

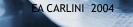


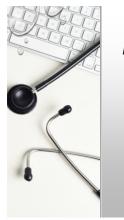
LEARNING OBJECTIVES

- DESCRIBE THE ENDOGENOUS
 CANNABINOID SYSTEM
- DESCRIBE THE PHARMACOLOGY OF THE MEDICAL MARIJUANA
- DIFFERENTIATE BETWEEN MARIJUANA AND CANNABIDIOL
- IDENTIFY POTENTIAL ADVERSE EVENTS AND
 DRUG INTERACTIONS



"VERY FEW DRUGS, IF ANY, HAVE SUCH A TANGLED HISTORY AS A MEDICINE. IN FACT, PREJUDICE, SUPERSTITION, EMOTIONALISM, AND EVEN IDEOLOGY HAVE MANAGED TO LEAD CANNABIS TO UPS AND DOWNS CONCERNING BOTH ITS THERAPEUTIC PROPERTIES AND ITS TOXICOLOGICAL AND DEPENDENCE-INDUCING EFFECTS."





MEDICAL MARIJUANA

RECREATIONAL VS. MEDICAL

BENEFIT VS. HARM

STATE VS. FEDERAL



"CBD WAVE"

- OVER 1000 CBD PRODUCTS BEING SOLD THROUGH INTERNET, DISPENSARIES, PHARMACIES, NATIONAL RETAIL STORES, BOUTIQUE SHOPS, ETC
- EXTENSIVE MEDIA COVERAGE
- INTERNATIONAL BUSINESS WITH ESTIMATED
 MARKET VALUE IN EXCESS OF \$60 BILLION
 OVER THE NEXT FEW YEARS





- ANXIETY
- CANNABIS USE DISORDER
- CROHN DISEASE
- DIABETES
- EPILEPSY
- HUNTINGTON DISEASE
- PARKINSONISM

- OPIOID USE DISORDER
- SCHIZOPHRENIA/PSYCHOSIS
- AUTISM
- CANCER

• PAIN

- SLEEP DISORDERS



- ENDOCANNABINOIDS
 - DERIVATIVES OF ARACHIDONIC ACID

ENDOGENOUS

- PHYTOCANNABINOIDS
 - INCLUDE HUNDREDS OF NATURALLY OCCURRING COMPOUNDS IN C. SATIVA
 - INCLUDES THC, CANNABINOL AND CANNABIDIOL
- SYNTHETIC CANNABINOIDS
 - LABORATORY PRODUCED CONGENERS OF THC AND CANNABIDIOL



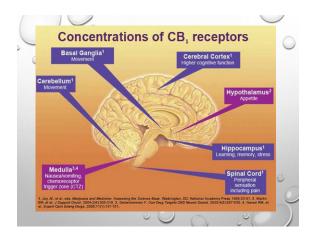
CANNABINOIDS

- THC
 - PSYCHOACTIVE, EUPHORIA, INCREASED REACTION TIME, LOSS OF MEMORY/COGNITIVE FUNCTIONING DECREASES, CLEARANCE HALF-LIFE OF LESS THAN 30 MINUTES AND IS NOT DETECTABLE IN URINE
- CBN (CANNABINOL)

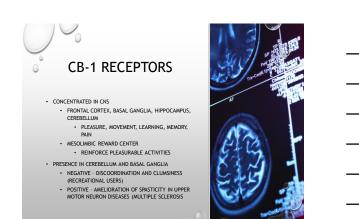
PAIN RELIEF, ANTI-INSOMNIA, PROMOTES GROWTH OF BONE CELLS, ANTIBACTERIAL, ANTI-INFLAMMATORY, ANTI-CONVULSIVE, APPETITE STIMULANT

- CBD
 - MAY MODIFY THC EFFECTS, INHIBITS CONVERSION OF THC TO 11-OH-THC (CYP450), FORMATION OF CBJ FROM THC DOES NOT OCCUR BY HEAT FROM SMOKING NOR BY HUMAN METABOLISM, BLOCKS ANXIETY AND PSYCHOLOGICAL SIDE EFFECTS PRODUCED BY THC INTAKE
- THC-COOH
 - LIPID SOLUBLE COMPONENT (METABOLITE), CAN BE STORED IN FAT CELLS FOR WEEKS TO MONTHS, FOUND IN BLOOD AND URINE, TYPICALLY APPEARS IN THE URINE WITHIN 60 MINUTES, BUT CAN TAKE AS LONG S4 HOURS, PRESENCE OF THE MAJOR THC-COOH JOOG INDICATES EXPOSUBE TO THC WITHIN 3 DAYS AFTER A SINGLE USE, TO APPROXIMATELY 30 DAYS IN HEAVY CHRONIC USERS

