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Article

POC-MON: A Novel and Cost-Effective Pocket Lemon Sniff Test (PLST) for Early Detection of Major Depressive Disorder.

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SUMMARY

Effective treatment of depression requires early detection. Major Depressive Disorder (MDD) is a global health and economic concern affecting over 300 million people, according to the World Health Organization. Approximately 21 million Americans experienced at least one depressive episode in 2017. A silent but deadly killer — depressive symptoms are frequently masked and therefore increases suicidal risk, resulting in about 1 million deaths annually, including teenagers. Undiagnosed and untreated depression is commonly linked to public bombings, mass killings, and school shootings in the U.S. Depressive symptoms overlap with olfactory regions, which led to several studies of the correlation between sense of smell and depression. The alarming rise of depression, its related crimes, suicides, and lack of inexpensive, quick tools in detecting early depression — this study aims in demonstrating decreased olfaction and depression correlation. Forty-two subjects (ages 13-83) underwent POC-MON (Pocket Lemon) assessment — an oven-dried lemon peel sniff test, subjected to distance measurement when odor first detected (threshold) and completed Patient Health Questionnaires (PHQ-9). POC-MON and PHQ-9 scores yielded a correlation of 20% and 18% for the right and left nostrils, respectively. Among male (n=17) subjects, the average distance of POC-MON and PHQ-9 scores produced a correlation of 14% and 16% for the right and left nostrils, respectively. Females (n=25) demonstrated a correlation of 28% and 21% for the right and left nostrils, respectively. These results suggest the correlation between olfaction and depression in diagnosing its early-stage, using a quick, inexpensive, and patient-friendly tool — POC-MON.

INTRODUCTION

Major Depressive Disorder (MDD), commonly known as depression, is a global public health and economic concern affecting more than 300 million people, according to the World Mental Health Survey conducted by the World Health Organization (WHO) in 17 countries (1, 2). It is one of the most common mental disorders in the United States, with approximately 17.3 million adults and 3.2 million adolescents having at least one major depressive episode in 2017 (3). Symptoms of MDD include feelings of depressed, worthless or hopeless, decreased interest or pleasure in activities used to enjoy, little energy or complaints of fatigue, sleep disorders, appetite changes, and difficulty in concentration, all of which can result in severe impairments in an individual's quality of life (2). It often comes with anxiety as well. If these problems become chronic or recurrent due to lack of treatment or left undiagnosed, depression can lead to suicide, which accounts to about 1 million deaths each year or 3000 cases per day (2). With factors such as age and sex, the distribution of depression prevalence changes. For instance, the typical ratio of depression in women to men is higher, 2:1. Depression is also higher in young adults (18-44 years) relative to older adults, with sex disparities during these times. In addition, the presence of depression may be masked by irritability or other medical complaints, making it difficult to diagnose, particularly among patients with comorbid diseases, substance abuse disorders, intellectual disability, brain injury, and dementia (4). Treatment of depression includes medications, psychotherapy, and medical procedures, such as electroconvulsive shock therapy. However, effective treatment requires early detection (4, 5).

Depressive symptoms are accompanied by brain alterations in several regions involving the orbitofrontal cortex, anterior and posterior cingulate cortex, insula, amygdala, hippocampus, and thalamus regions (6). These regions affecting symptoms of depression overlap with regions involved in olfaction, which led to several studies showing that olfactory processing and depression are linked. The association between olfaction and depression was first observed in rodents which had shown depressive behaviors as a result of olfactory bulb impairment-induced change in serotonin and dopamine concentrations (7-10).

On the other hand, patients diagnosed with depression exhibit reduced olfactory threshold, identification, and discrimination abilities (11, 12). Additionally, olfactory processing, as analyzed with chemosensory event-related potentials, has been found to be reduced in depression. After successful depression treatment, olfactory threshold and chemosensory processing appear to normalize. Therefore, it can be assumed that depression reduces the processing and perception of the resulting olfactory information. Furthermore, processing of olfactory stimuli should normalize after remission of depression if olfactory ability is a marker for depression (13, 14).

There are three systems used for the sense of smell: a)

Depression Severity (PHQ-9 Score)	Subjects (n)	Mean Nostril Distance (cm)		PHQ-9 Mean Score	Mean Age (years)	Depressed Males (%)	Depressed Females (%)
		Left (L)	Right (R)				
None (0)	3	25.5	26.4	0	66	0	3 (12)
Minimal (1-4)	21	21.8	22.2	2.52	44	9 (53)	12 (48)
Mild (5-9)	14	18.8	20.8	7	26	6 (35)	8 (32)
Moderate (10-14)	3	5.01	8.44	11.7	16	2 (12)	1 (4)
Moderate Severe (15-19)	1	12.7	3.7	17	29	0	1 (4)
Severe (20-27)	0	0	0	0	0	0	0

Table 1. Distribution of the Pocket Lemon Sniff Test (PLST) Measurements and Patient Health Questionaire-9 (PHQ-9) Scores among subjects. This table displays the measured mean distances (cm) obtained from PLST between left (L) and right (R) nostrils, as compared to the subjects (n=42) that are classified as having no, minimal, mild, moderate, moderately severe, and severe depression, according to their PHQ-9 scores. Mean age (yrs.) and the number (%) of depressed males and females were also calculated and compared to the number of subjects and their severity of depression, based on their PHQ-9 scores.

