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Ambiguities in the Efficacy of Selective Serotonin Reuptake Inhibitors
in the Treatment of Depression

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ABSTRACT

Major depressive disorder (MDD) is the most debilitating mental illness worldwide. Primary treatment of MDD is the administration of selective serotonin reuptake inhibitors (SSRIs). Deemed as the safest psychotropic drug thus far, SSRIs have been shown to reduce depressive symptoms and enhance the quality of life in youth, adult and geriatric populations. However, with rising numbers of individuals taking maintenance doses of SSRIs for five or more years, researchers are beginning to discover severe adverse side effects associated with prolonged treatment. The overall risks of long-term SSRI therapy include tachyphylaxis, tardive dysphoria, structural neurological abnormalities and suicide. SSRIs also have the potential to exacerbate depressive symptoms and leave patients in a paradoxical state. The equivocal efficacy of SSRIs can be traced back to ambiguous diagnostic methods, subjective symptom rating scales and the nation's unhealthy reliance on cost-effective medication therapies. A comparison of short-term and long-term potency, as well as longitudinal consequences, reveals that SSRIs are not as efficacious in the treatment of depression as researchers once believed them to be.

INTRODUCTION

Depression lies at the forefront of the mental health epidemic. With over 300 million people suffering from the mood disorder, this ailment has been acknowledged as the leading cause of disability worldwide (WHO 2017). According to the DSM-5, major depressive disorder (MDD) is characterized by psychological symptoms, such as persistent sadness, hopelessness, insomnia, suicidal ideation and loss of pleasure (American Psychiatric Association 2013). A key component of the diagnosis is that these psychological deficits can manifest into persistent physical symptoms including migraines, fatigue, digestive troubles and chronic pain. The oppressive effects of MDD impair social and occupational functioning to the point where quality of life is greatly diminished. In fact, studies have claimed that the severity of this affective

disorder is excessively more debilitating than chronic physical ailments, such as arthritis, hypertension and diabetes (Mourilhe and Stokes 1998). Fortunately, several classes of antidepressant drugs have been identified to help patients manage their depressive symptoms.

With 1 in 10 Americans over the age of twelve suffering from depression, it is no surprise that a stark 1 in 7 Americans take antidepressants daily (Pratt and Brody 2014). Over the years, a succession of antidepressant classes, including monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective monoamine-reuptake inhibitors (SSRIs/SNRIs) and mood stabilizers have been primary treatments for MDD. Of the four drug types, selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressant due to the fact that they tend to have minimal side effects, as well as the ability to treat a vast range of psychological disorders. However, as long-term clinical trials regarding SSRI efficacy begin to accumulate, the costs of SSRI administration appear to outweigh the short-term benefits. A widespread analysis of the positive and negative effects of SSRIs, including long-term trials and animal models, can help health professionals determine whether or not SSRIs are the optimal treatment for depression and possibly deduce why we have become a “Prozac nation.”

Taking into account the variability of causal factors underlying major depressive disorder, it seems unlikely that one “miracle pill” can be the solution to limitless heterozygous conditions of MDD. Despite decades of exhaustive research, a conclusive etiology of depression has yet to be discovered. Some characteristics of the disease, such as suicidal ideation, can be traced to decreased metabolism in the dorsolateral prefrontal cortex and reduced frontal lobe volume of clinically depressed patients (Pandya et al. 2012). In addition to this, extrinsic factors, such as stress and trauma, which elevate glucocorticoid levels may account for decreased hippocampal volume (Bremner et al. 2000). Further investigation of the localization of depression in the limbic system denotes increased activity in the amygdala of patients with

MDD. Increasing the complexity of the etiology, researchers have associated abnormal neurological connectivity with depression as well, the most notable being the amygdala-striatal-pallidal-thalamic-cingulate cortex pathway (Price and Drevets 2010). Lastly, underlying the pathology of MDD is a slew of genetic correlates. Disregarding environmental factors, meta-analyses have isolated over 26 candidate genes for MDD and an estimated heritability of 37% (Flint and Kendler 2014). Complicated by genetic predispositions, neurotransmitter imbalances, trauma and stress, if the definitive neuropathophysiological basis of depression is still under investigation, is a homogeneous administration of SSRIs truly an ideal treatment?