arijuana &^{a,}Tetrahydrocannabinol (THC), 2015, Mayo Clinic: Drugs of Abuse Testing, Ir://www.mayomedicalilabortaries.com/test-info/drug-bodo/marijuana.html (August 10, 2015) iestis, M. 2009, Human Cannabinod Pharmacokinetics, *National Institute of Health: Chem Biodivers*, v. 4(8), p. 1770-1804







CB-1 RECEPTORS

• HIPPOCAMPUS - MODULATE MOOD

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- PREFRONTAL CORTEX AND HIPPOCAMPUS -INFLUENCE CONCENTRATION, SHORT-TERM MEMORY, ATTENTION, AND TRACKING BEHAVIOR
- HYPOTHALAMUS APPETITE ("MUNCHIES")
- SPINAL CORD DORSAL PRIMARY AFFERENT TRACTS AND CENTRAL PAIN PATHWAYS -ANALGESIC ACTIONS





CB-1 RECEPTORS

- DOPAMINERGIC PATHWAYS IN REWARD CENTER - ABUSE AND DEPENDENCE
- VERY FEW RECEPTORS IN BRAINSTEM -MINIMAL EFFECT ON ANS
 NO KNOWN LETHAL OVERDOSE
 - REPORTED WITH THC

RANN RANN HEATED HEATEN HEATEN

UNDERSTANDING MEDICAL CANNABIS

http://steephilllab.com/wp-content/uploads/2014/01/Understanding-Medical-Cannabis-2.jpg





DRONABINOL (MARINOL)

- APPROVED 1985
- SCHEDULE III
- SYNTHETIC THC
- INDICATIONS
 - CHEMOTHERAPY INDUCED NAUSEA AND VOMITING
 - AIDS RELATED ANOREXIA AND WASTING





- DRONABINOL HAS GRADUAL ONSET OVER 30-60 MIN WITH DURATION OF EFFECT OF UP TO 6 HRS
- NABILONE'S ONSET IS 60-90 MIN BUT CAN LAST UP TO 12 HRS
- ANTIEMETIC EFFECT OF BOTH AGENTS IS APPROXIMATE OR GREATER TO THAT OF PHENOTHIAZINES
- NARROW GAP BETWEEN THERAPEUTIC DOSE AND ADVERSE EFFECTS EUPHORIA, DYSPHORIA, COGNITIVE CLOUDING, DROWSINESS, DIZZINESS

 - ADVERSE EFFECTS MORE PROBLEMATIC IN NAÏVE USERSE





DRONABINOL AND NABILONE

- VARIABLE ABSORPTION AND FIRST PASS EFFECTS RESULT IN UNPREDICTABLE BLOOD LEVELS
- SEROTONIN RECEPTOR ANTAGONISTS (ODANSETRON) HAVE REPLACED THESE FOR ANTIEMETICS GREATER POTENCY
- MORE PREDICTABLE ACTIONS
- MINIMAL PSYCHOTROPIC EFFECTS
- IV DOSING AVAILABLE
- NOT CONSIDERED FIRST LINE AGENTS FOR NAUSEA RESERVED FOR CASES RESISTANT TO STANDARD THERAPIES



THC AND CANNABIDIOL OPPOSE EACH OTHER

THC

- CANNABIDIOL
- EUPHORIA
- ANXIETY
- PSYCHOSIS
- COGNITIVE IMPAIRMENT
- HUNGER
- ANTI-ANXIETY
 ANTI-PSYCHOTIC
- NO COGNITIVE
 IMPAIRMENT

• NO EUPHORIA



NABIXIMOLS (SATIVEX)

- AVAILABLE IN CANADA PHASE III TRIALS IN US
 INDICATIONS
 - CANCER PAIN
- NEUROPATHIC PAIN (MULTIPLE SCLEROSIS)
 AVAILABLE AS AN ORAL SPRAY (2.7 MG THC + 2.5 MG CBD)
- CONTAINS BOTH THE AND CANNABIDIOL
- PROVIDES RAPID ONSET WITHOUT SEDATION AND MEMORY IMPAIRMENT



