

Treatment-Resistant Depression

AUGUST 2016

Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, clinicaltrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Treatment-resistant depression (TRD) is somewhat difficult to define due to a lack of consensus on how to operationally define it. At a minimum, TRD is defined as an inadequate response to at least one antidepressant for adequate dosing and duration in treating major depressive disorder (Fava 2003; Berlim 2007), but in practice, it appears that it is more commonly defined as lack of adequate response to at least two different classes of antidepressant medications for adequate dosing and duration (Berlim 2007). Since TRD applies

to a subset of individuals with major depressive disorder (MDD), the following sentences describe MDD diagnosis.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association 2013) is the current authoritative tool for classifying and diagnosing MDD. The following criteria (A-E) are outlined verbatim from the DSM-5 for the diagnosis of MDD, with criteria A-C representing a major depressive episode (MDE).

Criterion A – Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation.)
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Criterion B – The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Criterion C – The episode is not attributable to the physiological effects of a substance or to another medical condition.

Criterion D – The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

Criterion E – There has never been a manic episode or a hypomanic episode.

Prevalence

Estimates from the National Comorbidity Survey Replication study indicates a national lifetime prevalence of MDD in adults to be at 16.2% (Kessler et al. 2003) which, as of July 2015 population estimates (US Census Bureau) translates into more than 40.1 million US adults having had MDD sometime in their lifetime. Data from the same study also indicated that 6.6% of adults suffered from MDD in the last 12-months which, as of 2015 US Census Bureau estimates, affects approximately 16.3 million US adults. Of those experiencing MDD, 50-60% are estimated to not achieve adequate response to at least one 8-week antidepressant trial (Fava et al. 2003; Rush et al. 2006).

Current Therapies

According to the American Psychiatric Association's Practice Guideline for Treatment of Patients with Major Depressive Disorder, 3rd Edition (2010), both pharmacologic and non-pharmacologic therapies are used on MDD patients and, by extension, TRD patients. A combination of both pharmacologic and non-pharmacologic therapies may be recommended by clinicians depending on observed clinical features. A patient's initial preferences for treatment and any prior experiences with former treatment is also considered when developing a treatment plan. The following paragraphs in this section will discuss both pharmacologic and non-pharmacologic treatments that have targeted MDD patients in situations where comparative efficacy was ascertained or when TRD patients were specifically followed in the course of treatment. Lastly, it is important to introduce typical efficacy measures for MDD treatments: remission and treatment response. Remission in the literature refers to clinical absence of depressive symptoms (typically represented as a score below a set threshold to reflect clinical absence), while response typically refers to achieving at least a 50% reduction in depressive symptoms compared to baseline measures.

Pharmacologic Treatments

Clinical practice guidelines overwhelmingly agree with the use of antidepressants as the first line of pharmacotherapy for MDD patients (APA 2010), with many patients starting on one of the following medications before moving onto other pharmacologic options: a selective serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor (SNRI), mirtazapine, or bupropion. When patients do not show signs of remission or do not respond adequately to initial treatment, typical strategies in clinical practice are to switch (discontinue current treatment and switch to another antidepressant within the same class or in a different

class), combine (add another antidepressant on top of the current antidepressant treatment, or augment (add a non-antidepressant medication on top of current antidepressant treatment).

The National Institute of Mental Health (NIMH) funded the largest and longest running prospective study on depression treatment trials in primary and specialty care settings (Sequenced Treatment Alternatives to Relieve Depression; STAR*D) in patients who did not show remission of depressive symptoms to initial antidepressant treatment. This particular study was designed to reflect typical treatment course found in clinical practice, which allowed for high generalizability of results in actual clinical practice. MDD patients already receiving care in an outpatient setting (both primary and specialty care clinics) were allowed to participate in this study. Patients who did not experience remission with the initial antidepressant treatment (citalopram; Level 1 treatment) or found the treatment intolerable were given the opportunity to continue onto other treatment strategies (sequentially from Level 2-Level 4), which involved switching to or combining/augmenting with another antidepressant or other drugs thought to enhance antidepressant response. Patients at each Level of progression indicated which treatment options they would be amenable to trying among a specified selection list, and their selections were used to randomly assign participants to one of those options. With each Level progression, clinicians increasingly dealt with patients with greater treatment resistance (patients achieving remission did not go onto the next Level within the study, as the intended outcome was achieved).

