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The Efficacy of Antidepressants in Alleviating Anhedonia in Depressed Patients

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The Efficacy of Antidepressants in Alleviating Anhedonia in Depressed Patients

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Background

Every year, 14.8 million adults (6.7% of the US population) suffer from major depressive disorder.[1] According to the Diagnostic and Statistical Manual of Mental Disorders, depression is identified by changes in weight, energy, sleep, and concentration, feelings of worthlessness and guilt, and suicide ideation persisting two weeks or longer.[2] At least one of the symptoms must be either depressed mood or loss of pleasure.[2]

In terms of treatment, pharmacotherapy for depression achieves mixed results, and patient success in achieving remission often dependends on several factors. In double-blind, randomized controlled trials, antidepressants demonstrate small yet statistically significant advantages over placebo[3] but do not substantially improve patient symptoms. Meta-analyses have shown that almost 38% of patients on antidepressants did not achieve a response to treatment and 54% did not achieve remission.[4] While current antidepressant therapy options may help patients relieve some symptoms of depression, studies have found variable efficacy results overall.

The monoamine hypothesis provided the most well understood framework for treating depression.[5] It proposed that decreased function of norepinephrine and/or serotonin caused depression and reversal of the neurochemical imbalance restored health.[5] Unfortunately, depression affects the brain in a much more

complicated and deceptive manner. Stress and depression are associated with increased serotonin activity in the amygdala and prefrontal cortex (PFC) but decreased activity in the hippocampus.[5] Selective serotonin reuptake inhibitors (SSRIs) increase serotonin levels throughout the entire brain, making SSRIs beneficial in the hippocampus but counterproductive in the amygdala and PFC.[5] Serotonin in the amygdala actually has a pro-anxiety effect, which counteracts the antidepressant action in the hippocampus.[5] Numerous neurobiological factors need to be considered when treating depression.

Several symptoms constitute a depression diagnosis, and patient presentation can be variable.[5] Diagnosis of depression requires presence of five out of nine symptoms, so it is theoretically possible for two clinically depressed patients to only share one symptom.[6] Individual symptoms are linked to specific biological components and pathways, so it seems unlikely, for example, that the neural circuit mediating anhedonia would also be involved in feelings of guilt.[7] Distinguishing the neurobiological mechanism for each symptom of a patient's depression and accurately prescribing the right medication to address these symptoms is not clinically feasible, at least with the current medical understanding. But improving our understanding of how to treat specific symptoms may be the key to improving antidepressant efficacy.

Previous studies have not substantially investigated the relationship between depression and the symptom of anhedonia. Anhedonia is defined as the reduced ability to feel pleasure[8], and reports estimate that 37% of depressed individuals experience clinically significant anhedonia.[6] It plays an important role in achieving complete recovery from depression because the capacity to feel pleasure is needed for normal decision-making and reward-processing.[7] Besides being one of two core symptoms, anhedonia has been suggested to be an endophenotype for depression. Endophenotypes are subclinical traits associated with expression of an illness and represent the genetic liability of the disorder in non-affected individuals[8], meaning anhedonia may be involved in the hereditability of depression. Many twin and family concordance studies also revealed that hedonic capacity may be a heritable trait.[9] Another study showed that patients who were most anhedonic when depressed continued to have anhedonic responses after recovering from depression[10], implying anhedonia could play a role in relapse for patients in remission.[8]

The efficacy of current antidepressant therapies in relieving anhedonia is uncertain. Evidence suggests that the most common first-line pharmacotherapies, such as SSRIs, do not adequately address motivational and reward-processing deficits associated with anhedonia.[6] The inability to feel pleasure has primarily been associated with decreased activity in the mesolimbic dopamine

projection from the ventral tegmental area (VTA) of the midbrain to the nucleus accumbens.[5] The nucleus accumbens and ventral pallidum, both within the basal ganglia, have mu opioid and endocannabinoid receptors that mediate hedonic perception of rewards; anhedonic individuals with depression have decreased activity within these regions.[7] Overall, studies have been inconclusive in determining whether antidepressants positively affect these regions or not. It is important to note that anhedonia is not exclusively a symptom of depression; it is also involved in schizophrenia, Parkinson's disease, Alzheimer's disease, substance abuse disorder, and eating disorders.[7] It may not be reasonable to assume that antidepressants can restore the specific neurochemical abnormalities involved in anhedonia.