Serotonin, or 5-hydroxytryptamine (5-HT), is an essential monoamine neurotransmitter involved in mood regulation, motor skills, and autonomic processes such as appetite, digestion, sleep and sexual arousal. Serotonin is typically found in the gastrointestinal tract, as well as serotonergic neurons in the central nervous system, primarily within the medulla, pons, midbrain and raphe nucleus. In mammals, 5-HT neurons are concentrated in the brainstem and denoted as B1-B9 cell groups. Rostral raphe cell groups, B6-B9, project to the forebrain, while caudal raphe cell groups, B1-B5, project to the spinal cord. Outside of the brain, 5-HT can be found in the gut, thyroid, pancreas, mammary glands and placenta, independently operating at local levels (Gaspar et al. 2003). Dysregulation of the 5-HT system has been linked to several psychiatric ailments, such as major depressive disorders, generalized anxiety and attention deficit hyperactivity disorder (ADHD). 5-HT also plays an important role in embryonic neuronal cell proliferation and differentiation. Rodent animal models have demonstrated that alteration of 5HT_{1A} receptors during development can reduce hippocampal dendritic maturation and create atypical somatosensory cortex organization (Gaspar et al. 2003). Abnormal 5-HT systems are also linked to neurodevelopmental and behavioral disorders such as autism (Simpson et al. 2011).

Serotonin hypotheses regarding depression correlate decreased levels of 5-HT to depressive symptoms. Several studies have demonstrated that by directly utilizing serotonin antagonists, or indirectly reducing concentrations of tryptophan, the precursor of 5-HT, episodic depression can be elicited (Meltzer 1990). The main mechanism of action of SSRIs is the downregulation of 5-HT_{1A} receptors due to inhibition of serotonin reuptake transporters (SERT). Inhibition of serotonin reuptake leads to increased concentrations of serotonin in the synaptic cleft, causing prolonged stimulation of postsynaptic neurons and elevated mood. Despite definitive increases in neuronal 5-HT levels post SSRI administration, researchers are still trying to isolate which of the fifteen serotonin receptor types are responsible for exhibited drug efficacy (Homberg et al. 2009). As inconsistent results of SSRI therapy continue to be published, cascading neurotrophic hypotheses of depression, which correlate reduced levels of brain-derived neurotrophic factor (BDNF) to depressive symptoms, are beginning to replace narrow monoamine theories. Studies have found that BDNF mediates widespread neuronal maintenance, including neurogenesis of serotonergic neurons (Martinowich and Lu 2007). Analyzing the successes and shortcomings of SSRI therapy may help to improve the specificity of future depression medications and avoid induction of paradoxical effects from new-generation psychotropic drugs.

POSITIVE EFFECTS OF SSRIs

As the topic of mental illness becomes increasingly deinstitutionalized, millions of individuals are prioritizing their mental health and seeking psychiatric treatment. Due to their superior safety profiles, patients will inevitably be directed towards one of the several mainstreamed SSRIs approved by the FDA. The most common SSRIs include citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), paroxetine (Paxil) and sertraline (Zoloft). SSRIs are typically preferred over TCAs and MAOIs due to their favorable tolerance profiles

with fewer adverse side effects, simpler dosage maintenance, reduced number of drug interactions and increased safety in overdose (Mourilhe and Stokes 1998). Research has also shown that SSRIs are able to treat multiple forms of depression in all age groups, regardless of baseline thresholds, in a relatively quick manner. By alleviating depressive symptoms, SSRIs have increased patients' quality of life, which can be assessed through evaluations of behavioral responses, such as increased work productivity and decreased rates of suicide.

Unlike SSRIs, which solely target serotonin receptors, TCAs alter neuronal concentrations of norepinephrine, serotonin, and acetylcholine. Due to this larger pharmacological influence, TCAs have the potential to induce severe adverse side effects. Of utmost concern is TCA toxicity and overdose. Tricyclic overdose is one of the most common causes of self-administered drug poisoning alongside benzodiazepines and alcohol (Kerr et al. 2001). Accompanied by tachycardia, heart arrhythmias and seizures, doctors often resort to prescribing SSRIs to patients beginning antidepressant therapy, especially for adolescents, geriatric populations and individuals with pre-existing heart conditions. Due to these adverse side effects, patients receiving TCA therapy are significantly more likely to discontinue treatment than those administered SSRIs. In fact, a pair-wise comparison of TCA and SSRI therapy in younger populations aged 7-25, concluded SSRIs, particularly fluoxetine, to be significantly more effective and tolerable than TCAs (Quin et al. 2014). Increased tolerance of SSRIs allows patients to comply with appropriate treatment durations and achieve successful remission.

