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An Investigation of Atypical Antidepressants

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An Investigation of Atypical Antidepressants

An Interactive Qualifying Project Report
submitted to the Faculty of
WORCESTER POLYTECHNIC INSTITUTE
in partial fulfillment of the requirements for the
Degree of Bachelor of Science

Submitted to:
Professor Destin Heilman (advisor)

By:
Jonathan M. DeFeo

Abstract

In modern Psychiatric practice, the vast majority of patients diagnosed with Major Depression are given a Selective Serotonin Reuptake Inhibitor (SSRI). Although SSRIs are generally regarded as safe and in most cases have minimal side effects, their efficacy in many of those cases is minor and the patient is then moved to either a different SSRI or to another class of antidepressant. This project investigates other classes of antidepressants and compares their efficacy to SSRIs. Interviews with Psychiatrists are also included.

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1 Introduction

Major Depressive Disorder is a common syndrome the effect of which can range from mild to fatal. A 2004 study showed that as much as 8% of the American population has reported at least one major depressive episode in their lifetimes[1]. An episode is typically characterized by a loss of pleasure in any or all activities one normally would find enjoyable, lack of response to normally pleasurable stimuli, significant, abnormal weight loss or gain, suicidal thought, insomnia or hyper-somnolence, and an overall feeling of sadness or melancholy. Depression can be effectively treated with psychotherapeutic techniques, antidepressant medications, or both. The vast majority of people, however, receive only prescription medication[20].

The problem with the medication-only approach is that there are a very large number of medications available and any one of them might have some, little, or no effect[21]. It is impossible to determine which medication will work best for a patient without trial and error. Many medications do not show any significant clinical advantages over another, yet on an individual case-by-case basis, one may work significantly better than the other. Interestingly, many medications only demonstrate clinically significant results for severe depression and only have a minor effect on moderate depressive symptoms[10]. This is due in part to the extremely variable biological causes of depression; SSRIs only seek to re-balance serotonin levels in the brain, yet serotonin deficiency is only one of the many biological differences found in depressed patients compared to healthy patients.

This leads to a very interesting question: why, if the biological causes of depression are so varied, is such a singular approach taken to treat it? The answer to this question may lie with the fact that drugs are very expensive to develop and the companies that develop them need to focus on a single mode of action and use that in their advertising. The decades of advertising, both television and direct drug representation to doctors, has focused on serotonin and this kind of "programming" is difficult to undo. This is unfortunate, since there are drugs or combinations of drugs which seek to correct the multi-faceted chemical

explanations for depression.

2 Background

2.1 The Chemical Reason for Depression: The Monoamine Hypothesis

The Monoamine Hypothesis states that deficiencies in various monoamine neurotransmitters are responsible for corresponding symptoms of depression. There is a large body of research which supports this hypothesis and studies have been done on both animals and humans to monitor changes in brain chemistry as they relate to behavior [5].

Electrical signals in the brain are created by highly specialized cells called neurons. These cells are responsible for all of the brain's major functioning. These electrical signals are similar in many ways to the electrical signals in computer processors; electric current flows through each transistor's channel and based on the "path" that it took, different results are created.

A neurotransmitter is a chemical which neurons use to relay signals to other neurons and cells. They travel across the synapse; junctions between neurons. A neuron can have thousands of synapses to other neurons; most commonly the connection is between the axon (transmitter) and dendrite (receiver) . Electrical impulses in the axon (pre-synapse) release neurotransmitters which diffuse across the synaptic cleft and can bond with specialized receptors on the dendrite (post-synapse). This can cause an electrical impulse to generate in the dendrite. In this case, the neurotransmitter acts as an agonist, which produces a result in the post-synapse depending on the type of cell. There are also antagonists, which block this electrical impulse from occurring but bond to the same spot. After encountering their respective receptors, neurotransmitters are quickly taken back across the synapse by means of specialized proteins called transporters, which take the neurotransmitter back into the pre-synaptic cell through the neurotransmitter re-uptake pump.[19] Figure 1 shows a diagram of the synapse:

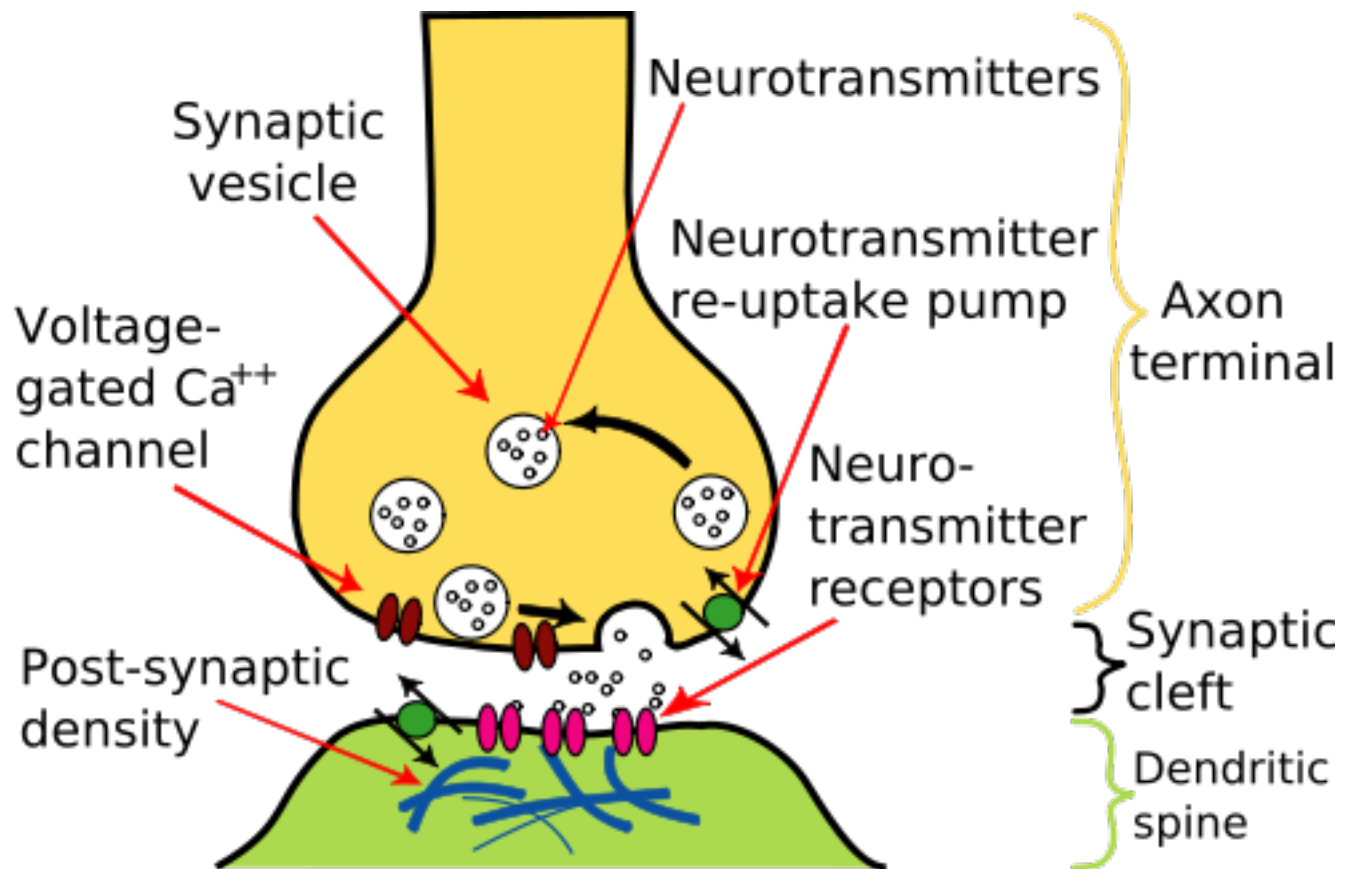


Figure 1: Diagram of the Synapse [19]

Depression is believed to be caused at least in part by deficiencies in certain neurotransmitters. This creates a lack of neuron responses in specific parts of the brain. According to the monoamine hypothesis, serotonin, norepinephrine, and dopamine are the neurotransmitters related to depression.

2.1.1 Serotonin

Serotonin is produced by the raphe nuclei in the upper brain stem. It is derived from tryptophan, an essential amino acid. Two enzymes are responsible for this process: tryptophan hydroxylase and amino acid decarboxylase. It cannot cross the blood brain barrier, so serotonin taken orally has no effect on the brain's serotonin levels. Serotonergic neurons, neurons which produce an electrical impulse as a response to serotonin, are found through-

out the brain. They have various functions including regulating sleep, mood, and appetite. Disruption of sleep, melancholic mood, and decreased appetite are all symptoms of major depression, and it is believed that those symptoms are a result of a lack of serotonin.[3] However, serotonin is not the only chemical identified to create disruptions in depressed patients.

2.1.2 Norepinephrine and Dopamine

Norepinephrine is primarily associated with triggering the fight-or-flight response but is also critical in regulating arousal and reward. It is tied into the dopamine system as well because norepinephrine is synthesized from dopamine by the enzyme dopamine- β -hydroxylase. Noradrenergic neurons begin the locus coeruleus, where the axons act on noradrenergic receptors in the thalamus, spinal cord, hippocampus, amygdala, and many other parts of the brain. [17]

Dopamine has strong effects on the brain's reward system, as well as cognition, and the motor system. Release of dopamine creates feelings of enjoyment and provides reinforcement to motivate people to continue doing actions that provide them pleasure. In patients with major depression, motivation and pleasure are severely impaired. Dopamine is perhaps the most critical neurotransmitter in depressed patients because the primary symptoms associated with depression are inability to feel pleasure from normally enjoyably activities and the associated lack of motivation to do them. The dopamine system is separate from the serotonin pathways.[2] Neurotransmitters however are not the only major factors in depressed people; just the only chemical ones.

2.2 Genetics

It has been shown that people with two long alleles of the serotonin transporter gene (5-HTT) are less likely to develop depression in their lives, whereas people with one long and

one short allele are more likely. This may be due to emergent behavior caused by decreased serotonin activity which permits other neurotransmitter systems to act in unwanted ways. It is currently not entirely known why the long allele of 5-HTT presents in fewer patients with depression. Serotonin is believed to have a regulatory effect on other systems in the brain, which governs internal responses to external factors. [4]

2.3 Environment

A depressive episode can be caused by any highly stressful event. Stressful events cause the Hypothalamic-Pituitary-Adrenal axis to activate in response to various stressors. The HPA axis influences the production of serotonin through the raphe nuclei. [4]

2.4 Types of Antidepressant Medication

2.4.1 Monoamine Oxidase Inhibitors (MAOI)

MAOIs work through a chemical reaction with monoamine oxidase A and B, enzymes which oxidize specific monoamines. Monoamine oxidase A mainly breaks down serotonin and norepinephrine, neurotransmitters that are associated with depression. It is also responsible for the catabolism of adrenaline and melatonin, a derivative of serotonin which is important in regulating the circadian rhythm. Monoamine oxidase B breaks down phenethylamine, a naturally occurring stimulant drug found in the brain as well as other trace amines. Dopamine, another important neurotransmitter, is broken down by either MAO-A or MAO-B. When an MAOI reacts with monoamine oxidase, the enzyme is permanently deactivated (colloquially referred to as a "suicide substrate") and cannot function until the protein is replaced by the body. Certain MAOIs are naturally occurring, such a harmaline, found in the bark of the jungle vine Ayahuasca. MAOIs intended to treat depression however are man-made; the most commonly still in use today are Isocarboxazid and Phenelzine.