In a study by Schrader, anhedonia did not correlate with depression severity in a chronically depressed population. Over a one-year period, depression severity was significantly reduced in patients who were being treated, while anhedonia scores remained relatively unchanged.[10] Additionally, self-report assessments of anhedonia are only moderately associated with depression severity.[7] If depression and anhedonia are diverging variables, it brings into question the existing strategies used to treat anhedonic depression. In order to create more effective treatments for depressed patients in the future, it will be crucial to understand how antidepressant therapies impact anhedonia. The primary objec-

tive of this study is to gain insight into whether antidepressants are efficacious in relieving anhedonia in patients with Major Depressive Disorder by measuring the relationship between anhedonia and depression severity.

Methods

Participants

We conducted a cross-sectional survey of adult patients, aged 20 years and older, with major depressive disorder and receiving antidepressant treatment. Patients were included primarily if they had depression. We also included patients receiving multiple antidepressants and patients with the following comorbid anxiety disorders: general anxiety disorder (GAD), post-traumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), and social anxiety disorder (SAD). Patients with schizophrenia, bipolar disorder, and substance abuse disorder were excluded. A 37-question paper survey was distributed to all patients prior to their visit with one of the six participating psychiatrists at three outpatient locations (see Appendix for entire survey).

This study was approved by the institutional review boards at Community Health Network and Butler University, and patients had the option to opt out of the study after reading an informed consent statement.

Materials

The paper survey took approximately 5-7 minutes to complete. It included the Snaith-Hamilton Pleasure Scale (SHAPS) to measure anhedonia (questions 1-14) and the Clinically Useful Depression Outcome Scale (CUDOS) to assess current depression severity (questions 15-32). Additional questions were included to gather demographic data such as age and sex, diagnosed mental illnesses, and therapy data. Relevant therapy data included how long the patient had been taking antidepressants, the name of prescribed medication(s), and whether the patient was involved in psychotherapy.

Procedure

Receptionists for the psychiatrists provided surveys to all patients in the waiting room before their visit. After completion, patients brought the survey to the psychiatrist who stored the survey until a researcher could pick it up. If any patient responses indicated thoughts relating to suicide ideation, the psychiatrist would address the concerns.

To score the SHAPS, a response of agree or strongly agree received a score of zero, and a response of disagree or strongly disagree received a score of one; when the responses were summed, scores greater than two signified presence of anhedonia.[11] The CUDOS had a range of scores from 0-72. Scores in the

range of 0-10 represented nondepressed patients, 11-20 indicated minimal depression, 21-30 indicated mild depression, 31-45 indicated moderate depression, and 46+ indicated severe depression.[12] Futhermore, a CUDOS score ranging from 0-20 represented patients in remission, and scores above 20 represented patients who still had depression.[12]

By combining the SHAPS and CUDOS into one survey, but still scoring separately, we related antidepressant efficacy in terms of depression severity and the ability to feel pleasure. The IBM SPSS statistics (version 23) software was utilized for descriptive statistical analysis.

Results

Between January 27, 2016 and March 8, 2016, 104 surveys were collected with 33 being excluded. The mean (SD) patient age was 44 (14) years and 83% were female ($p<0.001$). There were six psychiatric conditions identified in the patient sample. All patients had depression, and 66% of patients had a comorbid anxiety disorder. The most common anxiety disorder was general anxiety disorder, with over half of all patients presenting with it (Figure 1).

