Introduction

Major depressive disorder and anxiety disorders are most common psychiatric conditions in clinical practice. Depression affects upward of 16% of American adults in their lifetimes with a 12-month prevalence of 6.7% [1]. Specific phobia and social anxiety disorder are the most common anxiety disorders with lifetime prevalence rates of 18.4% and 13.0%, respectively. Panic disorder, generalized anxiety disorder, agoraphobia, and separation anxiety disorder have lifetime prevalence rates of 2%–7% [2].

There is an increased number of patients with treatment refractory mood and anxiety disorders which result in higher rates of medical and psychiatric comorbidity, persistent social and vocational disability, increased risk of suicide, higher healthcare utilization and psychiatric hospitalizations.
Treatment-resistant conditions require more intensive multimodal treatment approach, but on the other hand it is important to make sure that there is a good balance of benefits and potential negative effects of treatment. The first and most important rule in any medical treatment is best described by a Latin expression “primum non nocere”, which means “first, do no harm”. There are new treatments that are effective in the short run, but at the same time they are associated with negative effects such as developing tolerance, dependence or metabolic side effects. If the goal of treatment is to produce short-lasting improvements without taking into account potential detrimental effects, this treatment is not justifiable and should not be prescribed. Prescribing medications that could provide an instant symptomatic relief of patient’s suffering is popular nowadays in the era when quick solutions and immediate cessation of even minimal discomfort are expected from medical professionals.

**Benzodiazepines in the Past and Now**

Benzodiazepines (BZDs) were commonly prescribed medications in the treatment of anxiety disorders in the last few decades of 20th century. BZDs are effective medications, and for a long time they were first-line treatment for patients with anxiety disorders. No one was thinking seriously about the potential of developing prescription medication addiction at that time. BZDs were overprescribed as a long-term treatment and we have now millions of people who are addicted to BZDs.

According to Substance Abuse and Mental Health Services Administration (SAMHSA) Report in 2012 it was noted that the number of substance abuse treatment admissions for people addicted to both benzodiazepines and narcotic pain relievers increased 5.7 times between 2000 and 2010. SAMHSA Report from 2012 also conferred that benzodiazepine abuse is particularly dangerous at younger ages due to drug interactions which may impair or alter brain development [3].

A strong opposition to the use of BZDs in psychiatry and strict monitoring of benzodiazepine prescriptions started in the last decade. Currently, BZDs are not a recommended treatment option and prescribing these medications should be avoided at all costs. Discontinuing BZDs after a long-term use is extremely difficult and patients may require a high dose of quetiapine or olanzapine to have a similar anti-anxiety effect as lorazepam or clonazepam in a low to moderate dose range.

With regards to BZDs we have now a strict monitoring and auditing of BZDs prescription and strong recommendations that prescribing BZDs should be reduced and these medications should be prescribed only if necessary.

Selective serotonin reuptake inhibitors and Venlafaxine or Duloxetine are the first-line option for anxiety disorders, but there is a certain number of patients who respond very partially to these medications and with much better response to BZDs. In a number of cases selective serotonin reuptake inhibitors/serotonin norepinephrine reuptake (SSRIs/SNRI) are not more effective or sometimes even not equally effective when compared to BZDs when it comes to treatment of anxiety disorders.

As a result of SSRIs/SNRI inefficacy there is a new trend of recommending BZDs as augmentation strategy for SSRIs/SNRIs. Mark Pollack recommends clonazepam augmentation with an average dose of 2 mg daily for patients with refractory anxiety disorders who are responding partially to sertraline and venlafaxine [4]. Patients may respond very well to this treatment strategy, but the main question is if it is augmentation or patient is simply responding to benzodiazepine and not responding to SSRIs. Many patients may develop anxiety again upon discontinuing clonazepam. Another unresolved question is the recommended duration of benzodiazepine augmentation and how to prevent a long-term use of BZDs as it used to be in the past.

It seems that this reintroduction of BZDs into clinical practice under a different form or name (as augmentation) is causing again a risk of long-term treatment. In general, many patients with anxiety disorders prefer BZDs due to their efficacy. Most recently another serious reason for not prescribing BZDs arose and as a result a new viewpoint of demotivating or scaring patients to not use this class of medication. Long-term use of BZDs may be associated with an increased risk of dementia [5]. Out of the ten studies retrieved, nine reported an increased risk of dementia in benzodiazepine users and have therefore indicated that there appears to be a direct link between benzodiazepine use and dementia [6]. Long-term use of BZDs should be avoided among the elderly, who may be at a higher risk for developing dementia [7].