By preventing serotonin, norepinephrine, and dopamine deamination (the removal of

an amine group from a molecule), availability of these neurotransmitters in the brain are significantly increased. This aims to correct the "monoamine hypothesis" biological cause for depression. Because of their wide mode of action, MAOIs are highly effective at treating depression and there is strong clinical evidence which supports their efficacy, especially in patients for whom other types of antidepressants were ineffective.

The reason that MAOIs are no longer used as front-line treatment for depression is due to the fact that MAO is responsible for breaking down other trace dietary amines, such as tyramine (commonly found in aged wines and cheeses) and tryptophan, found in large quantities in eggs, cod, soybeans, and aged cheese. Normal ingestion of these compounds is not dangerous; however, in patients whose MAO enzyme is inhibited through taking an MAOI, these chemicals are not metabolized and persist in the body causing alarming issues such as a major hypertensive crisis or serotonin syndrome. The consumption of foods rich in tyramine while undergoing MAOI treatment and the resulting sudden increase in blood pressure has been dubbed "cheese syndrome" although any food containing tyramine can cause a hypertensive crisis. These dangers can be fatal, although there are fewer than 100 cases of death from complications with MAOIs. However, the public image of these drugs were permanently damaged since these side effects were not known when the first MAOIs came onto the market. MAOIs were briefly banned from sale in the United States due to deaths attributed to dietary amine consumption.

As a result of these dangers and the requirement of a specific, restrictive diet, MAOIs are currently only used for patients who do not respond to other types of antidepressants. [17]

2.4.2 Tricyclic antidepressants (TCA)

TCAs are the oldest class of antidepressants and were used as first-line treatment for depression since the 1950's. They are characterized by three carbon rings in their molecular structure. Amitriptyline is the most commonly prescribed TCA and is the most effective at

treating depression. Because of their age, TCAs are often used as the benchmark for efficacy of antidepressant and most clinical studies compare other drugs efficacy to a particular TCA.

TCAs all have varying modes of action, but the majority function by blocking the serotonin and norepinephrine transporters. These transporters are proteins which terminate the actions of their respective neurotransmitters. TCAs act as ligands for the transporters and prevent them from bonding to anything else. They have a very high affinity for serotonin and norepinephrine but not dopamine. They also have a high affinity for H1 and H2 histamine receptors, and for the muscarinic acetylcholine receptor which results in TCAs also acting as effective antihistamines and anticholinergics. These affinities create undesirable side effects such as lethargy, ataxia, drymouth, increased body temperature, tachycardia, and in severe cases delirium. These unpleasant and in some cases severe side effects are a reason TCAs have been supplanted by newer drugs for the treatment of depression.

Like many antidepressant drugs, TCAs are metabolized by the cytochrome P450 enzymes and as such drugs that inhibit these enzymes and lead to increased blood concentrations for the drug, increasing its toxicity and side effects. The P450 enzymes are a group of enzymes found in the liver which are responsible for catabolism of vast array of drugs; in some cases, such as hydrocodone, they break the substance down into biologically active metabolites. Hydrocodone has almost no affinity for opiate receptors and thus does nothing to prevent pain; after being broken down by CYP2A6 (one of the P450 enzymes) its metabolite, hydro-morphone, is what causes the painkilling effect. Other drugs, such as novocaine, are broken down into inactive metabolites. TCAs fall under the former category.

The primary reason TCAs are no longer used as first-line treatment is due to their high potential toxicity and consequently their potential to cause a fatal overdose. They are rapidly absorbed into the bloodstream as onset of overdose symptoms occurs quickly. Death is most commonly caused by the cardiac effects of acetylcholine antagonism. TCAs have been attributed to as many as 33% of all fatal poisonings, and 95% of deaths related to

antidepressants alone. These dangers are significant and thus TCAs are only administered to patients who do not respond to other antidepressant medications.[17] TCAs have been largely supplanted by SSRIs for first line treatment.

2.4.3 Selective Serotonin Reuptake Inhibitors (SSRI)

SSRIs are a newer class of antidepressants which, in the United States, are the most widely prescribed antidepressant. Sertraline, marketed as Zoloft, is the most commonly prescribed. They are almost exclusively used as first-line treatment for major depressive disorder. SSRIs' mode of action is to inhibit the re-uptake of serotonin into the presynaptic cell by bonding to serotonin transporter. This is different from the TCA drugs because SSRIs have high bonding affinity only for serotonin transporter and very minimal affinity to other monoamine transporters. This means that SSRIs have much more limited side effects and do not have any of the anticholinergic or antihistamine effects that TCAs do. [8]

SSRIs are therefore much less toxic than TCAs and are very difficult to achieve a dangerous reaction to an overdose. The most severe complication arising from overdose is serotonin syndrome, an excess of serotonin in the brain which can, in very severe cases, lead to seizures, coma, and death. SSRIs do have some minor side effects mostly related to depression itself. The most common reason for discontinuation due to side effects is sexual dysfunction. This is thought to be caused by SSRIs creating chemical imbalances in the brain in the dopamine pathways which directly influence sexual arousal and function. Drugs which cause large releases of dopamine such as amphetamines have been shown effective in treating the sexual dysfunction associated with SSRI use.

In some rare cases, a persistent syndrome called Post-SSRI sexual dysfunction may occur in which the patient's sexual symptoms last beyond discontinuation of the drug. This effect can last indefinitely.

SSRIs were the first type of psychoactive drug to be rationally designed; as opposed

to the trial-and-error used up to that point. This involves creating a molecule that has specific binding properties based on hypothetical benefits. In the case of SSRIs, the goal was to create a molecule that bonded to serotonin transporter. This is most commonly done using computer assisted tools and analysis. [17]

2.4.4 Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)

SNRIs are a more recent development than SSRIs, and are also very widely used. The most commonly prescribed is Venlafaxine, marketed as Effexor. They have been shown to have slightly higher efficacy than SSRIs due to their dual mode of action, blocking both serotonin and norepinephrine transporter. SNRIs have the same sexual side effects that SSRIs do, although with lower occurrence.[15] This combination of two modes of action is now very common in antidepressant medication, and serotonin and norepinephrine are not the only neurotransmitters affected by other dual-mode drugs.