Results from the Level 1 trial (citalopram) showed a 28-33% remission rate in MDD patients, with the majority achieving remission by the 7th week of treatment. In addition, roughly 9% reported citalopram as intolerable (Trivedi et al. 2006). Patients who continued to Level 2 treatment (those not achieving remission or finding the Level 1 trial intolerable) were given the option to switch to another antidepressant or combine citalopram with another antidepressant. Patients selecting the switch option were randomly assigned to be prescribed either within-class sertraline or another antidepressant of another class (bupropion-SR or venlafaxine-XR; Rush et al. 2006). Patients selecting to combine for the Level 2 trial were randomly assigned to combine either bupropion-SR or buspirone with citalopram (Thase et al. 2007). Those who switched treatment for Level 2 had remission rates that were comparable across all three antidepressants at roughly 25%, with most achieving remission within 5-6 weeks (Rush et al. 2006). Those combining citalopram with another antidepressant showed slightly higher rates of remission (~30%) compared to the switching strategy (Thase et al. 2007), although due to the nature of the study design, direct comparison of Level 2 switching and combining treatment strategies was not available. Overall, Level 1 and 2 treatment results indicate that clinicians can expect close to 50% of all MDD patients to achieve remission by trying two antidepressant treatments (via switching or combining) for adequate duration and dosage.

Patients undergoing Level 3 trials (those failing to achieve remission or experiencing intolerable effects from two antidepressant treatments (Levels 1 and 2)) were randomly assigned to an augmentation or switching strategy (Nierenberg et al. 2006; Fava et al. 2006). Patients in the augmentation trial were randomly assigned to receive citalopram with either lithium (a mood stabilizer) or triiodothyronine (T3; a thyroid hormone which may accelerate

patient response to antidepressants; Aronson et al. 1996). Those in the switch trial were randomly assigned to switch to mirtazapine (atypical antidepressant) or nortriptyline (tricyclic antidepressant). Overall, the augmentation trial showed remission rates at approximately 19-20% with no difference between lithium and T3 augmentation. However, those augmenting with lithium reported greater intolerable effects than with T3 (Nierenberg et al. 2006). Switching for Level 3 treatment showed comparable remission rates between mirtazapine and nortriptyline (overall remission at 10-16%) with similar tolerability across switching treatments (Fava et al. 2006).

Lastly, a Level 4 treatment trial was made available to patients who had failed to achieve depression remission (or experienced intolerable effects) with the three prior antidepressant treatments. In this trial, patients were randomly assigned to switch to either tranylcypromine (monoamine oxidase inhibitor) or given a combination of venlafaxine (serotonin-norepinephrine reuptake inhibitor) and mirtazapine. Both treatments lead to similar remission rates (overall remission roughly 10-15%; McGrath et al. 2006).

Overall, results from the STAR*D treatment trials generally mirror typical treatment strategies found in clinical practice for nonpsychotic MDD patients in an outpatient setting. Results indicate that roughly half of all MDD patients can expect to achieve symptom remission after two antidepressant treatments, with subsequent switching, combining, and/or augmentation trials leading to diminished remission rates over time. Taking all of the STAR*D data, Rush et al. 2006 estimated remission rates at Levels 1-4 at 36.8%, 30.6%, 13.7%, and 13.0%. Cumulative remission rates through Level 4 was estimated to be at 67%, indicating that roughly 33% of patients will not have achieved remission by their fourth trial. While there are limitations to the study design (lack of placebo, open-label treatment, lack of variety in Level 1 treatment, etc.), it provides clinicians information about what they might possibly expect from MDD patients over the course of sequential pharmacotherapy trials.

Non-Pharmacologic Treatments

Non-pharmacologic options have shown some promise for treating TRD, although the variety of treatments are less varied than pharmacologic interventions. Some commonly encountered treatments are: psychotherapy, electroconvulsive therapy, vagus nerve stimulation, and repetitive transcranial magnetic stimulation.

Cognitive-behavioral therapy (CBT) and its derivatives have shown to be somewhat effective in combination with antidepressants in individuals showing some antidepressant-resistance. For example, in a group of SSRI-resistant adolescents (similar to the Level 1 resistance found in the STAR*D trials), a combination of CBT and switching to another antidepressant (either within class or out-of-class) shows greater clinical response than those solely switching to another antidepressant alone (Brent et al. 2008). One of the Level 2 trials in the STAR*D study also examined switching from citalopram (Level 1 non-remission patients) to cognitive therapy or augmenting citalopram with cognitive therapy. Results from this Level 2 STAR*D study found that cognitive therapy lead to similar remission rates as Level 2 antidepressants (23-30%), regardless of whether it was used alone or as an add-on to

citalopram treatment (Thase et al. 2007). However, the time to reach comparable remission rates took longer in the cognitive therapy augmentation group (cognitive therapy + citalopram) compared to the citalopram augmentation (citalopram + another antidepressant medication).