NABIXIMOLS (SATIVEX)

- PEAK THC CONCENTRATIONS ARE APPROXIMATELY 20X LOWER THAN THOSE OBTAINED WITH SMOKED CANNABIS
- LOWER THC LEVELS REDUCE POTENTIAL FOR DEPENDENCE

EPIDIOLEX

PURIFIED FORM OF CBD

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- FIRST FDA APPROVED PLANT DERIVED CBD PRODUCT
- INDICATED FOR SEVERE FORMS OF EPILEPSY
- ORIGINALLY APPROVED AS A SCHEDULE I BUT RECLASSIFIED TO SCHEDULE V
- LABEL WARNING:
- DRUG TESTING
 - ADVISE PATIENTS OF THE POTENTIAL FOR POSITIVE CANNABIS DRUG SCREENS.



2018 FARM BILL

- EXCLUDED HEMP AND HEMP DERIVATIVES FROM SCHEDULE I DEFINITION OF CANNABIS
- ALLOWED FARMERS TO PRODUCE INDUSTRIAL HEMP LED TO A HEMP SURPLUS
- CANNABIS PLANTS CONTAINING <0.3% DELTA-9-THC AND THEIR DERIVED PRODUCTS WERE NO LONGER SCHEDULED PRODUCTS
 - CBD DELTA-8-THC
 - DELTA-10-THC
 - TETRAHYDROCANNABINOL-O ACETATE





- 84 CBD PRODUCTS TESTED FROM 31 DIFFERENT ONLINE DISTRIBUTORS
- 7 OUT OF 10 PRODUCTS HAD DIFFERENT LEVELS OF CBD THAN SPECIFIED ON THE LABEL HALF OF THE PRODUCTS HAD MORE CBD THAN
- INDICATED
- QUARTER OF THE PRODUCTS HAD LESS CBD THC IN 18 OF THE SAMPLES TESTED
- CONCERN OVER OFF-LABEL USE





CBD SAFETY

- LARGELY DERIVED FROM EPIDIOLEX CLINICAL DATA
- DOSE RELATED INCREASE IN HEPATIC ENZYMES AND LIVER INJURY
- METABOLISM
 - CYP3A4 AND 2C19 SUBSTRATE
- INCREASED RISK OF SEDATION/DROWSINESS
 WHEN USED WITH OTHER CNS DEPRESSANTS





- OCCURS AT VERY LOW LEVELS IN LEGAL HEMP PLANTS
 CAN BE READILY SYNTHESIZED FROM CBD
 - SYNTHETIC DELTA-8-THC CAN BE ADDED IN HIGH CONCENTRATIONS TO EDIBLES AND INHALATION PRODUCTS AND MARKETED AS LEGAL HEMP
 - PLANT MATERIAL WITH LOW DELTA-8- AND DELTA-9-THC ARE BEING LACED WITH SYNTHETIC DELTA-8 THC RESULTING IN MUCH HIGHER CONCENTRATIONS OF DELTA-8-THC THAN PRESENT NATURALLY





- DELTA-8-THC PRODUCTS HAVE NOT BEEN EVALUATED OR APPROVED BY THE FDA
 - FDA CONSIDERS THESE PRODUCTS AS SUPPLEMENTS
 CONCERNS OVER VARIABILITY IN PRODUCT
 FORMULATIONS
 - MAY BE MARKETED AS "HEMP PRODUCTS"
- ADVERSE EVENTS REPORTED
- DELTA-8-THC HAS PSYCHOACTIVE PROPERTIES
- SYNTHESIS OF DELTA-8-THC SYNTHESIS INVOLVES TOXIC
 CHEMICALS



DELTA-8-THC

ACTIONS SIMILAR TO DELTA-9-THC

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- LESS POTENT AND SHORTER DURATION OF ACTION THAN DELTA-9-THC (DOSE RELATED)
- SOME PRODUCTS CONTAIN VERY HIGH CONCENTRATIONS OF DELTA-8-THC LEADING TO ADVERSE EFFECTS