2.4.5 Norepinephrine and Dopamine Reuptaking Inhibitors (NDRI)

NDRI act on norepinephrine and dopamine transporter and thus increases the amount of both neurotransmitters in the postsynaptic cell . This is the only class of non-serotonergic drug commonly prescribed for depression. Bupropion, marketed as Wellbutrin, is the fourth most prescribed antidepressant in the United States. It has been shown to be more effective than SSRIs on its own and is also used to augment the performance of an SSRI. It does not cause sexual dysfunction or weight gain and has only isolated side effects. This indicates that sexual dysfunction is a function exclusively of serotonin reuptake inhibition, as drugs which do not effect it do not have sexual side effects.

It was commonly publicized that bupropion reduced the seizure threshold and was temporarily withdrawn from the market. This risk was highly inflated by the media and in reality was not significantly higher than other antidepressant medications. Seizures are more com-

mon among those with clinical depression and antidepressants may in fact help to prevent them. A sustained release version of the drug has since been released which maintains levels of the drug in the bloodstream at a slower rate, which reduces the seizure risk. [16]

Bupropion overdose is rarely fatal, although there have been cases where extremely large doses were taken that resulted in death. Its overdose danger comes from the increased amount of dopamine in the brain, which causes tachycardia and in very large amounts results in cardiac arrest.

Bupropion is considered an atypical antidepressant since it does not effect serotonin levels. The only commonly prescribed atypical drugs are bupropion and mirtazepine.

2.4.6 Noradrenergic and specific serotonergic antidepressants (NaSSA)

This class of atypical antidepressants is solely composed of Mirtazapine, marketed as Remeron. Its mode of action is completely different from the reuptake inhibitors and instead is a highly potent antagonist of H1, a histamine receptor, the serotonin receptors 5-HT2A, 5-HT2C, 5-HT3, and the alpha2-adrenergic receptor. It has no affinity for any neurotransmitter transporter. The antidepressant effect comes primarily from the antagonism of 5-HT2c which normally prevents dopamine from being released in the pleasure centers of the brain.

Mirtazapine therefore has none of the negative side effects related to increased amounts of serotonin, dopamine, or norepinephrine, instead making the available amount more effective. It is sometimes used in addition to another antidepressant in order to alleviate their side effects and improve their antidepressant effect.

It is the strongest histamine-1 antagonist on the market currently and causes powerful sedative effects. It is therefore most commonly taken at night, and has been shown to effectively treat insomnia. It has no anticholinergic properties however, so overdose danger is low. At 7 to 22 times the maximum dose, there is no indication of adverse cardiovascular effects. There is no medical report of a death related to mirtazapine. [23]

3 Comparison of Drug Efficacy

In this section, a comparison of the two most common atypical (i.e., not a serotonin reuptake inhibitor) antidepressants, mirtazapine (marketed as Remeron) and bupropion (marketed as Wellbutrin) to drugs in the SSRI family is performed. There are a great many studies directly comparing efficacies of these two drugs because they are interesting from a psychiatric perspective; neither of their mechanisms of action (as seen in section 2) effect serotonin transporter or serotonin reuptake. Every other antidepressant medication effects one or both of these.

3.1 Hamilton Rating Scale for Depression

The Hamilton Rating Scale for Depression is an up to 21 question multiple choice test which psychiatrists use to evaluate the severity of a patients depression. It has several sections of questions which are used to determine which specific symptoms are most severe in the patient. Some sections are worth more than one point, so the maximum score on the 21 question version is 29 points. These sections include mood, suicidal thought, insomnia, anxiety, loss of interest, and weight loss/gain. [7]

A score of 0 to 6 indicates no depression, between 7 and 17 indicated mild depression, between 18 and 24 indicates moderate depression, and anything over 24 is considered severe depression.

Virtually all psychiatrists use a form of the HDRS to evaluate patients and as many studies use it to determine how effective certain treatments are. In most studies, a difference of 2 points on the HDRS is considered clinically significant.

The HDRS is the most widely used rating scale in studies to determine the efficacy of antidepressant drugs. Virtually every study reports their findings as increases, decreases, or no change in the patients' HDRS score.

3.2 Mirtazapine

Please see section 2.4.6 for an explanation of its mechanism of action.

There has been extensive research on mirtazapine and its relative efficacy compared to other antidepressants. There are potentially many benefits to using mirtazapine as first line treatment due to the many specific areas of the brain it affects. Because its mechanism of action is so specifically targeted, rather than the more general approach of SSRIs, SNRIs, MAOIs, and TCAs, it has potential to be more effective with fewer side effects.

A study in the Journal of Clinical Psychiatry, performed at The Royal Masonic Hospital in London, which compared two groups of patients suffering from depression, gave one group fluoxetine (Prozac, an SSRI) and the other mirtazapine.[23] The fluoxetine group had 67 members and were given between 20 to 40mg of fluoxetine. The normal starting dosage of fluoxetine is 20mg. Members in the fluoxetine group had a mean HDRS score of 26.1 at the beginning of the study. The mirtazapine group had 66 members and was given 15 to 60mg per day. The normal starting dosage of mirtazapine is 15mg. An interesting effect of mirtazapine is that as dosage goes up, its sedative effect decreases. In the United States, only up to 45mg of mirtazapine is approved. Members of the mirtazapine group had a mean HDRS score of 26 at the beginning of the study. In studies of new antidepressants when compared to placebo, an improvement of 4 points is considered indicative of an effective antidepressant; e.g. if a drug performs 4 points better than the placebo, that is considered clinically significant and the drug is considered proven efficacious for treatment of depression. In this particular study, the mirtazapine group reached clinically significant improvement in HDRS score at day 21. The fluoxetine group did not reach this level until day 28. Interestingly, at day 21 and onwards, members of the mirtazapine group had an individual advantage over the fluoxetine group that ranged between 3.7 and 4.2 points. In other words, if the fluoxetine had been a placebo, the mirtazapine would be considered to be an effective antidepressant. This has not actually been attempted, but is way of stating how much more effective mirtazapine

is as an antidepressant in relative terms.