Electroconvulsive therapy (ECT) has shown to be quite effective, even showing evidence for being superior to some forms of antidepressants in patient response (Pagnin et al. 2004). However, it is rarely used as a first-line treatment; it is typically used as a last resort for patients. For example, it may be provided as an option for suicidal patients (Kellner et al. 2005) or when pharmacotherapies have been ineffective (Husain et al. 2005). While improvements in mood occur fairly rapidly, relapse is relatively high after ECT (Shelton et al. 2010). While maintenance ECT may prevent some relapse, memory impairments from this treatment can deter patients from opting for this treatment.

Vagus nerve stimulation (VNS) was approved by the FDA in 2005 for use in TRD, and it seems to be relatively well tolerated in patients (Nemeroff et al. 2006). Roughly 25-30% of patients have been shown to respond to VNS, with remission rates around 15-17% over short-term VNS (Nemeroff et al. 2006).

Repetitive transcranial magnetic stimulation (rTMS) is used experimentally to treat TRD and shows some effectiveness in response (Shelton et al. 2010). However, results also vary due to considerable methodological differences suggesting further study.

To conclude, the STAR*D trials - which mirror the sequential treatment strategies (pharmacotherapy and psychotherapy) typically found in clinical practice – showed that roughly two-thirds of nonpsychotic MDD patients will eventually achieve remission by their fourth treatment trial with adequate time and dosing. This also highlights that, with current strategies for addressing treatment-resistant individuals, there still remains a subset (~ 1/3) whose needs may not be satisfactorily met with current interventions. Besides the challenges of treatment-resistance, relapse is always a concern at any level of treatment, with relapse being more likely to occur for patients requiring more treatment steps. For example, 33% of those who achieved remission at Level 1 will relapse within a year while half of those who achieve remission by Level 4 will relapse within a year (Rush et al. 2006). Relapse also occurs earlier the more treatments steps a patient experiences (Rush et al. 2006).

Pre-Clinical Research

Preclinical research studies have begun in earnest since initial speculations about the role of the endocannabinoid system in depression pathophysiology (Hill & Garzalka 2005). This includes delivering phytocannabinoids (THC and CBD) as well as synthetic cannabinoids in animal models of depression. There has also been interest in manipulating the pharmacokinetic processes of cannabinoids (e.g., metabolism of cannabinoids) with novel compounds to also improve depressive symptomology in animal models. Representative cases of such studies are described below.

Bambico FR, Hattan PR, Garant J-P, Gobbi G. Effect of delta-9-tetrahydrocannabinol on behavioral despair and on pre- and postsynaptic serotonergic transmission. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2012; 38: 88-96.

This experimental study explored the administration of THC on serotonergic (5-HT) activity and depressive-like behavior in rats. SSRIs, which are often a first line treatment for depression, increase 5-HT transmission (particularly in the dorsal raphe and hippocampal regions). Therefore, this particular study explored whether THC might have similar effects as SSRIs on 5-HT_{1A} activity and induce antidepressant-like behavior in rats. Different rat groups received intraperitoneal injections of either THC (1 mg/kg), citalopram (an SSRI; 10 mg/kg), or vehicle solution (control), which were administered either as a single injection or repeated injections (over 5 days). In some cases, the CB-receptor antagonist rimonabant was also administered to examine for reversal of THC's effects in electrophysiological and behavioral measures.