TETRAHYDROCANNABINOL-O ACETATE

- MORE POTENT THAT DELTA-9-THC
- RELEASES TOXIC KETENE GAS WHEN HEATED



CANNABIS – DISEASE CONTRAINDICATIONS

- POTENTIAL RISKS OUTWEIGH BENEFITS UNDER THE FOLLOWING CONDITIONS
 - HYPERSENSITIVITY
 - UNDER THE AGE OF 25
 - PERSONAL OR FAMILY HISTORY OF PSYCHOSIS OR SCHIZOPHRENIA
 - CURRENT OR PAST HISTORY OF CANNABIS USE DISORDER OR OTHER ACTIVE SUBSTANCE USE DISORDER
 - DISORDER

 SIGNIFICANT CVS OR PULMONARY DISEASE
 - PREGNANT OR BREAST FEEDING

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COLORADO MARIJUANA ANALYSIS - MARCH 2015

- DENVER LAB ANALYZED MORE THAN 600 SAMPLES OF BUD PROVIDED BY CERTIFIED GROWERS AND SELLERS
 AVERAGE THC LEVEL WAS 18.7% AND SOME RETAIL POT
- AVERAGE THC LEVEL WAS 18.7%, AND SOME RETAIL POT CONTAINED 30% THC OR MORE LITTLE OR NO CANNABIDIOL (CBD) – THE AVERAGE CBD AMOUNT: 0.1%
 - RECALL: CBD LACKS DETECTABLE PSYCHOACTIVITY AND INSTEAD HAS ANTI-INFLAMMATORY, ANALGESIC, ANTI-NAUSEA, ANTI-ENETIC, ANTI-PSYCHOTIC, ANTI-ISCHEMIC, ANYIOLYTIC, AND ANTI-PSILEPTIFORM EFFECTS - THE "MEDICAL" IN MEDICAL MARIJUANA.



- DIFFERENCE IN METHOD OF USE
- IMPURITIES IN RECREATIONAL MARIJUANA (DUPONT, 2000)
 - 400 DIFFERENT CHEMICALS FROM 18
 DIFFERENT CHEMICAL FAMILIES
 - SMOKE CONTAINS MORE THAN 2000 CHEMICAL COMPOUNDS







CHALLENGES OF USING CANNABIS

CONTAMINANTS

- ASPERGILLUS FUNGUS AND BACTERIA -CAN LEAD TO PNEUMONIA
- HEAVY METALS (ALUMINUM, CADMIUM)
- ORGANOPHOSPHATE PESTICIDES
- GLASS BEADS AND SAND IN STREET CANNABIS -USED TO INCREASE WEIGHT BUT CAN DAMAGE ORAL MUCOSA AND LUNGS



SOME IMPORTANT CONCERNS

- THC AND OTHER COMPONENTS OF MARIJUANA AFFECT NEUROTRANSMITTERS AND CELL GROWTH PATHWAYS
 - THC CAN STAY IN THE BODY FOR WEEKS, ESPECIALLY IN MATERNAL TISSUES THAT MAY SERVE AS RESERVOIRS (DOG STUDIES)
- THC HAS HALF-LIFE OF 8 DAYS IN FAT DEPOSITS AND CAN BE DETECTED IN BLOOD FOR UP TO 30 DAYS
- THC READILY CROSSES THE PLACENTA, WHICH CAN SLOW CLEARANCE AND PROLONG HUMAN FETAL EXPOSURE

SOME IMPORTANT CONCERNS

- CONCENTRATIONS OF THC HAS INCREASED SIGNIFICANTLY SINCE 1970 (25-FOLD) AND MAY BE STRONGER IN EDIBLE FORMS
- THC AND CANNABIOIDS INTERFERE WITH FOLIC ACID
- CANNABINOID SIGNALING IS IMPORTANT ROLES IN DEVELOPMENT OF MOUSE EMBRYO





INCREASED HOSPITALIZATIONS DUE TO SYNTHETIC THC

- SEVERAL PATIENTS HOSPITALIZED
- SEVERE HALLUCINATIONS, NO GAG REFLEX, DIFFICULT BREATHING
- PRODUCTS INCLUDED "BOTANICAL SACHET", "SEXY MONKEY", "CRAZY MONKEY"



MARIJUANA ADDICTION?