Both drugs were well tolerated; similar numbers of patients dropped out due to side effects in each group. The only statistically significant difference was members of the mirtazapine group had a statistically significant change in weight from their baseline compared to the fluoxetine group. The study concluded that mirtazapine was significantly more effective after week 3, and this advantage continued during the entire course of the study.

Another study in the Journal of International Clinical Psychopharmacology performed a double blind 8 week study comparing the effects and tolerability of mirtazapine to citalopram (Celexa, a newer SSRI).[11] All patients in the study had scores of over 22 on the HDRS, indicating moderate to severe depression. Patients were then randomized into the two groups. The mirtazapine group had 137 members and were given between 15 and 60mg a day. The citalopram group had 133 members and was given between 20 and 60mg per day. By the end of the 8 weeks, the reduction in HDRS scores was significant; 9.1 points mean in the mirtazapine group, and 8.9 mean in the citalopram group. This indicates that as far as treatment of depression is concerned, citalopram and mirtazapine are equally as effective (a difference of .2 points is not statistically significant). However, at 2 weeks into the study, mirtazapine had an early advantage of a mean of 2.3 points. Although 4 point improvement is considered significant when comparing a drug to a placebo, when comparing two proven antidepressants the 2.3 point advantage to mirtazapine is considered clinically relevant.

Patients were also given a qualitative test called the Leeds Sleep Evaluation Questionnaire, which is self administered and specifically targets sleep related symptoms. The mirtazapine group had a much more rapid improvement in sleep, quality of sleep, and alertness in the morning, but this improvement equalized by the end of the 8 weeks.

3.6% of patients in the mirtazapine group dropped out due to side effects, weight increase and increased appetite being the two most common complaints. 3.0% of the citalopram group dropped out, most often complaining of sweating and nausea. Otherwise, there was

no clinically significant differences in tolerability and side effects between the two drugs.

The study concluded that both drugs are equally effective at treating depression and anxiety, and have nearly identical tolerability. The significant difference was the more rapid onset of efficacy for mirtazapine over citalopram.

Another study in the *Journal of International Clinical Psychopharmacology* investigated mirtazapine's ability to increase norepinephrine and serotonin neurotransmission in rats. An in vivo electrophysiological paradigm was placed in the rat to determine pre and postsynaptic serotonin neurotransmission. The study found that almost no difference in neurotransmission was found in the short term, but at the two week point there was a significant enhancement of activation of postsynaptic serotonin receptors. This could explain why mirtazapine has a more rapid onset of efficacy than either fluoxetine or citalopram. [6]

Lastly, a meta analysis of all studies comparing mirtazapine to amitriptyline (the most effective TCA) was performed and presented in the *Journal of International Clinical Psychopharmacology*. [9] The data was compiled for 364 patients taking mirtazapine and 368 patients taking amitriptyline. The compiled data included baseline measurements on the HDRS scale for both moderately and severely depressed patients. The study also included a comparison between mirtazapine and placebo. The study concluded that mirtazapine had a clinically significant improvement over placebo by 4.1 points, and 4.0 points over amitriptyline. 70% of patients responded to mirtazapine, compared to 73% of patients responding to amitriptyline. From this review, it seems clear that mirtazapine is more effective than amitriptyline, and consequently all TCAs since amitriptyline is by far the most effective TCA. It also has none of the dangers that TCAs carry and better tolerability. Mirtazapine has a much more rapid onset of efficacy than both fluoxetine and citalopram and this effect has been observed electronically in rat's brains. This implies that Mirtazapine is more effective than all SSRIs with similar tolerability and safety.

3.3 Bupropion

Please see section 2.4.5 for a explanation of its mechanism of action.

Because bupropion is not approved for antidepressant use outside of the United States (it is exclusively used as a smoking cessation aid marketed as Zyban) international journals do not have studies which examine its efficacy. However, there are still many published studies comparing its efficacy to other drugs in the United States. Bupropion is the fourth most prescribed antidepressant in the United States, after sertraline (Zoloft), Escitalopram (Lexapro), and Fluoxetine (Prozac). This makes it unique in that it is the only completely non-serotonergic drug that is commonly used.

A study published in the Journal of Clinical Psychiatry tested the efficacy of bupropion SR (sustained release) in comparison to the efficacy of paroxetine (Paxil, the next most prescribed antidepressant and an SSRI) in elderly patients over 60 years old.[22] 100 patients were randomly assigned to either group, with 48 patients taking bupropion, 100-300mg per day. 52 patients were assigned to take 10-40mg of paroxetine. Both groups took the drugs for 6 weeks. Efficacy was determined using the HDRS. As it turned out, after 6 weeks, there was no statistically significant difference in terms of efficacy between the two drugs. Both groups had over 10% of patients suffer headache, insomnia, drymouth, agitation, dizziness, and nausea. However, in the paroxetine group, over 10% of the patients had additional side effects including somnolence, diarrhea, constipation, and severe decrease in appetite. Thus, although the drugs had similar efficacy at treating depressive symptoms, bupropion showed a more favorable side effect profile and the study concluded that it is preferable for treating depression in the elderly compared to paroxetine.