Electrophysiological recordings were conducted in dorsal raphe and hippocampal 5-HT_{1A} neurons. For the behavioral measure, the forced swim test (FST; Porsolt et al. 1977; Can et al. 2012) was implemented to measure for depressive-like behaviors. The FST has often been used on rodents (typically rats and mice) in preclinical trials to test for efficacy of antidepressants. In the FST, rodents are placed into a cylinder filled with water levels sufficient to require them to engage in locomotor activity in order for them to not drown. Within this apparatus they cannot escape, and rodents can adopt a more active or passive coping strategy to survive in this environment. When rodents are actively engaged in not drowning, they will show significant locomotor activity (swimming, attempts to climb the walls of the cylinder, etc.) to stay afloat in the water. A more passive coping strategy typically manifests as significantly reduced locomotor activity that is just sufficient enough to keep them above water—this particular behavior is interpreted as learned behavioral despair (hopelessness or “giving up”). Rodents engage in the FST for two trials, the second of which is the trial of interest where measures of locomotor activity are collected (first trial introduces the rat to the environment and serves as a learning phase). The amount and duration of immobility, climbing, and swimming are recorded as dependent measures during the second FST trial. If rodents in an active treatment group spend less time in passive survival mode compared to control, a drug is interpreted as having antidepressant effects.

Repeated injections of THC (1 mg/kg) as opposed to a single injection of THC increased the frequency of swimming behavior in the FST, comparable to the citalopram rat group (compared to controls). Both the THC and citalopram groups showed decreased total time spent in an immobile state in the FST compared to controls, with the administration of rimonabant with THC reversing this effect. Electrophysiological recordings from the dorsal raphe 5-HT_{1A} neurons showed inhibitory, excitatory, and inert responses (neither inhibitory or excitatory) upon intravenous administration of THC (0.1-1.5 mg/kg). With concurrent administration of rimonabant, the excitatory responses that were elicited in some dorsal raphe 5-HT_{1A} neurons were blocked, effectively suggesting a role of cannabinoids in facilitating 5-HT transmission. 5-HT_{1A} neurons also showed enhancements in tonic receptor activity in the

hippocampus, which mirrors hippocampal 5-HT_{1A} tonic receptor activity with traditional antidepressant drugs.

Zanelati TV, Biojone C, Moreira FA, Guimaraes FS, Joca SRL. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT_{1A} receptors. *British Journal of Pharmacology*. 2010; 159 122-128.

This study was a set of three experiments investigating the effects of CBD on depressive-like behavior in rats. It also examined the role CBD might have in activating 5-HT_{1A} receptors by the combined delivery of a 5-HT_{1A} receptor antagonist and CBD. Lastly, due to some evidence suggesting that hippocampal brain-derived neurotrophic factor (BDNF) expression may increase with antidepressant drugs, the authors looked for a similar increase in BDNF expression with CBD.

- Experiment 1: Performance of CBD-injected rats (3, 10, 30, or 100 mg/kg) compared to imipramine-injected rats (30 mg/kg; a tricyclic antidepressant) and control (vehicle solution) on the forced swim test (FST) and open field test (OFT)
- Experiment 2: FST performance between the following rat groups
 - WAY100635 (a 5-HT_{1A} receptor antagonist) + CBD (30 mg/kg)
 - WAY100635 + vehicle solution
- Experiment 3:
 - Performance of CBD-injected rats (30 mg/kg) compared to imipramine-injected rats (30 mg/kg) and control on the FST
 - Analysis of brain-derived neurotrophic factor (BDNF) expression in the hippocampus between groups

The FST (Porsolt et al. 1977) measures a dimension of depressive behavior called learned behavioral despair, while the OFT measures anxiety-like behaviors (please see study directly above for details on the FST). In the OFT (Hall & Ballachey 1932), rodents are placed in a flat, open arena where they can freely roam (walls mark the boundary of this open field from which they cannot escape, and the open field is free of any objects or obstacles). The OFT is used to examine for anxiety-like behavior in rodents particularly to assess anxiolytic properties of drugs. Exploratory duration and behavior are the typical dependent measures in the OFT, although the specific operational definitions for both can vary across studies. In this particular study, researchers measured immobility time in the FST. The dependent measure in the OFT was distance traveled in the open space.

Compared to controls, the CBD (30 mg/kg) and imipramine groups both showed decreases in immobility time on the FST (Expt. 1 and 3), suggesting equivalency of both drugs in treating depressive-like behavior (learned behavioral despair). In addition, injection of a 5-HT_{1A} receptor antagonist (WAY100635) reversed the effects of CBD on the FST when compared to a CBD-only group (Expt. 2). No differences were found in the OFT between treatment groups (CBD, imipramine, and control). Lastly, the decreased immobility time that was found in the

CBD and imipramine groups on the FST was not associated with increased expression of BDNF in the hippocampus (Expt. 3). Authors concluded that the efficacy of CBD on depressive behaviors may follow an inverted U-shaped curve where a mid-range CBD dosage (30 mg/kg) may produce antidepressant-like effects equivalent to existing antidepressant treatments. In addition, since serotonergic (5-HT) receptor antagonism reversed CBD's behavioral effects, CBD may influence 5-HT transmission—a neurotransmitter system highly implicated in depressive symptomatology. Finally, contrary to some evidence, the reduction in depressive-like behavior on the FST was not associated with increased BDNF expression for either the CBD or imipramine groups.