Ninety percent of patients in the cohort had been on antidepressants for over two months; overall, 30% of patients reached remission and 43% of patients had anhedonia. Prevalence of anhedonia was moderately correlated with in-

creasing depression severity, according to a Spearman's rho equal to -0.57 ($p<0.001$) (Figure 2). The proportion of patients in the minimal/moderate depression and minimal/severe depression categories were statistically different within both the anhedonia and non-anhedonia groups ($p<0.001$), and no other significant differences were observed between depression severity groups for anhedonia. The proportion of patients with anhedonia was 5% in the remission group and 59% in the depression group ($p<0.001$). There was no statistical difference in anhedonia prevalence between patients with comorbid anxiety disorders and depression alone.

About 60% of patients were involved in psychotherapy along with their antidepressant regiment, and these patients had a statistically higher prevalence of anhedonia compared to patients on antidepressants alone ($p=0.018$) (Table 1). Moreover, 55% of patients participating in psychotherapy were moderately or severely depressed, while 33.3% of patients taking only antidepressants were moderately or severely depressed.

We compared the scores of individual questions on the CUDOS for patients with and without anhedonia. There was a statistically significant difference in responses to every question except questions 17, 18, 19, and 21 (Table 2).

Six common antidepressant classes were found in the cohort: SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), SSRIs plus bupropion, SNRIs

plus bupropion, SSRIs plus antipsychotics, and SNRIs plus antipsychotics. SSRIs and SNRIs were the most common classes of antidepressants prescribed in the cohort, and patients in these classes had the lowest prevalence of anhedonia and the highest levels of remission (Table 3). We found a higher prevalence of patients with moderate depression in the combination drug group (Figure 3), however, no statistically significant differences were observed for either depression severity ($p=0.46$) or anhedonia ($p=0.87$) between drug classes.

Discussion

Tool Selection

Historically, the best-known scales used to measure the ability to feel pleasure have been the Physical Anhedonia Scale (PAS) and the Fawcett-Clark Pleasure Scale (FCPS).[8] However, these scales are impractical due to their length and cultural bias.[11] Developed in 1995, the SHAPS provides a simple 14-question self-assessment scale that is largely unaffected by social factors and is easy to score.[11] When compared to the other two pleasure scales, hedonic capacity was strongly defined by the SHAPS[13], and the tool was proven to be reliable and valid while accurately measuring anhedonia without distortion due to age or sex.[8]

A common interviewer-administered scale used to assess the severity of depression in clinical settings is the Hamilton Depression Ratings Scale (HAM-D).

However, the full HAM-D would require too great a time commitment by the physicians to be relevant in this study. The Clinically Useful Depression Outcome Scale (CUDOS) is a self-report depression scale that measures depression severity in a similar manner to the HAM-D, while taking less time to complete. A study comparing the two scales showed that a valid cutoff for remission (based on the HAM-D threshold) was found[14], and a CUDOS score could be used to determine the severity of depression symptoms.[12]

Analysis

The original hypothesis of this study was that anhedonia may be independent of depression severity, and may even persist in patients who reach remission. However, there was a moderate correlation showing that anhedonia prevalence actually increased as the depression severity increased. Furthermore, all patients in the severe depression group had anhedonia while none of the patients in the non-depressed group had anhedonia, and prevalence of anhedoinia was substantially lower in the remission group compared to the depression group (Fig. 2). These results lead us to believe that anhedonia is not as persistent as previously expected and does relate to depression severity. We will need to see if similar trends occur when we have a larger sample size.

The overall efficacy of antidepressants in facilitating remission was poor at 30%, and anhedonia prevalence was high at 43%. This is troubling because 90% of patients in the study had been taking antidepressants for over two months, which is an important threshold where physicians hope to see a significant response to treatment. Yet, the results of our cohort were minimal. Our findings in this area do compare with previous studies[4,6], highlighting the poor effectiveness of antidepressants overall and specific to anhedonia.

The objective of this study was not to analyze the effect of psychotherapy on anhedonia prevalence, but it became relevant because 60% of patients participated in therapy along with their antidepressant regiment. Patients who were involved in psychotherapy tended to have more severe depression and fittingly had a statistically higher prevalence of anhedonia (tab. 1). It is possible that patients who are more severely depressed had a poor response to their medication and needed to supplement their treatment plan with psychotherapy. We could learn more about patient response to psychotherapy by measuring type and duration in the future.