A very wide study was conducted at the Harvard Medical School which compiled data from ten double blind, randomized studies that compared the efficacy of bupropion to SSRIs in depressed patients that presented with high levels of anxiety. On the HDRS, one of the sections has somnolence on one end of the scale and anxiety on the other. A score of 7 or

higher on this section indicates severe anxiety and 1275 patients in this study (out of a total of 2122) suffered from this level of anxiety.[14] The study showed that of those 1275 patients, improvement on the HDRS was greater for patients taking SSRIs than bupropion (65.4% vs. 59.4%, respectively). For the rest of the patients, with mild or moderate anxiety, there was no clinically significant difference between bupropion and SSRIs.

The study concluded that there was a minor advantage to treating patients with severe anxiety with SSRIs compared to bupropion. The "number needed to treat" statistic, an indicator of clinical significance, showed that nearly 17 patients would need to be treated for every one who responded more positively on an SSRI. This is above the limit of 10 patients, which is the accepted level for clinical significance. The final conclusion of the study was that there is theoretical (but not necessarily clinical or statistical) evidence that supports that serotonin plays a central role in regulating anxiety. Thus a drug such a bupropion, which has no effect on serotonin levels, does not perform as well as a drug that increases them.

A small study published in *The Annals of Pharmacotherapy* evaluated six independent studies comparing the efficacy of bupropion with that of SSRIs. The studies were evaluated independently and in duplicate. The studies combined 257 patients in total and included comparisons of fluoxetine, sertraline, and paroxetine. [13]

It was found with 95% confidence that there is no statistically significant difference in efficacy between bupropion and any of the SSRIs contained in the study. However, the study concluded that bupropion had clinically significant lower occurrence of nausea, diarrhea, somnolence, and sexual dysfunction.

There is a significant clinical evidence that bupropion has similar efficacy in treatment with SSRIs, but with fewer or less severe side effects. A major advantage is that bupropion has limited to no incidence of sexual dysfunction which is extremely important to many patients seeking treatment for depression; it is the most commonly reported reason for

discontinuation. [18]

4 Psychiatrist Interviews

During the course of investigating antidepressant efficacy, the opportunity was granted to interview three different psychiatrists about their prescription preferences and the reasoning behind them. For professional courtesy, their names will not appear and instead will be referred to as Psychiatrist A, B, and C. For this section alone, the pronoun "he" will be used exclusively regardless of the actual gender of the psychiatrist. This is for continuity and clarity's sake as well as to further reserve the doctor's identities.

The following questions were asked of each:

- What is your preferred first line treatment for depression, and why?
- Do you consider SSRIs to be more effective first line treatment tools than atypical medications?
- Do patients often have their own preferences?
- What is the most common reason for refusing or discontinuing a medication?

By asking what the preferred first line treatment is, it was expected to be able to determine if there was an unreasonable or unjustifiable bias towards SSRI medications. Going by the numbers, SSRIs are the most prescribed class of drug in the United States. The goal of this interview in general was to determine if that was because of their potential to treat depression or of other factors. The last two questions were to gauge how involved the patients were in their own medication plan versus how much information they took at face value from their doctor.

4.1 Psychiatrist A

Psychiatrist A specializes in treatment for depression and other mood disorders in young adults and adolescents. He practices psychiatry as part of the UMass Memorial Medical

group.

Psychiatrist A's first line treatment for depression is fluoxetine (marketed as Prozac). His reasoning is that it is very safe and gives a good indication of how a patient responds to antidepressant medications. To some degree, he is not as concerned with its efficacy at medicating depressive symptoms, but more interested in the patient's side effect profile. One example that he explained was a patient for whom Prozac acted as a sedative; the patient became increasingly tired at all hours of the day and was sleeping 12-14 hours at a time. This gave him an indication that the SSRI class (whose members are all derived from and have nearly identical mechanisms of action to Prozac) might cause excessive somnolence in this particular patient; with this information, the patient was moved to venlafaxine (marketed as Effexor) which includes noradrenergic reuptake inhibition, which proved effective at treating the patient's symptoms without having such a drastic effect on sleep.

In many cases, Prozac proved effective at treating patients depressive symptoms. Psychiatrist A attributed this to a combination of factors; for a certain group of patients, Prozac effectively treated them by its intended mechanism of action, serotonin reuptake inhibition. For another group, he believes placebo effect and optimism resulting from accepting treatment play an important role in their recovery. The drug itself might not actually be doing any biological good (or harm), but the patient believes that they are being treated and their mood and temperament improves. In many cases, people seeking treatment for major depression are in reality suffering a depressive episode as a result of environmental factors such as job loss, relationship issues, and other factors which most people normally feel depressed about. For this group of patients, the episode is temporary and changes in their environment are responsible for improving their mood rather than the drug. Since this placebo effect is often very effective, the drug becomes redundant.

Psychiatrist A reasoned that if the drug itself or some kind of placebo effect make a patient feel better, then treatment is successful regardless of the actual physical effect of

the drug. He prefers Prozac due to its high level of safety, extremely long half life (which allows easy discontinuation without withdrawal effects), and minimal to no side effects in most patients. Initial antidepressant selection, he explained, is a hit-or-miss process since it is impossible to know how a patient will respond to a medication until they have taken it for several weeks. To his recollection, nearly every antidepressant has the same statistical chance of improving a patient's condition. At the very worst, it gives him more information about the patient in order to make a more informed prescription decision. Because Prozac has such a long half life, it is very easy to switch to a different drug. There is no need to taper a dosage of Prozac to avoid withdrawal; a patient taking Prozac will have traces of it in their blood for as long as a month after discontinuation. He admits that newer SSRIs and SNRIs can produce better results; but Prozac's safety, half-life, and extremely inexpensive and readily available generic formulations make it his personal preference for first line treatment.

For patients who have troublesome side effects or who are not effectively treated with Prozac, he prefers to move the patient to Citalopram (marketed as Lexapro). It is a very new SSRI with very minimal side effects, a shorter (but still long enough to prevent withdrawal symptoms) half life, and better clinical efficacy. For patients who still do not respond to treatment he prefers venlafaxine, as it is readily available as a generic preparation and its added norepinephrine reuptake inhibition can produce better results.