Gobbi G, Bambico FR, Mangieri R, Bortolato M, Campolongo P, Solinas M, et al. Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. *Proceedings of the National Academy of Sciences*. 2005; 102(51): 18620-18625.

Researchers in this study administered a fatty acid amide hydrolase (FAAH) inhibitor (slows breakdown of anandamide, an endocannabinoid) and observed for antidepressant-like activity in rats, as well as observing for any changes in 5-HT and noradrenergic (NE) transmission (both neurotransmitter systems implicated in mood regulation). Performance on the forced swim test (FST) and tail suspension test (TST) were observed with single or repeated intraperitoneal injections of URB597 (an FAAH inhibitor), desipramine (a tricyclic antidepressant), or a CB-receptor antagonist rimonabant in conjunction with URB597. (FST has been previously discussed above as a method for measuring of antidepressant-like efficacy in rodents; therefore, FST procedure will not be described here). Similar to the FST, the TST is considered a measure of learned behavioral despair as rodents cope with an inescapable, aversive environment. It is therefore commonly used in assessing antidepressant efficacy in rodents. In the TST, rodents are suspended by their tails causing them to face downward. While rodents initially engage in active locomotor activity (strategies to upright itself), suspension over time generally gives way to passive coping strategies (i.e., greater time spent in an immobile state). In this particular study, immobility time was the primary measure on the TST, while time spent on floating, swimming, and struggling were the primary measures in the FST.

Results from Gobbi et al. showed that higher, single doses of URB597 lead to observable decreases in immobility time when compared to control (vehicle solution), with a 0.1 mg/kg dose of URB597 showing equivalency in immobility time reduction to a single 20 mg/kg and 10 mg/kg dose of desipramine and paroxetine (an SSRI), respectively. In addition, a single dose of rimonabant (1 mg/kg) prior to URB597 administration reversed the immobility time reduction to levels similar to control. Results on the FST with repeated injections of URB597 also showed similar trends (greater reductions in immobility time with higher dosages) and a reversal of effects with rimonabant administration. Lastly administration of URB597 increased 5-HT and NE neuronal firing respectively in the dorsal raphe nucleus and the locus ceruleus, with rimonabant administration reversing this effect.

Clinical Trials

A search through MEDLINE and ClinicalTrials.gov in mid- August 2016 yielded no published or on-going studies investigating the effects of cannabis or cannabinoids on treatment-resistant depression (or major depressive disorder more generally) as a primary measure. However, a search for endocannabinoid system modulators resulted in one completed study experimenting with a novel FAAH inhibitor on major depressive disorder. This study, while not published in a journal, is listed on the study sponsor's website with details on some methodology and results: [An Eight-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Dose-Finding Study, with Escitalopram \(10 mg daily\) as Active Control, to Evaluate the Efficacy, Safety and Tolerability of Three Fixed Doses of SSR411298 \(10, 50, or 200 mg daily\) in Elderly Patients with Major Depressive Disorder \(FIDELIO\)](http://en.sanofi.com/img/content/study/DFI10560_summary.pdf) (http://en.sanofi.com/img/content/study/DFI10560_summary.pdf)