The relative safety of SSRIs has been demonstrated across multiple age groups, including children, who are increasingly sensitive to drug effects compared to physiologically mature adults. Of critical importance, is the fact that multiple types of SSRIs have proven to be effective

in the treatment of depression, not just one. For example, Emslie's assessment of acute treatment of depression in children and adolescents prescribed fluoxetine (Prozac) compared to placebo exhibited significantly improved sub scores in mood, behavior, somatic and subjective measures on the Children's Depression Rating Scale (CDRS-R) (2002). Improvement arose after just one week of treatment, and remained for the entirety of the eight-week study. At the end of the trial, 41.3% of fluoxetine-treated patients were eligible for remission, while only 19.8% of placebo controls met remission criteria (Emslie et al. 2002). In addition to fluoxetine, randomized controlled trials (RCTs) of paroxetine (Paxil) for the treatment of adolescents with MDD have also denoted significant improvement according to the Hamilton Depression Rating Scale (HAM-D) (Keller et al. 2001). The tolerability and efficacy of SSRIs is also prevalent in children and adolescents treated with sertraline (Zoloft) who reported significant improvement on CDRS-R scores compared to placebo (Wagner et al. 2003). Effectively treating adolescents with MDD early on in life has the potential to decrease the development of substance abuse disorders, lower the number of suicide attempts and minimize future economic burdens due to decreased hospitalization rates in adulthood (Wagner et al. 2003).

In addition to effectively treating patients of all ages, SSRIs also alleviate multiple depression severities, regardless of baseline symptoms. While several studies claim that antidepressants are only effective in patients with major depression, longitudinal data analyses have found that SSRIs have statistically significant benefits regarding multiple thresholds. In Gibbons et al.'s meta-analysis of adult, geriatric and youth populations administered fluoxetine or venlafaxine, patients in all age groups showed improved outcomes in the CDRS-R, the HAM-D and estimated response and remission rates, compared to placebo (2012). Regardless of baseline data, alleviation of depressive symptoms was exhibited, with fluoxetine-treated adults experiencing the most improvement (35%) and geriatric patients experiencing the smallest drug-

placebo differentiation rates (19%) (Gibbons et al. 2012). Likewise, Fournier and colleagues found antidepressants, such as paroxetine, to mitigate depressive symptoms, regardless of baseline severity (2010). However, patients with more severe cases of depression exceedingly benefitted from antidepressant treatment compared to patients with moderate baseline symptoms (Fournier et al. 2010).

A newfound benefit of SSRIs in the treatment of depression is the drug's rapid alteration of neurological activity. Doctors typically prescribe antidepressant treatments that are 6-8 weeks in length. Patients prescribed antidepressants report feeling positive effects after 4-6 weeks. While some skeptics argue that this period of time is too long, studies have shown that SSRIs induce neurological changes after just a few hours following administration. Cheng et al. investigated this argument by utilizing fMRI monitoring over an 8-week period of escitalopram administration to 48 novel MDD patients (2017). The purpose of this study was to examine whether or not remission rates could be predicted during early stages of SSRI therapy. Researchers found that neuronal signaling changes occurred in the occipital lobe, dorsolateral/dorsomedial prefrontal cortices and middle cingulate cortex just five hours after patients' first dose, and strongly indicated positive endpoint remission (Cheng et al. 2017). This rapid alteration in neuronal activity may confer the rapid efficacy of SSRIs. Notably, early predictors would allow patients to choose an optimal antidepressant and avoid the roundabout method of prescription trial-and-error. This "personalized" method of prescription would reduce the number of ineffective medications prescribed to patients and reduce the perceived timeline efficacy of SSRIs from 4-6 weeks to possibly just one week.

In order to determine whether or not SSRIs truly increase patients' quality of life, researchers have investigated social and occupational functioning of individuals with MDD before and after treatment. Remarkably, through trickle-down effects, SSRIs benefit the

individuals who take them, as well as the overall environments they operate in on a day-to-day basis. Depression not only creates financial tolls on individual patients with MDD, but also the national economy as a whole. Research has shown that depression in the workplace leads to increased absenteeism and decreased productivity (Gilmour and Patten 2007). As a result of excess disability days and subpar productivity outputs, depression takes an economic toll on society. The costs of depression are equivalent to an approximate \$2.6 billion annual deficit in Canada (1998) and a \$51.5 billion deficit the US (2000) (Gilmour and Patten 2007). Fortunately, studies denote that remission rates following treatment of escitalopram in workers with MDD coincided with significantly improved productivity, as measured by the Montgomery-Asberg Depression Rating Scale (MADRS), the Lam Employment Absence and Productivity Scale (LEAPS), the Health and Work Performance Questionnaire (HPQ) and the Sheehan Disability Scale (SDS) (Sarfati et al. 2017). Therefore, SSRI therapy has cascading benefits for workers, employers and the economy at large.