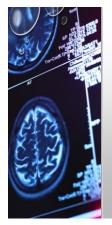
- MARIJUANA USE DISORDER (ADDICTION IN SEVERE CASES)
- 30% OF THOSE WHO USE MARIJUANA MAY HAVE MARIJUANA USE DISORDER
- PEOPLE WHO BEGIN USING MARIJUANA BEFORE THE AGE OF 18 ARE 4-7X MORE LIKELY TO DEVELOP MARIJUANA USE DISORDER



MARIJUANA USE DISORDER

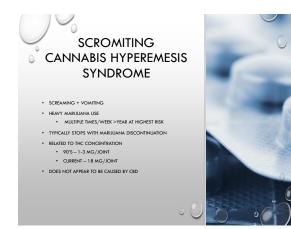
- OFTEN ASSOCIATED WITH DEPENDENCE
- WITHDRAWAL SYMPTOMS

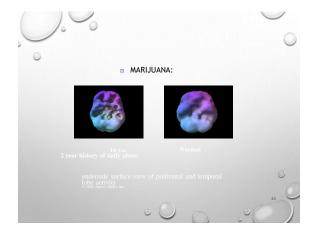
 - MOOD AND SLEEP DIFFICULTIES
 - DECREASED APPETITE



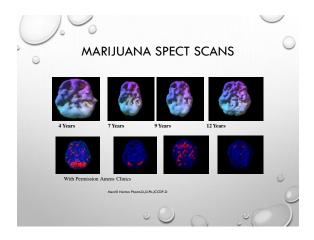
MARIJUANA USE DISORDER

- SYMPTOMS PEAK WITHIN FIRST WEEK AND LASTS UP TO 2 WEEKS
- DEPENDENCE OCCURS DUE TO BRAIN REDUCING PRODUCTION AND SENSITIVITY TO ENDOCANNABINOID RECEPTORS (DOWNREGULATION)
- IN 2015, ESTIMATED THAT 4 MILLION PEOPLE IN THE US MET CRITERIA FOR MARIJUANA USE DISORDER WITH 138,000 VOLUNTARILY SEEKING TREATMENT.















ADDICTION





THERAPEUTIC BENEFITS **OF CANNABINOIDS**

- "INSUFFICIENT EVIDENCE EXISTS FOR THE USE OF MEDICAL CANNABIS FOR WHICH ITS USE IS ADVOCATED. DESPITE THE LACK OF EVIDENCE, VARIOUS US STATE GOVERNMENTS HAVE RECOMMENDED CANNABIS FOR THE MANAGEMENT OF MORE THAN 50 MEDICAL CONDITIONS"
- "CANNABIS IS USEFUL FOR SOME CONDITIONS, BUT PATIENTS WHO MIGHT BENEFIT MAY NOT GET APPROPRIATE TREATMENT BECAUSE FO SUFFICIENT AWARENESS REGARDING THE EVIDENCE SUPPORTING THE OR OCH VISION FROM FEDERAL LAW DEEMING CANNABIS ILLEGAL"

KP HILL. JAMA 322: 974-75



- RISKS OF FALLS IN ELDERLY ESPECIALLY WHEN COMBINED WITH OTHER CNS DRUGS OR BP MEDS
- NO CONTROL OVER WHAT THE PATIENT IS GETTING IN DISPENSARIES
- · PATIENTS OFTEN DO NOT KNOW HOW MUCH THC OR CBD THEY ARE ON.





ALABAMA MEDICAL MARIJUANA

- CONVENTIONAL THERAPY OR MEDICAL



QUALIFYING CONDITIONS

- AUTISM SPECTRUM DISORDER
- PANIC DISORDER
- · DEPRESSION
- · PTSD
- CROHN'S DISEASE
- TOURETTE'S SYNDROME
- PARKINSON'S DISEASE
- SPASTICITY ASSOCIATED W/MOTOR NEURON DISEASE
- · EPILEPSY OR SEIZURE CONDITION TERMINAL ILLNESS

SICKLE CELL ANEMIA

- + HIV/AIDS RELATED NAUSEA OR WEIGHT LOSS
- CANCER RELATED CACHEXIA, NAUSEA, VOMITING, WEIGHT LOSS, OR CHRONIC PAIN
- PERSISTENT NAUSEA NOT RESPONSIVE TO TRADITIONAL TREATMENT
- CHRONIC OR INTRACTABLE PAIN NOT RESPONSIVE TO CONVENTIONAL TREATMENT