Patients with anhedonia answered 14 out of 18 questions on the CUDOS statistically differently than patients without anhedonia. This along with the moderate correlation between anhedonia prevalence and CUDOS score shows that the CUDOS could be utilized to determine presence of anhedonia. Topics

where patients with anhedonia answered similarly to patients without anhedonia include changes in appetite, difficulty sleeping, and feeling fidgety (tab. 2), so these aspects of depression may be unaffected by anhedonia.

We cannot confidently claim that SSRIs and SNRIs are the most efficacious in alleviating anhedonia due to the cross sectional nature of our survey and low sample size. It is possible that patients on only an SSRI or SNRI had successful response to the initial antidepressant treatment and did not need further medication. Similarly, patients in the combination medication groups may not have had successful response to the initial drug (which was likely an SSRI or SNRI), and needed additional pharmacotherapy. This would explain the high prevalence of anhedonia and the low levels of remission in the combination medication groups (tab. 3).

We were unable to look at response to treatment because we did not have specific patient medication information. Performing a longitudinal study in the future may be valuable to better observe how depression severity and anhedoina change in individual patients over the entire antidepressant treatment period.

While the drug groups cannot be compared at this point, we can observe that for every drug class, most of the distribution was centralized at minimal, mild, and moderate depression levels with very few patients at the extremes (Fig. 3). One possibility is that all the drug classes may be effective at helping patients

decrease the severity of their depression, but are not capable of completely alleviating it in most cases.

In order to more closely examine the effect of different drug classes on the prevalence of anhedonia, it will be necessary to perform a longitudinal study and have access to patient charts. Being able to follow individual patients over time and knowing the exact duration of their medications would allow for a more significant understanding of how various drug classes are affecting anhedonia and depression severity over time. It would also be beneficial to implement a control group that has not begun antidepressant treatment, but this would be difficult to implement in practice due to ethical considerations.

We have to be wary in assuming our data is generalizable because of the setting and low sample size in some groups. Since every patient in this study was visiting a psychiatrist, it is likely that a primary care physician was unable to adequately address the issue and the initial treatment was not effective. Therefore, patients in this study may have had more severe depression diagnoses than the general population. Moreover, the vast majority of participants were female, making it difficult to assume males would have similar responses. But females are twice as likely to be diagnosed with depression as compared to males[15], so our patient sample was not too significantly skewed from depression rates in the general population.

Conclusion

It appears that focusing on the treatment of a patient's depression as a whole is the most effective strategy to treat anhedonia. We did not find a specific antidepressant class or any other factor that had a significant advantage in treating anhedonia compared to others. Performing a longitudinal study with access to patient medication charts would be the next step to validate the findings of this study.

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Appendix: Paper Survey

Check the following conditions you are currently being treated for…

- ◯ Depression
- ◯ General Anxiety Disorder (GAD)
- ◯ Post Traumatic Stress Disorder (PTSD)
- ◯ Obsessive Compulsive Disorder (OCD)
- ◯ Attention-Deficit/Hyperactivity Disorder (ADHD)
- ◯ Social Anxiety Disorder (SAD)
- ◯ Schizophrenia
- ◯ Bipolar Disorder
- ◯ Substance Abuse Disorder

IF YOU CHECKED **SCHIZOPHRENIA, BIPOLAR DISORDER, OR SUBSTANCE ABUSE DISORDER** YOU ARE FINISHED WITH THIS SURVEY. IF YOU CHECKED **DEPRESSION** PLEASE COMPLETE THE FOLLOWING QUESTIONS.

When did you begin taking antidepressants for your current episode of depression?

a) Within the last 2 months

b) More than 2 months ago

Are you currently participating in any type of psychotherapy?

a) Yes

b) No

What is your age? What is your sex?

What antidepressant medication(s) do you take for your current episode of depression?

This questionnaire is designed to measure your ability to experience pleasure ***in the last few days***.
It is important to read each statement ***very carefully***.
Tick ***one*** of the boxes to indicate how much you agree or disagree with each statement.