The final and most controversial component of SSRI efficacy is the debate as to whether or not SSRIs reduce suicidal ideation, suicide attempts and mortality rates. Approximately 800,000 people commit suicide every year, more often than not as a result of mental illness (WHO 2017). To investigate this issue, Tiihonen et al. used the National Hospital Discharge Register of Finland to monitor 15,390 patients that took antidepressants from 1997 to 2003 (2006). Their focus pertained to subjects hospitalized from suicide attempts. Upon admittance, the type of antidepressant prescribed further categorized qualifying patients. The antidepressant classes included SSRIs (fluoxetine, citalopram, paroxetine, sertraline or fluvoxamine), TCAs, serotonergic-noradrenergic antidepressants (SNAs) or no antidepressant use. Overall, the SSRI fluoxetine corresponded to the lowest rates of suicide, while the SNRI venlafaxine hydrochloride corresponded to the highest risks of suicide (Tiihonen et al. 2006). Authors hypothesized that

SSRIs solicited fewer suicides due to their superior tolerability, and fewer deaths overall by diminishing the risk of cardiovascular and cerebrovascular related deaths. Interestingly, non-antidepressant users exhibited significantly more suicide deaths; while patients taking antidepressants engaged in more suicide attempts the longer they maintained their treatment (Tiihonen et al. 2006). While data may show that SSRIs reduced short-term mortality rates, this does not address the concern that attempts of suicide can exponentially increase with long-term use. Additional research must be conducted that considers all components of suicide risk, not solely mortality.

NEGATIVE EFFECTS OF SSRIs

While SSRIs can be moderately effective in alleviating depressive symptoms in patients with major depressive disorder, a wide range of negative side effects have been reported with antidepressant use as well. Common adverse side effects include nausea, sleep disturbances, sexual dysfunction, appetite changes, headache, dry mouth, increased suicidal ideation, weight gain and tachyphylaxis (Ferguson 2001). SSRIs also have the potential to increase depressive symptoms. This proliferation has created novel medical terminologies such as tardive dysphoria, SSRI-induced depression and SSRI-induced indifference. The efficacy of SSRIs is further complicated by a meta-analysis of placebo response rates, indicating stable year-to-year fluctuations ranging from 35-40% (Furukawa et al. 2016). While it appears that the majority of current published clinical trials regarding SSRIs tend to focus on exposing the potential detriments of antidepressants, and thus may suggest biases, the growing list of adverse effects should not be taken lightly.

A meta-analysis of 131 RCTs conducted by Jakobsen and colleagues concluded that the harmful effects resulting from SSRI use outweigh the potential beneficial effects (2017). Results show that SSRIs significantly increased the risk of serious (hospitalization, suicidal

ideation/attempts, worsening depression, hemorrhages, death etc.) and non-serious (tremor, nausea, somnolence, insomnia, dizziness, fatigue etc.) adverse effects compared to placebo (Jakobsen et al. 2017). Additional findings conclude that typically, 64% of patients experience, on average, 2.9 side effects with prolonged antidepressant use (Bet et al. 2013). Although this number may seem miniscule, concerns may be heightened depending on the severity of the specific side effects experienced. As studies regarding long-term antidepressant use increase, data is beginning to infer that side effects may increase in number for patients with severe depression, as well as comorbidity (Bet et al. 2013).

Although SSRIs are supposed to treat depressive symptoms, they have the potential to exacerbate them as well. Commonly known as the “SSRI paradox,” emotional side effects such as apathy, emotional blunting and numbness have been commonly experienced among patients using SSRIs. Collectively, these symptoms, which coincide with low motivation, exhibit delayed onset and are dosage-dependent (exacerbated at higher SSRI doses), have been deemed as “SSRI-induced indifference” syndrome (Sansone R and Sansone L 2010). In order to reduce the ambiguity of self-reported studies in similar cases of anhedonia, McCabe et al. used functional magnetic resonance imaging (fMRI) to investigate the effects of SSRIs on the neural mechanisms regarding rewarding and aversive stimuli (2010). After 7 days of treatment, subjects administered citalopram displayed decreased BOLD activation in “punishment” areas of the brain, such as the lateral orbitofrontal cortex, in response to aversive stimuli (sight/taste of moldy strawberries) (McCabe et al. 2010). This finding appropriately coincides with antidepressant’s ability to reduce exacerbated reactions to negative triggers. However, McCabe also discovered that patients administered citalopram displayed decreased BOLD activation in reward centers of the brain, such as the ventral striatum and medial orbitofrontal cortex, in response to positive stimuli (sight/taste of chocolate) as well (2010). This blunted response to rewarding stimuli is