**Alternatives for BZDs in Treatment of Refractory Anxiety Disorders**

Gabapentin, pregabalin, buspirone or even atypical antipsychotics are usually recommended for patients with anxiety disorders with a poor response to SSRIs/SNRIs. Clinicians may have ethical dilemmas about using atypical antipsychotics with their metabolic side effects instead of relatively harmless BZDs.

The Canadian guideline for the management of patients with mood disorders and comorbid anxiety disorders recommends gabapentin and quetiapine as a first-line option for the pharmacologic treat-
ment of comorbid anxiety symptoms/disorder in patients with bipolar disorder [8]. Pregabalin is a medication with anti-anxiety potential which may help with reducing an excessive use of BZDs. The results from a Norwegian study demonstrated that patients who started pregabalin reduced more significantly the use of BZDs compared to those on gabapentin [9]. However, there is evidence that both gabapentin and pregabalin are medications with a potential of misuse. Careful evaluation of a previous history of drug abuse is essential while prescribing gabapentin [10]. In our experience, patients with a long-term use of BZDs usually require a higher dose range of gabapentin or pregabalin which in turn increases a potential risk of addiction to these medications.

Buspirone is non-benzodiazepine anxiolytic that was first marketed in 1986. Buspirone is approved for treatment of generalized anxiety disorder, but it is also effective as augmentation in treating depression. Unfortunately, buspirone is usually not very effective for patients with previous long-term use of BZDs.

In summary, most of the available medications for patients with anxiety disorders with no response to antidepressant medications have either undesirable adverse effects/detrimental effects or addictive potential with a long-term treatment. There is another radical and, we would say, negative movement in the treatment of trauma-related disorders, particularly posttraumatic stress disorder (PTSD) that may also reflect on anxiety disorders per se. This is using synthetic cannabinoids and more recently medical marijuana in the treatment of variety of medical conditions, and a potential of uncritical usage of these substances in the treatment of PTSD, anxiety disorders, and mood disorders.

Synthetic Cannabinoids for PTSD and Other Anxiety Disorders and Mood Disorders

Both endocannabinoids and the compounds in marijuana bind to proteins called cannabinoid receptors in the brain and throughout the body. There are two cannabinoid receptors called CB(1) and CB(2) receptors that can be activated by endogenously released ‘endocannabinoids’ or exogenously administered compounds in order to reduce the physical and psychological symptoms [11]. Nabilone is a synthetic cannabinoid that was approved for use by Health Canada in 1982 for the treatment of cancer therapy-induced nausea. Nabilone has also been tried in inflammatory bowel disease, dystonia, spasticity in neurological disorders, Parkinsonism, chronic pain, and fibromyalgia.

There is a new practice of using synthetic cannabinoid, nabilone for treating nightmares associated with severe PTSD. Canadian military psychiatrist Fraser published an open label study of using nabilone in patients with PTSD in 2009 and suggested that nabilone is beneficial in the treatment of nightmares associated with PTSD, it increases sleep time and is not being associated with development of tolerance [12]. The results of another study by the same group of authors has demonstrated that nabilone in dose of 3 mg reduces the frequency and intensity of nightmares in the military population of patients with a history of non-response to traditional therapy [13]. Nabilone is currently a commonly prescribed medication for nightmares associated with various clinical conditions. Long-term use of nabilone is unfortunately not uncommon. Some patients may report improvement in mood and anxiety symptoms with cannabinoids and there is a tendency among clinicians of prescribing nabilone or even medical marijuana for patients with anxiety and depression with unknown long-term consequences.

The disadvantages of prescribing nabilone are plentiful, some of which include the fact that there are no data about long-term use and treatment outcomes as well as the occurrence of some patients switching to marijuana over time because it is better tolerated and less expensive [14]. Another major deleterious effect is that nabilone is perceived to produce more undesirable side effects when compared to marijuana. Some of the more common side effects of nabilone include the following: somnolence, dizziness, euphoria, depression, fatigue, apathy, dry mouth, ataxia, visual disturbances, headaches, and concentration difficulties [15]. It is clear that nabilone is not well tolerated and side effect profile is not favorable for psychiatric conditions, particularly mood disorders.