- PATIENT SHOWS PROOF OF ALA RESIDENCY
- MED MARIJUANA CARD ISSUED (\$65)
- PATIENT ENTERED INTO STATEWIDE CANNABIS REGISTRY
- MINORS
 - UNDER 19 YO GOES THROUGH SAME PROCESS
 - MUST HAVE A DESIGNATED CAREGIVER

 - BOTH MINOR AND CAREGIVER MUST BE ALA RESIDENTS AND REGISTERED WITH STATE CANNABIS COMMISSION





ALA MED MARIJUANA LAW:

- DOES NOT LEGALIZE MARIJUANA FOR EVERYONE
- RECOGNIZES THAT "RECREATIONAL MARIJUANA REMAINS A SIGNIFICANT THREAT TO PUBLIC HEALTH AND SAFETY" · PENALTY FOR VIOLATING THE LAW
 - CLASS B FELONY IF YOU POSSESS, DISTRIBUTE, MANUFACTURE, OR USE MARIJUANA W/O LICENSE INCLUDING IF YOU'RE GIVEN THE DRUG BY A REGISTERED PATIENT, CAREGIVER OR DISPENSARY
 - JAIL IF YOU POSSESS >70 DAILY DOSES, EVEN WITH MED MARIJUANA LICENSE



ALA MED MARIJUANA -DOSE

- CAN BE PRESCRIBED FOR UP TO 12 MONTHS AT A TIME
- DAILY DOSAGE CAN'T EXCEED 50 MG THC BUT MAY BE INCREASED TO 75 MG IF PRESCRIBER DETERMINES IT'S "MEDICALLY APPROPRIATE" OR IF PATIENT IS TERMINALLY ILL
- IF DOSAGE EXCEEDS 75 MG, PATIENT'S DRIVER LICENSE WILL BE SUSPENDED.



MARIJUANA -ACCEPTABLE FORMS

- NON-SUGAR COATED GELATINOUS CUBE, CUBOID

ALA MEDICAL MARIJUANA – NON-APPROVED DOSAGE FORMS

- - STATE CANNIBIS COMMISSION WILL ESTABLISH "ONE UNIVERSAL FLAVOR" FOR THE JELLY CUBES AND LOZENGES





- EMPOYERS DO NOT HAVE TO ALLOW OR ACCOMMODATE THE
 USE OF MEDICAL MARIJUANA
 - THEY CAN REFUSE TO HIRE OR LET SOMEONE GO EVEN IF DRUG IS USED LEGALLY
 - MAY CREATE A DRUG TESTING POLICY AGAINST MED MARIJUANA
 - MAY REQUIRE EMPLOYEES TO NOTIFY THEM IF THEY START
 USING THE DRUG LEGALLY
 - EMPLOYERS AREN'T REQUIRED TO PAY FOR DRUG THROUGH MEDICAL INSURANCE OR REIMBURSEMENT PLANS CAN DENY WORKERS COMP FOR SOMEONE WHO FAILS A DRUG TEST OR REFUSES TO TAKE ONE





ALA MED MARIJUANA -WORKPLACE

LITTLE LEGAL DEFENSE FOR EMPLOYEE

- CAN'T SUE THE EMPLOYER
- IF FIRED CAN BE CONSIDERED HAVING BEEN DISCHARGED FROM JOB BECAUSE OF
- · MAY BE MORE DIFFICULT TO COLLECT





INGESTION OF COMMERCIALLY AVAILABLE COLD-PRESSED HEMP SEED OIL RESULTED IN POSITIVE WORKPLACE DRUG TEST (J ANAL TOXICOL 21, 1997)

- THC- COOH DETECTED
- NO BEHAVIORAL EFFECTS OBSERVED
- PRODUCTS MAY HAVE THC
- VERY HIGH DOSING





MEDICAL MARIJUANA MISCALCULATION

 A 52-YEAR-OLD MAN WHO HAD RECEIVED TREATMENT FOR ANAPLASTIC ASTROCYTOMA RESENTED TO THE ED WITH ACUTE DELIRIUM AND CARBLED SPECH. THE INITIAL WORKUP IDENTIEPE IN OCLEAR CAUSE. TWAS THEN LIAMENED THAT HE HAD REEN USING A HIGHLY CONCENTRATED FORMULATION OF LIQUID MARILLANA AT HOME, WITH 10 TO 20 TIMES THE RECOMMENDED DOGS OF TETRAHYDROCANNABINOL PER 0.1 ML OF FLUID.

NEJM 381: 1086-87, 2019