counterintuitive to the initial purpose of SSRI administration. Compared to reboxetine, a noradrenaline reuptake inhibitor, which increased reward center activation, McCabe's study introduces the possibility that antidepressants should be prescribed according to stricter symptom domains. If a patient's most prevalent symptom were anhedonia, decreased energy or loss of motivation, perhaps noradrenaline reuptake inhibitors would be a more effective treatment than SSRIs.

While some research findings, such as Tiihonen's longitudinal analysis mentioned previously, deduce lower suicide rates in SSRI-users, a plethora of studies have concluded opposite results. Paradoxically, Tiihonen's study reported that patients taking antidepressants experienced, on average, a 39% increased risk of suicide attempts (2006). He also mentions that while fluoxetine coincided with the lowest risk of suicide, paroxetine exhibited a 5-fold higher mortality rate (Tiihonen et al. 2006). Due to the fact that researchers use previous suicide attempts as the main risk factor for predicting suicide, it is logical to propose that if the study had continued, more attempts would be successfully completed. A meta-analysis conducted by Fergusson et al. deduced a significant association between suicide attempts and the use of SSRIs (2005). The odds ratio of suicide attempt increased from 1.14 in placebo groups to 4.55 in SSRI users (Fergusson et al. 2005). In addition to suicide attempts, suicidal ideation has also been reported to increase during SSRI therapy. Perlis et al.'s 12-week clinical trial of fluoxetine concluded that 14.3% of patients developed prominent thoughts of suicidal ideation that were not present during initial baseline screening (2007). Similarly, Hunter et al. noted that 13.5% of patients administered fluoxetine or venlafaxine developed treatment emergent suicidal ideation during clinical trials (2010). Interestingly, quantitative electroencephalographic tests isolated a consistent decrease in midline and right frontal cordance biomarkers just two days after drug administration (Hunter et al. 2010). While screening for suicidal ideation susceptibility is still

under investigation, the increased risk of suicide during SSRI therapy remains a public concern after the FDA mandated black box warnings on fluoxetine, paroxetine, sertraline and citalopram in 2004.

One of the main challenges in deducing the efficacy of SSRIs in RCTs is the placebo effect. The placebo effect is rather common in antidepressant therapies. This may be due to the fact that depressive symptoms are often ambiguous and can be exacerbated or alleviated through simple changes in mental thinking. For example, the common depressive symptom of hopelessness, can be mitigated by administering a potentially effective pill, due to the fact that patients become hopeful in its therapeutic effects and believe in its false efficacy. Khin et al. (2011) analyzed the phenomenon of the placebo effect in all clinical antidepressant trials conducted by the FDA from 1983 to 2008. Over the course of 25 years, drug efficacy decreased while placebo responses remained stable (Furukawa et al. 2016). In fact, only 53% of MDD trials were deemed to be successful (Khin et al. 2011).

Similar studies have also shown that antidepressant drug-placebo differences coincide with baseline severity. Kirsch et al. found that moderate to severe cases of depression exhibited little to no drug-placebo differences, and only patients with extremely severe MDD benefitted slightly from antidepressants (2008). In fact, 82% of drug responses were able to be duplicated by placebo treatments (Kirsch et al. 2008). Due to the fact that drug companies and the FDA prefer not to publish negative trials of SSRI efficacy, RCTs demonstrating the placebo effects of SSRIs are difficult to obtain. A double-blind placebo-controlled study of fluoxetine in depressed Alzheimer's patients exhibited no significant differences between treatment groups (Petracca et al. 2001). In fact, both fluoxetine and placebo patients exhibited similar improvements in mood, as designated by the HAM-D, and obtained remission rates of 47% and 33%, respectively (Petracca et al. 2001). Biases in research publications complicate efficacy rates, however,

insights into major depression in comorbid conditions have shown concrete evidence of the placebo effect in SSRI clinical trials.