Psychiatrist A prefers SSRIs above all due to their safety and usually does not consider atypical medications. He had three patients who suffered seizures while taking bupropion (marketed as Wellbutrin) which turned him off of the drug. He did qualify, however, that two of the seizures were potentially a result of other factors; one patient had discontinued both his bupropion and clonazepam prescriptions at the same time against medical advice. Rapid withdrawal from clonazepam, a benzodiazepine which acts as a strong GABA (gamma-Aminobutyric acid, an inhibitory neurotransmitter) agonist, can cause similar effects to

alcohol withdrawal (also a GABA agonist): tremors, ataxia, sweating, coma, death, and seizures. The other patient had an undocumented history of seizures which Psychiatrist A was not aware of; having a seizure drastically lowers the seizure threshold, increasing the chances of having another seizure. He had only prescribed mirtazapine once that he could recall as the patient asked for it specifically.

Many patients do have their own preferences, he found, and more often than not he is very willing to accommodate them. His reasoning is that if a patient has a positive perception of the drug, so much the better, as any positive change in mood is good. Sometimes, patients will refuse his recommended medication; either they had anecdotal reason to dislike the particular drug, had a bad experience with it before, or had a family member who did not respond to the medication. In these cases, Psychiatrist A explained that for the same reason positive perception of a drug can help treatment, negative perception can impede it.

Psychiatrist A found the most common reason for discontinuation was sexual side effects. He remarked that the irony is not lost on him that sexual activity is one of the few activities that is still enjoyable in depressed patients. In these cases, he does his best to accommodate the patient; in some cases though, sexual dysfunction persists through different medications. Before his bad experiences with bupropion, he usually moved these patients to it since it has no sexual side effects.

4.2 Psychiatrist B

Psychiatrist B specializes in bipolar and major depressive disorders in adults. He is in private practice in Pittsburgh, PA.

Psychiatrist B greatly prefers SSRIs as first line treatment. He most commonly starts patients off with escitalopram because it is "very mild, very safe". He claimed he rarely had to switch patients to other medications. as in most cases the escitalopram proved effective. Even though generics are available, he prefers to prescribe brand name Lexapro, as he believes

it is more effective than the generic version. Since insomnia is often a symptom of depression, he also tends to prescribe lorazepam (a medium half-life, medium strength benzodiazepine) or zolpidem (marketed as Ambien). These drugs have their own risks and side effects but are both extremely effective sleep aids.

Psychiatrist B admitted that alternative antidepressants are also "very mild, very safe" and can be just as effective at treating depression, but he still prefers SSRIs (specifically Lexapro), due to their more proven track record and simple, manageable side effects (if they even present at all). He specifically did mention that he does not prescribe bupropion for patients with anxiety symptoms, as the mild stimulant effect the drug has can amplify anxiety. This is consistent with the study discussed in section 3.3.[14] He also does not prefer mirtazapine as although it is safe and effective, in his experience Lexapro had better success. For patients that do not respond to Lexapro, he prefers to move them to desvenlafaxine (marketed as Pristiq). He believes, that although there is no generic available, it is more effective than alternatives. In reality, it is simply the active metabolite of venlafaxine (marketed as Effexor) which does have a generic available; Wyeth's patent on Effexor ran out in 1999, so they introduced Pristiq as a way of getting more brand name (i.e. expensive) prescriptions for very little R&D investment. Clinically it does not seem to be more effective than any other SNRI, but the argument could be made that more patients will respond better to it as it removes the patient's need to metabolize the drug (since it is already in an active form). This removes a variable from the equation of whether or not the drug will work.

In his practice, most patients do not have their own preferences and the vast majority accept his recommendations. He occasionally has patients specifically request bupropion due to apprehension about the sexual side effects of SSRIs. Sexual side effects remain the most common reason for discontinuation or dissatisfaction with a given medication.

4.3 Psychiatrist C

Psychiatrist C specializes in mood and personality disorders; for many of his patients, depression is a relatively minor issue compared to the symptoms associated with Avoidant, Borderline, or Schizoid Personality Disorders. He practices psychiatry with a group of other doctors in private practice in Pittsburgh, PA.

Psychiatrist C has no real preference for first line treatment; he adamantly believes that for each drug, it will work well for 20% of people, work adequately for the next 40%, and not work at all for the next 40%. This is irrespective of side effects, as the drug could be very effective at treating depression but also cause unmanageable side effects and thus the patient will want to discontinue.

Psychiatrist C does not believe any one drug to be generally more effective than the other. He sees antidepressants as one tool used to treat depression; rather than one drug being objectively better than another, they are different tools for different jobs. Selecting the right "tool" for the job is paramount, although it can potentially be a long, seemingly random process. Since there are so many different medications, any one has around a 20% chance of being very effective; it could be sheer luck that results in this intersection though. He claims you could pick a drug out of a hat and about one in five draws will result in the best possible treatment option.

If a patient does have their own preference, which some do, he (along with Psychiatrist A) believe that any positive thinking that goes into treatment for depression is good news, so he will almost always go with a patient's specific request. He has not had bad experiences with any particular drug and has no particular affinity for one either. Because many of his patients suffer from very severe mental disorders which effect their day-to-day functioning significantly more than depression, treatment for depression is a secondary concern to them and as such, antidepressant selection is one of the least of their worries. There is currently no medication that can unilaterally treat APB, BPD, or SPB; instead, management of their

symptoms is more important. The major treatable symptom associated with all of them is severe anxiety, and treatment of this with antipsychotics or anxiolytics is their primary concern. Unfortunately, severe personality disorders are a chronic condition which can only be truly managed with behavioral therapy.

5 Results and Discussion

In reviewing the literature available which compares the two most common atypical (drugs which do not inhibit reuptake of serotonin) antidepressants, bupropion and mirtazapine, it was found that both have advantages over SSRIs and other drugs which effect the reuptake of serotonin as their primary mode of action.