	Strongly disagree	Disagree	Agree	Strongly agree
1. I would enjoy my favorite television or radio program.				
2. I would enjoy being with my family or close friends.				
3. I would find pleasure in my hobbies and pastimes.				
4. I would be able to enjoy my favorite meal.				
5. I would enjoy a warm bath or refreshing shower.				
6. I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread.				
7. I would enjoy seeing other people's smiling faces.				
8. I would enjoy looking smart when I have made an effort with my appearance.				
9. I would enjoy reading a book, magazine, or newspaper.				
10. I would enjoy a cup of tea or coffee or my favorite drink.				
11. I would find pleasure in small things, e.g. bright sunny day, a telephone call from my friend.				
12. I would be able to enjoy a beautiful landscape or view.				
13. I would get pleasure from helping others.				
14. I would feel pleasure when I receive praise from other people.				

For each item, please indicate how well the statement describes you during the ***past week***, including today. Circle the number in the columns next to the item that best describes you.
0 = not at all true (zero days) 1 = rarely true (1-2 days) 2 = sometimes true (3-4 days) 3 = often true (5-6 days) 4 = almost always true (every day)

	0	1	2	3	4
15. I felt sad or depressed.					
16. I was not as interested in my usual activities.					
17. My appetite was poor, and I didn't feel like eating.					
18. My appetite was much greater than usual.					
19. I had difficulty sleeping.					
20. I was sleeping too much.					
21. I felt very fidgety, making it difficult to sit still					
22. I felt physically slowed down, like my body was stuck in mud.					
23. My energy level was low.					
24. I felt guilty.					
25. I thought I was a failure.					
26. I had problems concentrating.					
27. I had more difficulties making decisions than usual.					
28. I wished I was dead.					
29. I thought about killing myself.					
30. I thought that the future looked hopeless.					

31. Overall, how much have the symptoms of depression interfered with or caused difficulties in your life during the past week?

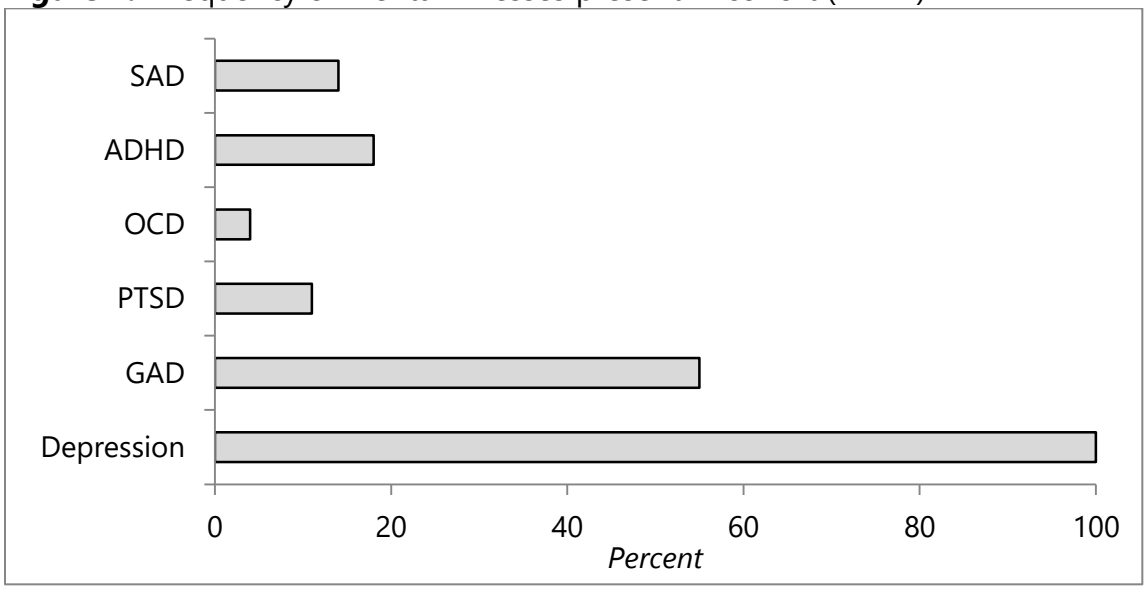
    0) Not at all
    1) A little bit
    2) A moderate amount
    3) Quite a bit
    4) Extremely