This Sanofi-sponsored trial was a multi-center randomized, double-blind, placebo-controlled study investigating the effects of an endocannabinoid system modulator compared to a selective serotonin reuptake inhibitor (SSRI escitalopram) and placebo on depression symptoms in elderly MDD patients (n = 525). The endocannabinoid system modulator being tested was SSR411298, which is a fatty acid amide hydrolase (FAAH) inhibitor, which effectively slows the metabolism of endocannabinoids. Patients in the study (n = 525) were 60 years or older and had been diagnosed with MDD, as well as having been documented to have had a recurrent episode at least 1 month prior to their first visit for the trial. Patients were given either SSR411298 (at 10 mg (n = 105), 50 mg (n = 106), or 200 mg (n = 105)), Escitalopram (10 mg, n = 103), or placebo (n = 106) via the oral route. Treatment duration was 8 weeks. The primary measure was the 17-item Hamilton Depression Rating Scale (HAM-D). Secondary measures were: 1) Montgomery and Asberg Depression Rating Scale, 2) Clinical Global Impression scale, 3) Hamilton-Depression mood, factor, and core items, 4) 15-item Geriatric Depression Scale, 5) Sheehan Disability Scale, and 6) Hamilton-Anxiety Rating Scale. At Day 56 of treatment, none of the SSR411298-treated groups showed any significant change from baseline on the HAM-D total score compared to placebo. This was in contrast to the escitalopram group which did show significant decrease in the HAM-D score from baseline when compared to placebo. Therefore, while patients in the escitalopram group did show improvements in depression symptoms, those in the SSR411298 group did not show the same effect. Results from secondary measures are sparse, with the only statement suggesting that efficacy from secondary measures cannot be conclusively determined. Some study details were listed on ClinicalTrials.gov, although more information is contained on Sanofi's website (link provided above): [An Eight-Week Study of SSR411298 as Treatment for Major Depressive Disorder in Elderly Patients \(FIDELIO\)](https://clinicaltrials.gov/show/NCT00822744) (<https://clinicaltrials.gov/show/NCT00822744>)

Observational Studies

No observational studies were found that systematically investigated cannabis use in individuals to specifically treat depression. However, there has been some research to explore whether cannabis use increases depression risk due to some evidence linking mental health

issues with cannabis use. While these cannabis-depression relationship studies are not specifically approached to understand if cannabis can treat depression, any studies that explore this question can be used to evaluate for any evidence of cannabis helping to alleviate depression (if cannabis use isn't associated with increased depression risk, is cannabis use associated with decreased depression risk?). Recent longitudinal studies suggest no risk to slightly elevated risk of depression with cannabis use, with representative cases of these studies discussed below. The final study included in this section is a cross-sectional survey that investigated cannabis use and depression.

Lev-Ran S, Roerecke M, Le Foll B, George TP, McKenzie K, Rehm J. the association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. *Psychological Medicine*. 2014; 44: 797-810.

This meta-analysis examined the association between cannabis use and depression from longitudinal studies. Criteria for meta-analysis inclusion were 1) publication within a peer-reviewed journal, 2) prospective longitudinal, population-based data, 3) exposure variable explicitly defined as cannabis use rather than substance use, 4) depression as the outcome variable (depressive symptoms and/or clinical depression), 5) study controlled for baseline levels of depression in their participants or excluded participants who already had depression at the start of the study, and 6) study presented data with an odds ratio (OR) of depression risk from cannabis use, or presented data in a way that would allow for calculation of OR. This resulted in 14 articles being included in the meta-analysis of a total of n = 76,058 participants.

Main findings: when comparing cannabis use against controls, the pooled OR was 1.17 indicating slightly elevated risk for depression with cannabis use. In a separate analysis of heavy cannabis users (using cannabis at least once a week or having cannabis use disorder), the OR increased to 1.62. When these analyses were recalculated with a subset of studies scoring highest on methodological quality (8 studies), the pooled OR of these studies was 1.12 and 1.34 for cannabis users and heavy cannabis users, respectively. Overall, this meta-analysis indicated a slightly increased risk of depression with cannabis use, with this risk increasing with heavier cannabis use. However, it should also be noted that the lowerbound of the 95% confidence intervals for these ORs were close to 1, which calls for further study and standardization of methods across studies to better understand the relationship between cannabis use and depression.

Harder VS, Morral AR, Arkes J. Marijuana use and depression among adults: testing for causal associations. *Addiction*. 2006; 101: 1463-1472.

This study analyzed cannabis use frequency and depression symptoms from participants in the National Longitudinal Survey of Youth of 1979 (NLSY79). While the survey collected data periodically from youths starting in 1979 (including cannabis use patterns), a depression measure was not included until the 1990s using the Center for Epidemiological Studies Depression scale (CES-D; Radloff 1977). Therefore, analysis of the relationship between cannabis use and depression was on longitudinal data at adulthood.