This is not to say that SSRIs, SNRIs, TCA, and MAOIs are ineffective drugs. Different antidepressant drugs are like different size socket wrenches in a tool set; some tools are ineffective for certain patients and other tools need to be used, just like trying to loosen a 17mm nut with a 16mm socket wrench. It is a good thing that there is now such a wide array of effective and safe drugs which all have the potential to help a patient overcome depression.

Statistically, mirtazapine is by far the most effective antidepressant currently on the market, showing very significant improvements in HDRS scores compared to SSRIs and TCAs. The side effect profile is also extremely favorable, as is the lack of potentially serious complications arising from overdose. Mirtazapine also acts as a very effective sleep aid that carries none of the negative side effects normally associated with sleep medications. Because it accomplishes this through histamine rather than GABA, which drugs such as benzodiazepines and their derivatives, including zolpidem (Ambien), effect, there are no potentially fatal or extreme side effects from withdrawal. Also, for the same reason, there is no memory loss or occurrence of sleep walking, driving, or other strange sleep activities commonly associated with drugs such as zolpidem. Sleep is significantly disrupted in depressed patients; it doesn't take a psychiatrist to know that without proper rest, all of the symptoms of depression are worsened.

Evidence suggests that due to its rapid onset of efficacy and additional insomnia treatment, mirtazapine may be the best among first line treatments for depression. Because it becomes rapidly efficacious (compared to other antidepressants), the patients does not have

to wait for relief from their symptoms. Even if, in the end, it proves ineffective as an antidepressant, because of its unique mode of action it is perfectly suited to be used in conjunction with any other antidepressant. At the very least, it is an effective tool for treating insomnia in depressed patients.

Mirtazapine has been shown to increase response rates in patients who have had several failed antidepressant medication trials.[12] Therefore, if patients did not respond to mirtazapine another drug could be added in conjunction and the chances of that drug successfully treating the patients is significantly increased. Mirtazapine has no sexual side effects and is extremely safe, even in the case of a massive overdose (see section 2.4.6).

Bupropion also has promise as first-line treatment. The newer sustained release versions have no increased seizure risk compared to any other antidepressant and as such it is safe. It has similar efficacy to SSRIs but with fewer side effects, importantly a lack of sexual dysfunction.

Like Mirtazapine, bupropion can also be used effectively in conjunction with other drugs to give a wider mode of action for treatment. Combined with an SSRI in cases where bupropion itself was ineffective (or vice versa) there is clinical evidence to show that antidepressant response is similarly increased.[24]

In cases where patients present with severe anxiety, bupropion should probably not be used as first line treatment.

Interestingly, all three psychiatrists that were interviewed tended towards the serotonin reuptake inhibitors as first line treatment when there is a large amount of information demonstrating clinically significant superiority of mirtazapine and bupropion. This may have to do with the fact that bupropion initially had a rocky start on the market, with highly publicized claims of increased seizure risk. With the development of sustained release formulations, this is no longer an issue. Mirtazapine was developed in Europe and as such does not have a large "mind share" in the United States, nor does it have the advertising efforts (and millions

of dollars) behind it that the SSRI do.

6 Conclusion

This investigation started out as a very specific report targeted at non-serotonergic drugs. Because SSRIs (and their advertisements) are so prevalent in the United States, there have been an increasing number of skeptics who doubt their efficacy. There have also been a small number of studies done which showed that fluoxetine performed no better than placebo and its initial antidepressant approval was both due to cherry picked studies. These claims, however, are not grounded in proper science and are dubious at best.[21] During the course of researching for and writing this report, it was expected to find a large number of studies that were obviously botched in favor of SSRIs or had questionable financial backers which could add bias to the study. However, this turned out not to be the case. Many studies following strict, accepted scientific procedures corroborated the efficacy of SSRIs. It became very obvious during the course of the investigations which studies were grounded in proper science and which were biased and had a "bottom line" other than providing unbiased data. The studies which used double blind techniques also used techniques to eliminate researcher bias, such as having two researchers independently evaluating data to ensure one person's opinions were not influencing the results. Proper studies of fluoxetine, the oldest and least effect member of the SSRI family, has efficacy at least comparable to older antidepressants but with greatly reduced side effects and greatly increased safety. Newer SSRIs are significantly more effective; their development has not stagnated and better drugs are being released regularly.

This report argues for making mirtazapine the go-to, first line treatment for major depression. It has been shown to be clinically more effective than any other antidepressant, has comparatively fast onset of relief of symptoms, and fewer side effects. It is the opinion of the author that if mirtazapine were more commonly used, there would be a less cynical view of antidepressants and psychiatry in general. Perhaps further investigation, in the form of another IQP, could be performed to find out exactly how to accomplish such a thing; as of

now, no one has the means to convince the entire body of psychiatrists to switch their preferences overnight. A possible avenue to pursue would be to assemble an effort to disseminate as much correct, properly researched information about antidepressant efficacy as possible. This could be in the form of a website, journal article, or other published material. Another potentially interesting project to pursue would be to publish the results of an anonymous poll of students with depression; what were their personal experiences with various drugs? Although anecdotes are not scientific, they are much more interesting to the layman than scientific reports and thus spread faster and more effectively.

It would be ill-fitting to end a report on the treatment of depression on a depressing note. Therefore, looking on the positive side, it is undeniable that treatment for depression is now better than it ever has been. The outlook for a depressed patient is spectacular compared to even 20 years ago due to the huge array of new and improved medications. Certainly, one drug can be considered "better" than the other, but when it comes to alleviating suffering, it is unproductive to think in such terms. Modern psychiatry has excellent, safe, and effective tools to treat an illness that claims thousands of lives and causes millions to live unhappily. Treatment is only going to get better from this point, and in all likelihood, it will.

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