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Antidepressants Misrepresented

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In the first week of 2010, a study performed by researchers at the University of Pennsylvania made waves as it circulated through every major national news outlet. The study, a meta-analysis of six independent studies conducted at various points in the past 20 years, was conducted in order to determine the relative benefit of antidepressant medications over a placebo, for depressed patients with a varied range of baseline symptom severities.[1] The results of the study led to the publication of articles in various medias with titles such as U.S. News & World Report's "Do You Really Need That Antidepressant?" and USA Today's "Study: Antidepressant lift may be all in your head."[2, 3] Indeed, the conclusion that the researchers came to was that in cases of mild or moderate depression, some of those common antidepressants were no more useful than a mere sugar pill.

I was fairly troubled when I perused through the various articles and stories that covered this study, seeing that in many cases, the media was up to its usual old tricks of sensationalizing and misrepresenting the most recent "hot medical study" of the week. Sending a message to the American people that trivializes the effects or usefulness of antidepressants is a very precarious game, and as I shall imminently elaborate, even more unfortunate when that message is based on a study with several inherent flaws.

> ***"Not only is depression under-diagnosed… diagnosed patients are often under-treated!"***

The class of drugs known as 'antidepressant medications' (ADMs) encompasses a multitude of compounds whose members are often prescribed for a wide variety of psychiatric disorders. One of these is major depressive disorder, a multi-factorial mood disorder that most likely arises due to a complex interaction of biological, psychological, and social factors including drug and substance abuse. Depression is a disorder that can range from having mildly intrusive to severely debilitating effects on a patient's life. The most characteristic psychological symptoms of depression are low mood, low self-esteem, loss of interest & pleasure, excessive rumination, and feelings of worthlessness. These are more often than not accompanied by the physical symptoms of insomnia, drastically decreased appetite, weight loss, headaches, and fatigue.[4]

The identification and treatment of depression is of great interest to the American people. While the lifetime prevalence of depression in most countries falls between 8-12%, the United States has roughly 17% of its population afflicted.[5] Antidepressants are the third-most widely prescribed class of drug in the US, with an estimated 10% of women and 4% of men taking them.[2] Unfortunately, it is widely agreed in the medical community that not only is depression under-diagnosed, but that diagnosed patients are often under-treated! The investigators actually had a praiseworthy motive for the study at hand; their literature search revealed a

marked paucity of pharmacological studies in which participants had baseline scores below 23 on the Hamilton Depression Rating Scale (HDRS), the minimum score for "very severe depression". Bearing in mind that the majority of ADM patients may be considerably below a score of 23 (it was shown that 71% of participants in a recent survey had HDRS scores less than 22), the investigators' task at hand of examining those who were "less" depressed would seem very worthwhile.[6]

It is important to bear in mind that in the world of depression treatment, antidepressants share the throne with psychotherapy. Or at least, ideally they do. In the modern world's quick-fix, medicated society, too often psychotherapy is overlooked or unwanted. Indeed, from 1996 to 2005, the use of ADM in the U.S. doubled, while the use of psychotherapy declined.[7] When in reality, the various forms of psychotherapy (which include cognitive behavioral therapy, group therapy, and psychoanalysis) may have just as much, if not more, to offer than ADMs in terms of treatment.

This past summer, I worked in the Behavioral Health Center (BHC) of Westchester Medical Center under the supervision of B-2 inpatient unit physician Dr. Jay Draoua. I spent the bulk of my days observing or participating in the evaluations and treatments of the admitted patients, many of which had depression. As a rule, my current personal standpoint as an idealistic burgeoning medical student is still one that prefers to avoid pharmacological treatment as much as possible, especially when other forms of treatment are available. This means that for psychiatric disorders such as depression, in addition to the helpful standbys of exercising, eating healthy, and pushing one's self into socialization, I highly advocate psychotherapy as a therapeutic tool. With the patients I have observed in the BHC, antidepressants have been highly useful in the stabilization of recently admitted patients; however, antidepressants are not supposed to be advertised as a long-term solution to for depression. As I have witnessed, to truly treat depression, one must examine the core of the patient, explore the roots of the underlying issues or events that triggered their pain, and have them come to an understanding with their illness. The patient has to approach an appreciation and respect for themselves. Only then can you put depression beyond the reaches of remission, something that antidepressants are not able to do.

However, as I mentioned, antidepressants do have substantial merits of their own. The idea is to normalize certain neurotransmitters in the brain that are involved in regulating mood, thus potentially alleviating the altered levels which are sometimes associated with depression. This can provide immeasurable benefits for the patient on their road to recovery. Often, patients must be brought to a higher level of functioning before any meaningful psychotherapy can even begin. In other cases, they can stabilize a mildly – or moderately -– affected patient from relapsing into a severe episode. Perhaps most often, they can provide a subtle boost in functioning for men and women going about their daily lives and work, without which they would be increasingly burdened by whichever depressive affliction haunts them.

For these reasons, I feel somewhat offended by the way in which this study's results are presented by the authors and the media. As I perused the content of this meta-analysis, I built a list of several troubling concerns I had regarding the methods involved, and how the results were portrayed.