However, there is again paradoxically a tendency to consider cannabinoids in the treatment of mood disorders, probably as a result of the lack of new medications for mood and anxiety disorders. The endocannabinoid (eCB) system may play a role in the control of mood. In one of the recently published papers targeting the endocannabinoid (eCB) system is viewed as an attractive and novel approach to the treatment of depression and other mood disorders [16]. These new treatment trends without any well designed evidence based studies to prove its efficacy and safety may sound more as a big experiment in psychiatry rather than any scientifically justified treatment method.

Augmentation Strategies in Treatment-Resistant Depression

There are a number of augmentation strategies for depressed patients with a partial response to antidepressant medications. Atypical antipsychotic augmentation has become almost the standard of care for treatment-resistant depression (TRD). Stimulant augmentation is less established and less supported augmentation strategy for TRD compared with other more commonly used augmenting strategies and this is because there are no clear recommendations about the dosage of stimulant medication for augmentation, duration of treatment and the clear goal of treatment. In spite of these limitations,
stimulant augmentation is more popular lately, particularly in North America, and many patients prefer stimulants over atypical antipsychotics. Some clinicians unreasonably prescribe stimulant medications with a belief that they are serving the patients’ best interests, although there is no strong evidence for the efficacy of stimulant augmentation.

Stimulant medication may produce a prompt and significant reduction in some type of residual symptoms of depression such as daytime sleepiness, poor alertness, lack and concentration and lack of energy. Some individuals may feel better within hours of taking stimulant medication, but there will be no sustained benefits even with prolonged use. Improvements with stimulants disappear almost immediately after discontinuing stimulant medication. There is no consensus if a long-term use of stimulant medication, such as in attention deficit hyperactivity disorder (ADHD), is acceptable in patients with TRD [17].

Australian open study conducted by Gordon Parker and colleagues from the Black Dog Institute in Sydney demonstrated that psychostimulants may be an efficacious antidepressant option for managing unipolar or bipolar melancholic depression. In the group of 50 patients stimulants were ‘very effective’ in managing symptoms of melancholia for 20% of the bipolar and unipolar patients, ‘somewhat effective’ for 50% in each group and ‘ineffective’ for some 30% of each group [18]. Authors used methylphenidate (5-60 mg daily) and dextroamphetamine (5-20 mg) and most patients (84%) received stimulant as an augmentation strategy.

In the literature review from 1988 to 2013 conducted by Corp et al. Modafinil and Armodafinil are effective treatment options for refractory unipolar and bipolar depression. Randomized clinical trials data on dopaminergic stimulants are too limited to justify their use as the first-line augmentation for depression with the exception of some promising results with lisdexamfetamine [19], but still limited data mostly pertaining improvement in executive dysfunctions and depressive symptoms with lisdexamfetamine in patients with mild major depressive disorder (MDD) [20].

The main issue which arises is that sometimes, even with partial improvements in energy level and cognitive symptoms of depression with stimulant medications, clinicians may continue prescribing stimulants for a few years or longer.

Long-term use of stimulants in a higher dose range for augmentation is not recommended and should not be acceptable. At the same time, a new trend of promoting stimulants as antidepressant might justify a long-term use of stimulants. However, if we accept Gordon Parker’s suggestion of using stimulant medications potentially as antidepressant instead of augmentation, it will be a big shift in psychiatry, giving up of etiological treatments in psychiatry and simply providing the medications for symptoms or a group of symptoms. Such treatment conceptualization would be a change of paradigms in psychiatry. Hopefully it will be only a temporary crisis in psychiatry.

### Ketamine in Treatment-Resistant Depression

Ketamine is a non-selective N-methyl-D-aspartate (NMDA) receptor antagonist which was used as an anesthetic induction agent for diagnostic and surgical procedures, primarily in pediatric surgery and veterinary medicine. In terms of drug class, ketamine can be categorized as a dissociative anesthetic, hallucinogen, and psychotomimetic medicine. Recreationally it is used for its psychedelic and dissociative effects [21]. Ketamine abusers generally tend to take the drug either parenterally, intranasally, or orally in doses of 60+ mg, 100+ mg and 200+ mg range per each instance, and it is sometimes taken up to 2-3 g per day by frequent abusers.