32. How would you rate your overall quality of life during the past week?

    0) Very good; my life could hardly be better
    1) Pretty good; most things are going well
    2) The good and the bad parts are about equal
    3) Pretty bad; most things are going poorly
    4) Very bad; my life could hardly be worse

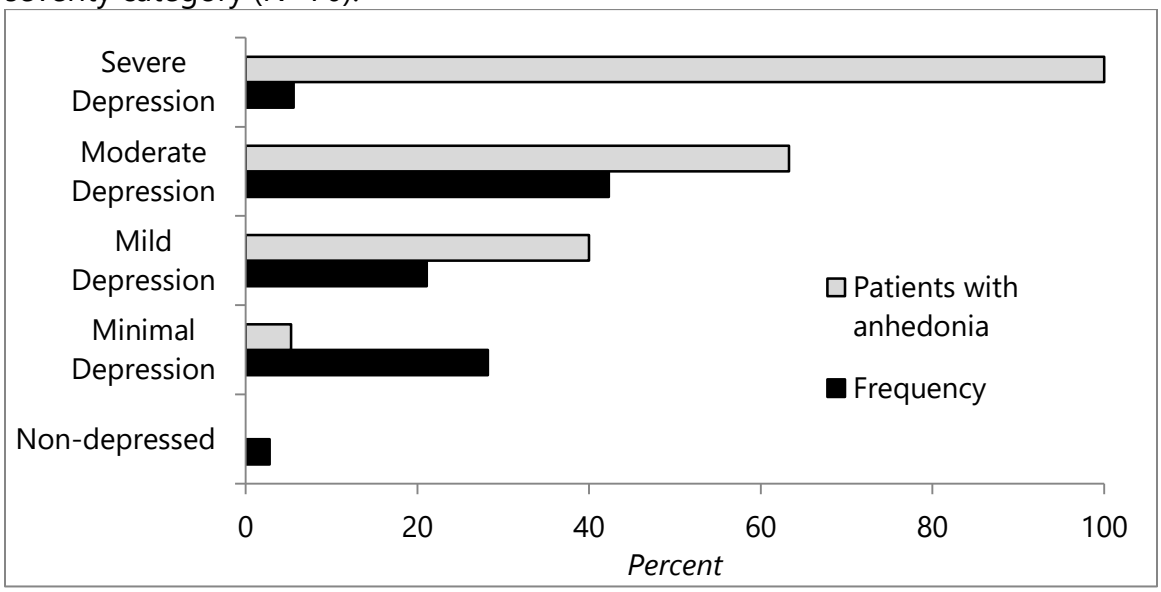
Tables and Figures

Figure 1. Frequency of mental illnesses present in cohort (N=71)



**data reported as n (%)*

Figure 2. Frequency of patients and prevalence of anhedonia in each depression severity category (N=70).



**Patients with anhedonia is reported category (%)*
***Frequency is reported n (%)*

Table 1: Frequency of anhedonia and remission in patients treated with antidepressant(s) and in patients treated with antidepressant(s) plus psychotherapy.

	Frequency (N=67)	**Anhedonia (N=66)**	**Remission (N=67)**
Antidepressant therapy	40%	23%	37%
Antidepressant plus psychotherapy	60%	53%	30%

**data reported n (%)*

Table 2: Scoring of CUDOS questions for patients with anhedonia and without anhedonia.