To begin with, the literature search which was conducted by the investigators to find studies for their meta-analysis reached all the way back to 1980. Out of the over 2000 studies they searched, their exclusion criteria (for studies without placebo controls, or ones examining special subpopulations, etc.) narrowed the number of studies they included in their final meta-analysis down to just six. Of these six, three of them compared the ADM imipramine to placebo, and three compared the ADM paroxetine to placebo. Imipramine belongs to an older class of drugs developed in the 1950's, the tricyclics (TCAs), a highly effective group of antidepressants which are still used for treatment-resistance depression when other drugs fail, though they can sometimes cause mania or hypomania on a maintained dosage.[8, 9] Today, the TCAs are less popular due to the advent of antidepressant drug classes with less severe side effects, such as the selective serotonin reuptake inhibitors (SSRIs). A 2007 ranking of the most commonly prescribed ADMs in the U.S. put imipramine at thirteenth with 1.524 million, which is less than one-third of the twelfth-ranked nortriptyline and a mere fraction of the top four ranked ADMs (which all top 20 million on their own).[10] Using such a rarely-prescribed and antiquated drug to represent the whole range of ADMs and their supposed ineffectiveness on mild depression is just poor practice, in my opinion. The investigators make note of several of their study's limitations, but this is not one of them. It is quite a shame that they have allowed ADMs to be presented to the public this way, with half of their data coming from this particular drug.

> ***"Often, patients must be brought to a higher level of functioning before any meaningful psychotherapy can even begin."***

Paroxetine, a SSRI and the fifth-most prescribed ADM in the U.S. in 2007, was the other drug used in the studies. However, compared to the three SSRIs that were more popular (sertraline, escitalopram, and fluoxetine), paroxetine is associated with several concerning side effects such as weight gain, increased risk of suicidality, and high risk of withdrawal syndrome.[11, 12, 13] Again, not a drug most representative of the antidepressants Americans would be likely to use. Neither one of the two ADMs used on patients in the meta-analsyis are popularly used as first-line agents for depression. Even if they were used as the first treatment, as they were in these studies, it is well known (and even taught to us in first year Behavioral Sciences in medical school) that very often the first-line of treatment is not effective, and that two or three classes of ADMs may be tried before finding one that the patient responds to.

Another area of concern to me was that the investigators set a minimum criterion of a 6-week treatment duration period for symptom scores when selecting studies to include. In fact, the average treatment duration for the six studies was only a little over eight weeks, which seems to be an alarmingly short time to stop the recording data for a depression study. ADMs are renowned for their need to take several weeks in order to begin to take effect. Two to three weeks is usually the minimum standard, and for an ADM's effect to take even longer than that is by no means rare. In particular, the rate of symptom improvement can greatly vary by drug and by person. Imipramine in particular has been shown to have a slower rate of symptom improvement than other drugs in the treatment of depression, and even though it can lag behind its

peers after six weeks of treatment, its effect is by no means over – a continued improvement in symptom score is still observed beyond that six week mark.[14] The investigators' findings seem to, unfortunately, only apply to acute treatment, not the continuous or maintenance ADM treatment that millions of Americans find themselves on.

Further flaws in this recent study can be found in the types of patients who were chosen to be excluded from this meta-analysis. Almost 600 studies were stricken from inclusion because the depression patients were dysthymic or were from a special sub-population (i.e. a certain ethnicity). Dysthymia is a mood disorder which is best described as chronic depression, but at a lesser intensity… the patient must have the symptoms of a depressed mood for at least two years, but without the presence of a major depressive episode. The very definition of dysthymia, which is to have a "less severe" depression, seems to suggest that its patients would suit perfectly for the present meta-analysis, which has a great interest in patients who score lower on a depressive symptom scale. If the proposed trend of less-severely depressed patients showed an equal response to placebo was also discovered in dysthymic patients, which would contribute greatly to the investigator's current conclusions. However, it has been well shown over the years that the three main classes of ADMs (SSRI, TCA, and monoamine oxidase inhibitors) have a noted pharmacological effect over placebo in the treatment of dysthymia patients, especially in the short term.[15] It should also be noted that the results of this meta-analysis do not apply to inpatient populations or children, two sizable groups which were also excluded from the study.

My last criticism of the meta-analysis at hand is the use of the depression symptom scoring criteria. All six studies involved used the Hamilton Depression Rating Scale (HDRS), in which patients scoring 8-13 have "mild" depression, 14-18 are "moderate", 19-22 are "severe", and greater than 23 are "very severe". The results of the current analysis demonstrated that there was a small effective difference between ADM and placebo when the patients had a baseline below a score of 23. In addition, the National Institute for Clinical Excellence's standard for significant difference between ADM and placebo (meaning the HDRS difference is 3 or greater) was not met until patients had a baseline of 25 or greater.

Most media articles reporting this study emulate the claim that ADMs only work if one is "severely depressed," i.e. has a HDRS score of 23 or greater. However, taking the ratings on the HDRS scale literally is very misleading. Resistance to the use of HRDS labels by mental health practitioners is nothing new. "The Hamilton concept of 'severe', I think many psychiatrists would think of as 'moderate'," said Dr. Mark Olfson, a professor of clinical psychiatry at Columbia University.[16] The Hamilton scale, developed in the 1960's, is widely used because of tradition in the field, but in reality it suffers from a sort of "grade inflation" that can classify patients in very misleading, and especially more severe, ways.

The authors of this meta-analysis recognized some of the limitations of their study, particularly the caveat about the psychometric measuring properties of the HDRS. However, many of the items I noted above were not spoken for. I would agree with the author's call for more studies examining patients with a wide range of baseline depression severities, as their claim that there is relatively little data on lesser depressed patient's responses to antidepressants appears to be valid. I would hope, though, that with future studies to be done, they could rectify some of my current critiques regarding the methods of analysis, and accurately present their conclusions to the public and media.

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