Two main questions were explored in this study that were addressed in two different models: 1) whether depressive symptoms were associated with past-year cannabis use (Model 1), and 2) whether depressive symptoms were associated with the last few years of cannabis use (4 years; Model 2). Essentially, the two models addressed whether depressive symptomology manifests rapidly or slowly with cannabis use. To control for any differences at baseline across participants, the authors used measures collected at the beginning of the survey (or the first time it was collected in the survey) as baseline covariates. This resulted in 55 and 82 baseline covariates being selected for control in Model 1 and Model 2, respectively. In total, 1252 past-year cannabis users and 7498 non past-year cannabis users were included in Model 1. A total of 184 cannabis users (last few years of cannabis use) and 1805 non users were included in Model 2. Authors used propensity score weighting to create comparison groups (users vs. non-users) that would only differ on their cannabis use in consideration of baseline covariates. Overall results on weighted data showed a nonsignificant odds ratio (OR) of 1.13 in Model 1, suggesting no increased risk of depression within one year of cannabis use. Similarly, Model 2 results showed a nonsignificant OR of 1.51. Limitations should also be considered, however, given that both Models still had ORs greater than 1 and that Model 2 was underpowered (which explains the greater spread in the 95% confidence interval in this model). Therefore, if there is any observed risk of depression with cannabis use, careful control of confounding factors may eliminate most or all of this apparent risk. While this study highlights the usefulness of methods in controlling for baseline covariates, it also emphasizes the need for greater systematic, prospective study of variables to avoid such intensive post-hoc variable control to avoid overfitting propensity score models.

Denson TF, Earleywine M. Decreased depression in marijuana users. *Addictive Behaviors*. 2006; 31(4):738-42.

This study is included in this section because it is sometimes cited and interpreted erroneously as evidence that cannabis use can decrease depression. This study, which received grant support from the Marijuana Policy Project, was an internet survey which recruited individuals via drug policy organizations (organizations not disclosed in paper). A total of $n = 4494$ participants completed the internet survey which included items from the Center for Epidemiological Studies Depression scale (CES-D; Radloff 1977) as well as questions on frequency of cannabis use. Whether the survey itself was just restricted to CES-D questions and frequency of cannabis use is not clear, nor are the instructions that were given to participants to specify the purpose of the study. Frequency of cannabis use was used to group participants into three user group categories: 1) Daily Users ($n = 3323$), 2) Weekly Users ($n = 861$), and 3) Never Users ($n = 310$). Total scores on the CES-D were subsequently analyzed and compared across these three participant groups, as well as comparing participant groups by CES-D scale's 4 sub-domains of depressed affect, positive affect, somatic and retarded activity, and interpersonal symptoms. Authors indicated that the Never Users group reported more depressive symptoms than both the Daily Users group and Weekly Users group (the Daily User group and Weekly Users group did not significantly differ in CES-D scores). However, when reviewing the total scores between the 3 participant groups, none of the three groups' scores reached the threshold to indicate clinical depression risk. A score of 16 or higher on the CES-D is typically indicative of some depressive symptomology that may require further clinical

assessment for depression (Radloff 1977). In contrast, total scores in this paper (reported as trimmed means) were several points below this threshold (~5-8 points below threshold), which indicates that all patient groups – regardless of their cannabis usage frequency – were not within the range indicative of clinical depression risk. Therefore, any statistical differences reported between groups in this paper is measuring differences in CES-D scores in individuals that are, overall, not depressed. Lastly, it should be noted that the study did not include any information to decipher whether survey participants also consumed other substances regularly besides cannabis. Since depression is correlated with the use of other substances, it is unclear whether it would have been appropriate for the study to control for this particular confound in their analyses.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of treatment-resistant depression were found.

References

- American Psychiatric Association (APA). Practice Guideline for the Treatment of Patients with Major Depressive Disorder. 3rd ed. Arlington, VA: American Psychiatric Association; 2010.
- Aronson R, Offman HJ, Joffe RT, Naylor CD. Triiodothyronine augmentation in the treatment of refractory depression: a meta-analysis. *Archives of General Psychiatry*. 1996; 53(9):842–848.
- Bambico FR, Hattan PR, Garant J-P, Gobbi G. Effect of delta-9-tetrahydrocannabinol on behavioral despair and on pre- and postsynaptic serotonergic transmission. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2012; 38: 88-96.
- Berlim MT, Turecki G. What is the meaning of treatment resistant/refractory major depression (TRD)? A systematic review of current randomized trials. *European Neuropsychopharmacology*. 2007; 17: 696-707.
- Brent D, Emslie G, Clarke G, Wagner KD, Asarnow JR, Keller M, et al. Switching to another SSRI or venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression. *Journal of the American Medical Association*. 2008; 299(8): 901-913.
- Can A, Dao DT, Arad M, Terrillion CE, Piantadosi SC, Gould TD. The mouse forced swim test. *Journal of Visualized Experiments*. 2012; 59: doi: 10.3791/3638
- Denson TF, Earleywine M. Decreased depression in marijuana users. *Addictive Behaviors*. 2006; 31(4):738-42.
- Fava, M. Diagnosis and definition of treatment-resistant depression. *Biological Psychiatry*. 2003; 53(8): 649-659.