LONG-TERM EFFECTS

Like any type of drug that may be used regularly for long durations of time, the efficacy of SSRIs is likely to decrease as patients develop a tolerance for them. It is hypothesized that tachyphylaxis, or tolerance in regards to reduced antidepressant efficacy, prefaces susceptibility to overall treatment-resistant depression (TRD). In order to investigate the progression of this phenomenon, Amsterdam and colleagues studied the effects of prior antidepressant use in potential novel responders administered sertraline (2009). The results concluded that each course of antidepressant exposure equated to a 20% decrease in response to initial sertraline therapy (Amsterdam et al. 2009). Subjects who took the most antidepressants (4+) prior to SSRI therapy exhibited the smallest drug responses. This alludes to the possibility that a stepwise reduction in SSRI efficacy can cumulate into complete tachyphylaxis. In fact, past antidepressant therapy negatively correlated to declining remission rates. Prior consumption of just one antidepressant exhibited, on average, a 36.8% remission rate, while only 6.9% of patients who took four or more antidepressants achieved remission (Amsterdam et al. 2009). Such findings connote that SSRIs are most effective during first-time use and should only be used for acute depression.

The fact that SSRI efficacy will decrease with each exposure is alarming, due to the fact that 50-80% of individuals suffering from MDD are at risk of experiencing minor (2-4 weeks) or major (9+ months) recurrent depressive episodes (El-Mallakh et al. 2011). With a projected 30-50% of patients susceptible to TRD, El-Mallakh et al. proposed that increasing rates of TRD might result from tardive dysphoria (TDp), or antidepressant-induced chronic depression (2011). Tardive dysphoria is a combination of diminished drug efficacy (tachyphylaxis) and an active progression of worsening depressive mood caused by continuous antidepressant administration

(El-Mallakh et al. 2011). TDp is a parallel to tardive dyskinesia, and its effects may not be reversible. The pro-depressant effects of SSRIs were prevalent in Fux et al. when panic disorder patients administered fluvoxamine for anxiety reported experiencing emergent, novel depressive symptoms during SSRI treatment (1993). Similarly, sertraline administered to healthy patients induced suicidal ideation and depressive symptoms (Healy 2000).

The concern of antidepressant's pro-depressant effects is heightened in regards to gestation. Despite encouraging expecting mothers to halt the use of antidepressants during pregnancy, some choose to continue their medications. By investigating 5-HT levels in the offspring of SSRI-using mothers, researchers can gain insight into whether or not SSRIs can induce proliferated neurological responses across generations. To investigate this possibility, Simpson et al. treated in vivo and in vitro models of pre- and perinatal rat pups with citalopram (2011). Perinatal citalopram-exposed pups exhibited behavioral abnormalities, such as exaggerated freezing responses to stimuli, excessive neophobia and juvenile play avoidance (Simpson et al. 2011). Structurally, treated pups had altered 5-HT raphe circuits with decreased density of SERT-ir fibers in limbic and primary somatosensory cortical areas, abnormally thickened and shortened SERT-ir axons and reductions of TPH (5-HT marker) (Simpson et al. 2011). In terms of callosal axonal architecture, citalopram caused degeneration and distorted morphology of oligodendrocytes, as well as disorganized tonotopy. Structural abnormalities increased linearly in severity with higher doses of SSRIs. Of significant importance, is the fact that the behavioral and structural changes induced in citalopram-exposed pups persisted into adulthood. This long-term effect poses the question as to whether or not secondary exposure to SSRIs during embryonic development will lead to the creation of a depression-prone generation. Further research is necessary in this novel area, especially with human participants.

Researchers have begun to speculate that prolonged SSRI use may cause impaired digestion, absorption and storage of nutrients, thus inducing nutrient depletion, diminished antidepressant response rates and increased adverse side effects. Patients with mental illness typically exhibit deficiencies in omega-3 fatty acids, B vitamins, magnesium, and neurotransmitter precursors (Naghashpour et al. 2011). In previous research findings, fluoxetine administration decreased levels of melatonin in blood samples of patients with MDD (Childs et al. 1995). Depressed subjects were also noted to have smaller serum concentrations of riboflavin than non-depressed subjects (Naghashpour et al. 2011). For individuals experiencing treatment-resistant depression, new therapeutic strategies that focus on enhancing endogenous augmentation agents seem to be a plausible means for improved treatment. Studies have shown that supplemental doses of omega-3 eicosapentaenoic (EPA) fish oil, S-adenosylmethionine (SAME), methylfolate and vitamin D, in conjunction with antidepressant therapy, leads to the reduction of adverse side effects while increasing drug efficacy (Sarris et al. 2016). For example, Nehmets et al. (2002) administered 20 MDD patients with either placebo or 2g of EPA daily. EPA patients experienced an average 12.4 reduction in their HDRS ratings, while placebo mean reduction was only 1.6 (Nehmets et al. 2002).

