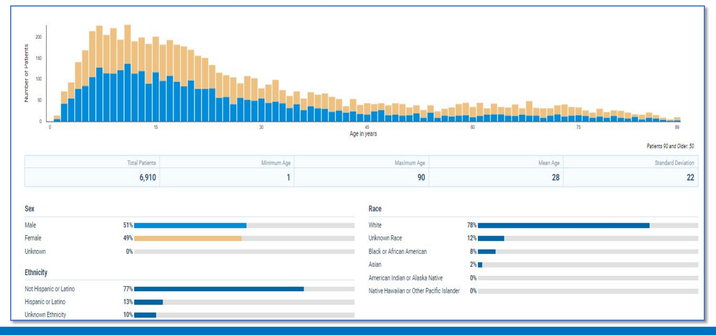


Figure 3. Demographics, Epidiolex Cohort



We identified 34,130 individuals with CDP exposure, 31,610 with CBD exposure, and 6,910 with Epidiolex® exposure (**Figures 1-3**). The CDP cohort had a mean age of 50 (SD:±22) years, 61% female, and 83% White. These individuals rarely (~4-5%) had a diagnosis recorded for conditions for which Epidiolex® is indicated (**Figure 4**). Patients' characteristics in the CBD cohort mirrored those in the CDP cohort as most (93%) of the exposures in the CDP cohort were CBD; the remainder (7%) included cannabinol, hemp, cannabis seed oil and whole extract, and cannabigerol. The Epidiolex® cohort included individuals with a mean age of 28 (SD: ±22) years, 51% female, and 78% White. Of them, 29% had recorded a diagnosis of Lennox-Gastaut syndrome, <1% of Dravet syndrome/tuberous sclerosis complex, and 50% of other epilepsies; 23% and 11% were concurrently on clobazam and valproate, respectively (**Figure 5**).

Figure 4. Clinical Characteristics, Days [-365, 0]

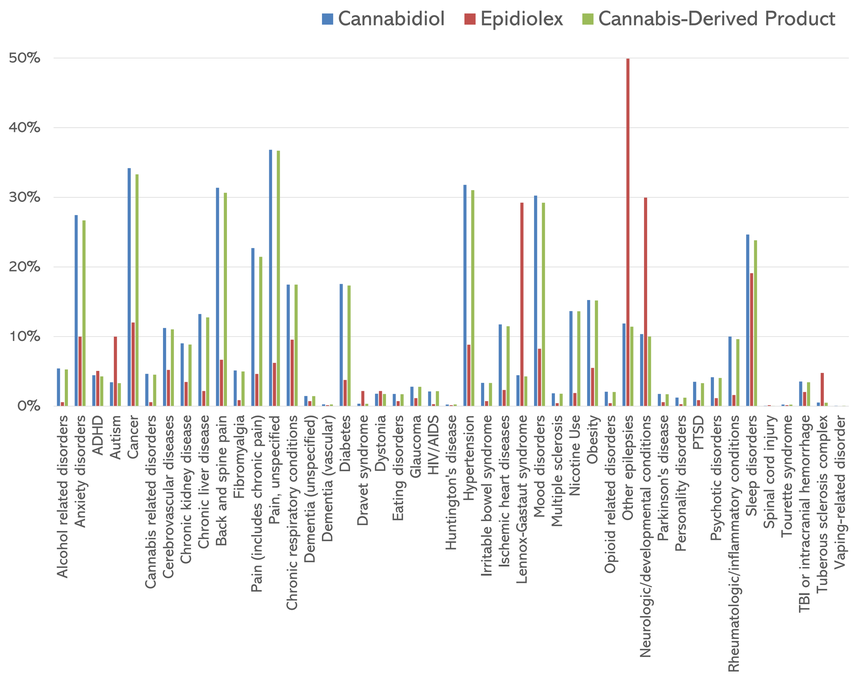
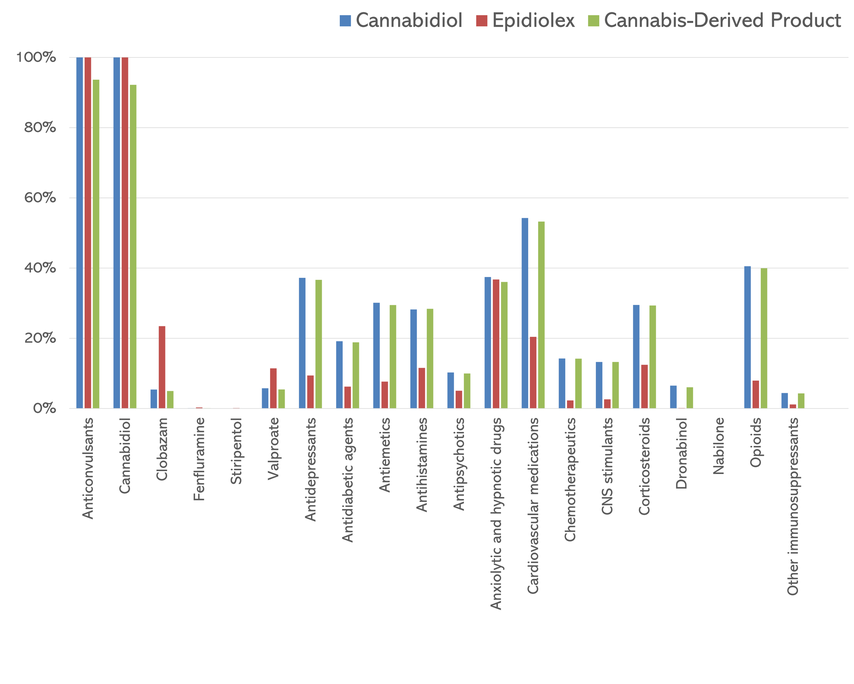


Figure 5. Co-exposures, Days [-30, 0]



Results suggest it is possible to identify non-FDA-approved CDPs exposures from clinical notes from recent and frequently refreshed data. However, the current NLP-based algorithms mostly identify non-approved CBD exposures and do not fully distinguish from the FDA-approved CBD product. In order to expand FDA's surveillance capabilities, further work may be warranted to develop and validate algorithms to identify other CDPs, besides CBD, and to restrict the use of EHR data for safety surveillance to HCOs with both NLP capabilities and brand name CBD information.

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The authors have no conflicts of interest to disclose.

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