Ketamine is usually effective for depression and produces fast improvement in depressive symptoms. There are trials of ketamine in patients with TRD and ketamine has rapid antidepressant effects in patients with TRD [22]. Ketamine is typically administered by a series of up to six IV infusions (0.5 mg/kg). Ketamine causes depersonalization and some patients develop depersonalization after each infusion. Effects of ketamine are short-lasting and there is no sustained benefit. About 76% of patients relapse two to three weeks after stopping ketamine infusions [23].

There is a tendency of using oral formulations of ketamine and intranasal ketamine, but if the goal of prescribing oral ketamine is providing more sustained antidepressant effects, and if treatment should be provided for an extended period of time, then the risk of addiction may be increased. There are not set guidelines when it comes to deciding on how long ketamine should be administered [21]. A possible outcome of this practice, when the patients are given ketamine orally, could result in a very similar situation as with benzodiazepine in the past, perhaps even worse. Scientific community is aware that there are risks when it comes to ketamine use which may eventually lead to dependence, but at the same time there remain a number of questions which will have to be answered such as defining a safe dose, recommended frequency, and the extent of the dependence and tolerance to this drug. The duration of maintenance therapy has not yet been defined and this will be a crucial step in order to try to retain some benefits obtained from the treatment.

Long-term exposure to ketamine, particularly in a higher dose range, may result in developing tolerance, drug craving, flashbacks, and possible psychological withdrawal symptoms. Ketamine potential for abuse and neurotoxicity should not be neglected [24]. Finally, it is also important to mention that while there are a number of articles on ketamine dependence in literature, there are no large-scale studies, and hence the prevalence of ketamine dependence is to this day unknown.
Controversies about Medical Marijuana

Medical marijuana has emerged recently as a possible treatment option for various medical conditions including cancer, hepatitis C, Parkinsonism, spasticity associated with multiple sclerosis (MS), chronic pain, neuropathic pain, and Glaucoma. High-tetrahydrocannabinol (THC) medical marijuana (15-22% THC) prescribed to patients for medical conditions is very potent and it is not known if this new marijuana is more addictive than marijuana as a recreational drug. Therefore, it would be essential to have a clear policy about prescribing medical marijuana [21].

Whiting et al. completed a systematic review of benefits and adverse events of cannabis and cannabinoids and established that there was low-quality evidence to support the use of cannabinoids in nausea and vomiting due to chemotherapy, weight gain in human immunodeficiency virus (HIV) infection, sleep disorders, and Tourette syndrome. The paper also stated that cannabis and cannabinoids did not show efficacy for suppressing anxiety, although it did mention that there was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity [25]. Common adverse events as a result of using cannabis and cannabinoids include dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

Psychiatric patients are unlikely candidates for medical marijuana. In case of patients with history of substance use disorder physicians should be very cautious with prescribing medical marijuana for medical conditions [21].

There is a misconception that medical marijuana compared with recreational marijuana may have anti-anxiety effects. In general, marijuana may transiently help anxiety, but it increases baseline anxiety. It should be pointed out that marijuana could trigger panic attacks, particularly in younger people. Chronic cannabis use is associated with higher prevalence of anxiety disorders, although cannabis use is not the only risk factor sufficient for the development of a long-term anxiety [26].

Several studies show an association between marijuana use and onset of mood disorders and psychosis. Regular marijuana use is also associated with increasing symptoms of depression. Marijuana use also worsens the course of bipolar disorder. Regular cannabis use leads to an increased risk for suicidal ideation in males and possibly increased suicide attempts. Lastly, we should take into consideration the detrimental effects of marijuana on the brain development, especially in adolescents.

Nowadays there is a tendency of recommending medical marijuana for psychiatric conditions, including schizophrenia, depression and anxiety disorders. Papini et al. reported of marijuana being used successfully in treating PTSD symptoms in veterans [27]. It is a bit surprising because substance abuse, including cannabis abuse is a common psychiatric comorbidity/complication in patients with PTSD, but now we have a situation of using cannabis for PTDS treatment. We can ask ourselves again the same question about the nature of this change in psychiatry and it may be interpreted either as a change of paradigm in psychiatry or a temporary confusion around appropriateness of using cannabis in treating psychiatric conditions.

References