Coenzyme Q10 (CoQ10) is a critical cofactor in mitochondrial electron-transport chains that exhibits antioxidant properties by mediating as an electron donor (Aboul-Fotouh 2013). CoQ10 has been known to protect against neuronal cell damage in neurodegenerative disorders, such as Alzheimer's and Parkinson's disease. Rezin et al. (2009) found CoQ10 plasma levels to be significantly depleted in depressed patients. To further investigate these findings, Aboul-Fotouh (2013) used chronically stressed rats to test the effects of CoQ10 treatment on hippocampal oxidative/nitrosative stress pathways, DNA damage and depressed behavior. In summary, CoQ10 treated rats outperformed depressed control groups in forced swimming and

open field tests. In addition to improved behavior, CoQ10 restored endogenous defenses, such as enzymes CAT and GP_x, thereby reducing levels of MDA, nitric oxide and 8-OHdG in the hippocampus (Abdoul-Fotouh 2013). The antidepressant properties of CoQ10 suggest that the treatment of depression exceeds the narrow focus of serotonin deficiency. Psychiatrists should consider treating patients for oxidative damage, rather than monoamine depletions, especially those who are non-responders or have reached the point of tachyphylaxis.

INCREASED DIAGNOSIS AND PRESCRIPTION RATES

Increased prevalence of depression and skyrocketing numbers of authorized prescriptions for antidepressants indicates a societal cause for concern within the field of mental health. Factors that may contribute to this epidemic include improper diagnosis of depression, lack of initial exploration of non-drug remedies, increased utilization of antidepressants as an umbrella treatment by primary care doctors and the perception of unrealistic antidepressant efficacy due to biased research publications. Such factors raise red flags when analyzing clinical research trials including test subjects who may or may not truly have MDD.

Aside from definitive, statistically supported types of depression such as seasonal affective disorder (SAD), bipolar disorder and postpartum depression, the broad continuum of generalized mild to severe depression is difficult to discern. Ambiguity in depression criteria has led to an increase in improper diagnosis and over-prescription of antidepressants. There has been great controversy of the DSM-5's expanded definition of depression, which equates the mental illness to grief from bereavement. The most recent definition allows sadness due to loss to be deemed as depression, despite a miniscule duration of two weeks and lack of characteristic symptoms, such as functional impairment and suicidal ideation (Parker 2013). While grief follows a sequence of typical stages, such as shock, guilt, anger and resolution, major depression

is much more variable and long-term. Grief should not be considered depression, but rather a normal, episodic sadness that follows the loss of a loved one (Dowrick and Frances 2013).

Treating grief the same way one treats a neurological disorder, such as depression, increases risks of adverse side effects in healthy patients, and more importantly, does not “cure” the emotion.

Studies have also found that more primary care doctors, rather than psychiatrists, are prescribing antidepressants as a general solution for patients experiencing mood disorders. A recent study investigating the accuracy of clinician-identified depression in 5,639 patients revealed that only 38% of subjects met the DSM-IV 12-month major depressive episode (MDE) criteria (Mojtabai 2013). In order to reduce the number of antidepressant prescriptions written for patients who lack a legitimized psychiatric diagnosis, doctors should use multiple assessments, recommend alternative therapies prior to drug use and pursue increased knowledge regarding depression thresholds (Mojtabai 2013).

The last component of rising prescription rates that should be considered is society’s mainstreamed attitude and conviction towards the efficacy of antidepressants. A meta-analysis of 74 FDA-registered studies testing 12 antidepressants and involving 12,563 patients revealed biases in published reports of drug efficacy (Turner et al. 2008). Of the 74 studies, 37 out of 38 positive trials were published, while only 3 out of 36 significantly negative trials were published. In addition to this, 11 published trials with questionable results were manipulated to suggest a positive outcome. Collectively, 94% of the published studies conveyed positive effects of antidepressants, when in reality; only 54% of the studies were truly efficacious according to FDA standards (Turner et al. 2008). These significant results raise concern. Unpublished trials should be published in order to accurately assess the effects of antidepressants. Withheld

information alludes to unrealistic confidence in drug efficacy and puts patients at risk of adverse effects.