Fava M, Rush AJ, Wisniewski SR, Nierenberg AA, Alpert JE, McGrath PJ, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. *American Journal of Psychiatry*. 2006; 163(7): 1161-72.

Gobbi G, Bambico FR, Mangieri R, Bortolato M, Campolongo P, Solinas M, et al. Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. *Proceedings of the National Academy of Sciences*. 2005; 102(51): 18620-18625.

Hall C, Ballachey EL. A study of the rat's behavior in a field: a contribution to method in comparative psychology. *University of California Publications in Psychology*. 1932; 6: 1-12.

Harder VS, Morral AR, Arkes J. Marijuana use and depression among adults: testing for causal associations. *Addiction*. 2006; 101: 1463-1472.

Hill MN, Gorzalka BB. Is there a role for the endocannabinoid system in the etiology and treatment of melancholic depression? *Behavioral Pharmacology*. 2005; 16(5-6): 333-352.

Husain SS, Kevan IM, Linnell R, Scott AI. What do psychiatrists mean by medication resistance as an indication for electroconvulsive therapy? *Journal of ECT*. 2005; 21(4): 211-3.

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The epidemiology of major depressive disorder. *Journal of the American Medical Association*. 2003; 289(23): 3095-3105.

Kellner CH, Fink M, Knapp R, Petrides G, Husain M, Rummans T, et al. Relief of expressed suicidal intent by ECT: a consortium for research in ECT study. *American Journal of Psychiatry*. 2005; 162(5): 977-982.

Lev-Ran S, Roerecke M, Le Foll B, George TP, McKenzie K, Rehm J. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. *Psychological Medicine*. 2014; 44: 797-810.

McGrath PJ, Stewart JW, Fava M, Trivedi MH, Wisniewski SR, Nierenberg AA, et al. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. *American Journal of Psychiatry*. 2006; 163(9): 1531-41.

Nemeroff CB, Mayberg HS, Krahl SE, McNamara J, Frazer A, Henry TR, et al. VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. *Neuropsychopharmacology*. 2006; 31: 1345-55.

Nierenberg AA, Fava M, Trivedi MH, Wisniewski SR, Thase ME, McGrath PJ, et al. A comparison of lithium and T3 augmentation following two failed medication treatments for depression: a STAR*D report. *American Journal of Psychiatry*. 2006; 163(9): 1519-30.

Pagnin D, de Queiroz V, Pini S, Battista Cassano G. Efficacy of ECT in depression: a meta-analytic review. *Journal of ECT*. 2004; 20(1): 13-20.

Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. *Nature*. 1977; 266(5604): 730-2.

Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Applied Psychological Measurement*. 1977; 1(3): 385-401.

Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, et al. Bupropion-SR, Sertraline, or Venlafaxine-XR after failure of SSRIs for depression. *New England Journal of Medicine*. 2006; 354(12): 1231-42.

Shelton RC, Osuntokun O, Heinloth AN, Corya SA. Therapeutic options for treatment-resistant depression. *CNS Drugs*. 2010; 24(2): 131-161.

Thase ME, Friedman ES, Biggs MM, Wisniewski SR, Trivedi MH, Luther JF et al. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. *American Journal of Psychiatry*. 2007; 164(5): 739-52.

Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *American Journal of Psychiatry*. 2006; 163(1): 28-40.

U.S. Census Bureau. QuickFacts United States: Population estimates, July 1, 2015. Retrieved August 15, 2016, from <https://www.census.gov/quickfacts/table/PST045215/00>

Zanelati TV, Biojone C, Moreira FA, Guimaraes FS, Joca SRL. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. *British Journal of Pharmacology*. 2010; 159 122-128.

Minnesota Department of Health
Office of Medical Cannabis
PO Box 64882,
St. Paul, MN (zip) 55164-0882
(phone) 651-201-5598
Health.Cannabis@state.mn.us
www.health.state.mn.us



To obtain this information in a different format, call: 651-201-5598. Printed on recycled paper.