Question	Topic	p value
15	I felt sad or depressed	**< 0.001***
16	I was not as interested in my usual activities	**0.001***
17	My appetite was poor, and I didn't feel like eating	*0.058***
18	My appetite was much greater than usual	*0.671***
19	I had difficulty sleeping	*0.855***
20	I was sleeping too much	**<0.001***
21	I felt very fidgety, making it difficult to sit still	*0.061***
22	I felt physically slowed down, like my body was stuck in mud	**<0.001***
23	My energy level was low	**0.001***
24	I felt guilty	**0.012***
25	I thought I was a failure	**<0.001***
26	I had problems concentrating	**0.025***
27	I had more difficulties making decisions than usual	**0.006***
28	I wished I was dead	**<0.001***
29	I thought about killing myself	**0.008***
30	I thought the future looked hopeless	**<0.001***
31	Overall, how much have the symptoms of depression interfered or caused difficulties in your life during the past week	**0.002***
32	How would you rate your overall quality of life during the past week	**<0.001***

**P value (bold) represents statistically different reponses*

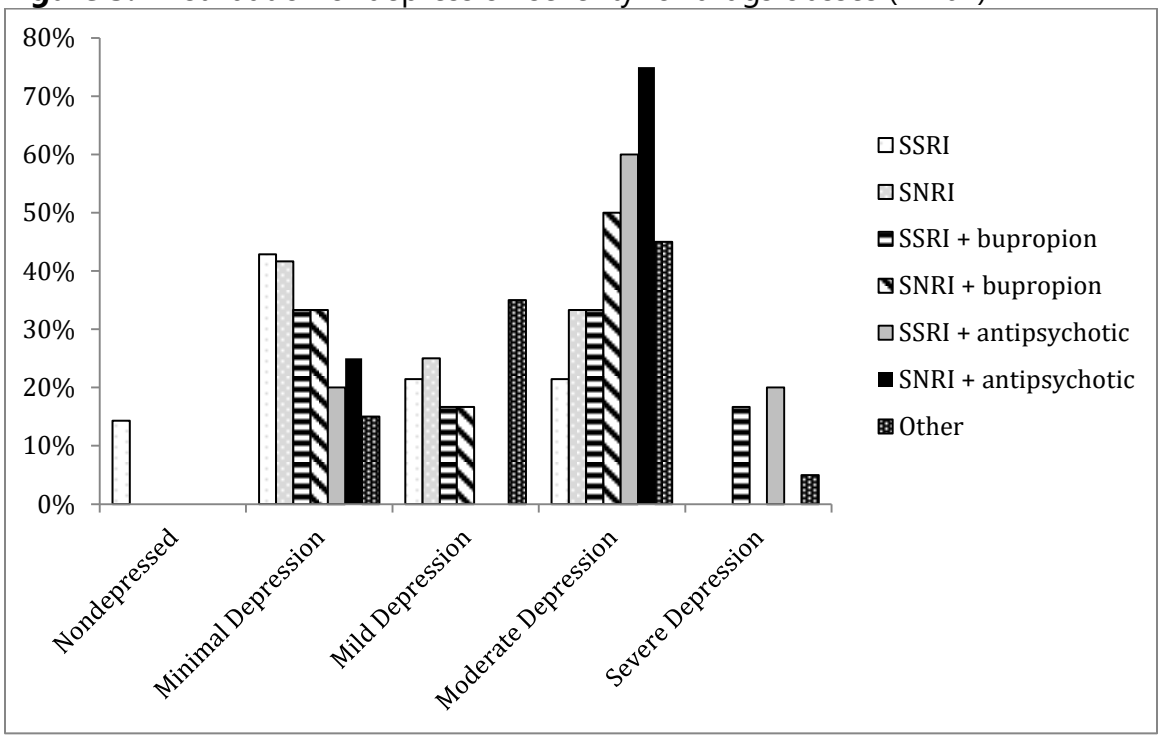
***P value (italized) represents statistically not different responses*

Table 3: Frequency of anhedonia and remission in patients being treated with various antidepressant classes.

	Frequency (N=67)	**Anhedonia (N=66)**	**Remission (N=67)**
SSRI	21%	31%	57%
SNRI	18%	25%	42%
SSRI + bupropion	9%	50%	33%
SNRI + bupropion	9%	50%	33%
SSRI + antipsychotic	8%	40%	20%
SNRI + antipsychotic	6%	50%	25%
Other	30%	45%	15%

**data reported n (%)*

Figure 3. Distribution of depression severity for drugs classes (N=67)



**data reported as category (%)*