CONCLUSION

Several limiting factors should be kept in mind while analyzing MDD research. First and foremost, a large majority of individuals with MDD do not meet DSM-5 criteria. Misdiagnosed MDD subjects may skew the results of clinical trials. In addition to ambiguous diagnostics, subjective measures of symptom severity may lead to inconclusive data. The most commonly used measure of depression is the Hamilton Depression Rating Scale, which is organized into 17-29 symptomatic classes. Health professionals utilize a point system to score patients' symptoms on each item. While small scores (0-7) clearly indicate normal mood, and large scores (24+) indicate severe depression, in-between ratings are hard to differentiate (Sharp 2015). Several meta-analyses found substantial differences between antidepressant users and placebo, however a vague cut-off of one to two points on HAMD-R scores inhibited the yield of statistically significant data. Self-reported depression rating scales, such as the Beck Depression Inventory-II (BDI-II) and Clinically Useful Depression Outcome Scale (CUDOS), are also useful and cost-effective, but run the risk of patient biases. Although alternative diagnostic recommendations, such as fMRI may deduce more conclusive data, imaging may be costly. Objective diagnostics and more concrete measures of depressive symptom severity are necessary in the mental health field.

While selective serotonin reuptake inhibitors may improve depression severity for acute cases, the efficacy of antidepressant use is clouded by high placebo response rates. Patients who achieve endpoint remission, either by valid antidepressant action or false perceptions of healing, are still advised to continue SSRI treatment for at least six months to minimize risk of relapse

(Reid and Barburi 2010). Even after successful treatment and discontinuation, studies show that more than 90% of remitted patients will experience residual depressive symptoms, such as insomnia, hypersomnia and anxiety after SSRI use (Iovenio et al. 2011). Of the 50-80% of patients who are projected to experience an additional depressive episode, long-term research of cumulative reduced drug efficacy (20%) with each prior antidepressant treatment does little to comfort those in need (Amsterdam et al. 2009).

As time goes on, research regarding the adverse effects of SSRI use appears to be increasing in severity. Initially, patients report having a positive response to antidepressants, however, observations of prolonged drug use at high doses results in tachyphylaxis and exacerbated tardive dysphoria. 30-50% of patients will develop treatment-resistant depression and find themselves stuck in a depressive state with symptoms much worse than they had at the beginning of their therapeutic journey (El-Mallakh et al. 2011). This may be due to antidepressant-induced structural abnormalities, such as decreased dendritic arborization, which has not yet been shown to be reversible (El-Mallakh et al. 2011). Precautions should be taken in regards to the duration of SSRI prescriptions. The main limitation to the validity of long-term randomized clinical trials testing SSRI efficacy is time. Although the average length of SSRI clinical trials are 6-8 weeks in length, the current average duration of antidepressant prescriptions is 4.8 years in length (Reid and Barbui 2010). More longitudinal studies are needed to coincide with prolonged SSRI use.

Lastly, with an ever-growing choice of alternative treatments, patients should not resort to immediate drug use and expect a miracle pill to fix all of their symptoms. Cognitive behavioral therapy (CBT) has proven to be just as effective as SSRI medications and reduce the risks of experiencing adverse side effects (DeRubeis et al. 2008). Hypotheses regarding nutrient

deficiencies, which may underlie the majority of depressive symptoms, also blur the logic of the monoamine hypotheses of depression. For instance, Eby G and Eby K (2006) administered depressed patients daily supplements of magnesium and found that nutrient augmentation restored subjects' sleeping patterns, decreased emotions of anxiety and depression, reduced the occurrence of headaches and improved short-term memory. Ketogenic high-fat, low-carb diets have also exhibited antidepressant properties, eliminating almost all depressive symptoms and increasing energy levels (Murphy et al. 2004). Before patients are diagnosed with depression, they should undergo simple blood testing to determine whether or not their symptoms are a result of nutrient imbalance, or true neurological impairment.

Overall, SSRIs are a fast-acting, convenient and cost-effective remedy to depression. However, many prescribers overlook the fact that SSRIs are mainly effective for short-term, moderate depression. With side effects ranging from nausea, anhedonia and tachycardia, to suicide and neurological morphologies, the benefits of taking SSRIs do not outweigh the costs. Although SSRIs have been a successful treatment for some individuals, they do not “cure” patients of their mood disorders, but rather simply mask or intensify it. Despite our nation’s glorified perception of SSRIs, research has shown that SSRIs are truly not as efficacious as the media portrays them to be.

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