olfactory system, which allows us to recognize what a smell is, b) trigeminal system, which enables us to determine whether an odor is irritating or pleasing (named after the trigeminal nerve, which is responsible for feeling sensations in the entire face, such as sting or painful), and c) vomeronasal system, which is used for detecting pheromones. Pure odorants (i.e., limonene, vanillin, decanoic acid, peanut butter) are single compounds that only activate the olfactory system, which means that they only smell and do not create a reaction in the trigeminal system (15). Those who have lost their sense of smell are still able to distinguish many smells because of the reaction by the trigeminal system. In other words, pure odorants must be used in sniff tests for clinical trials in order to be effective. Olfactory functions are classified into a) threshold, an absolute sensitivity in odor detection through the least stimuli, b) identification, the recognition of an odor, and c) discrimination, the differentiation between scents (15). In this study, we aimed to get as close to a pure limonene odorant as possible by using dried lemon peels due to limonene's easily recognizable scent and readily reproducible properties (i.e., available all year) in any clinical setting. The limonene oil used in the study, although common in most citrus fruits, was extracted from its most abundant and all-season available source, lemon (16). Other pure odorants or scents were excluded in the study because of their extensive and recent utilization in sniff tests in most clinical trials. Threshold sensitivity was tested among subjects.

Routine screenings in primary care and other clinical settings should be provided to people of all ages in order to enable earlier identification of depression, and appropriate clinical intervention if necessary. Several diagnostic tools for depression, which may require copyright permission prior to use, are available: the Patient Health Questionnaire, 9th version (PHQ-9), the MacArthur Foundation Initiative on Depression and Primary Care Depression Tool kit, and the Medicare Learning Network "Screening for Depression" booklet (17). Some tools utilize a screening measure of odor identification, such as The University of Pennsylvania

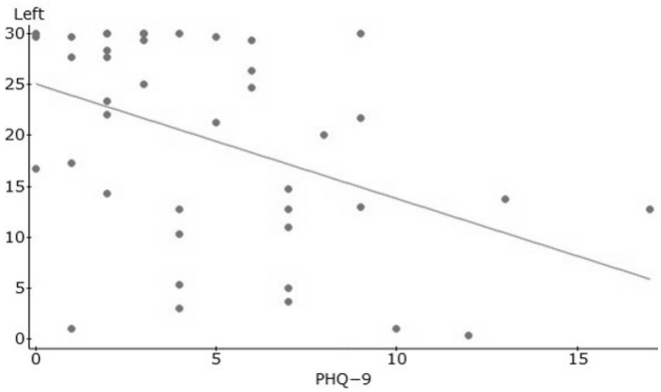

Figure 1. Correlation of the PHQ-9 Scores and PLST on left nostrils among subjects. Each point corresponds to the subjects' PHQ-9 scores (x-axis) and POC-MON assessments, or the odor threshold distance measurements, for the left nostril in centimeters (y-axis). Similar linear regression conveyed a correlation of 18% (SE=9.2271272, p=0.0052) for the left nostril among subjects (n=42).

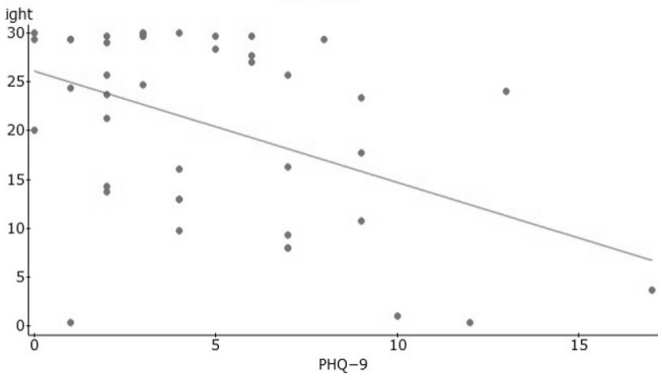

Figure 2. Correlation of the PHQ-9 Scores and PLST on right nostrils among subjects. This figure includes the subjects' PHQ-9 scores (x-axis) and POC-MON assessments for the right nostril in centimeters (y-axis). Similar linear regression shows a correlation of 20% (SE=8.7261902, p=0.003) for the right nostril among subjects (n=42).

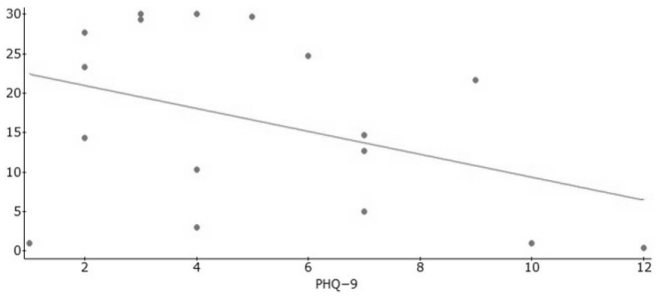

Figure 3. Correlation of the PHQ-9 Scores and PLST on left nostrils among male subjects. Data points represent the PHQ-9 scores (x-axis) and POC-MON assessments for the left nostril in centimeters (y-axis) among male subjects (n=17). Similar linear regression yielded a correlation of 16% (SE=10.817786, p=0.1136) for the left nostril among male subjects.

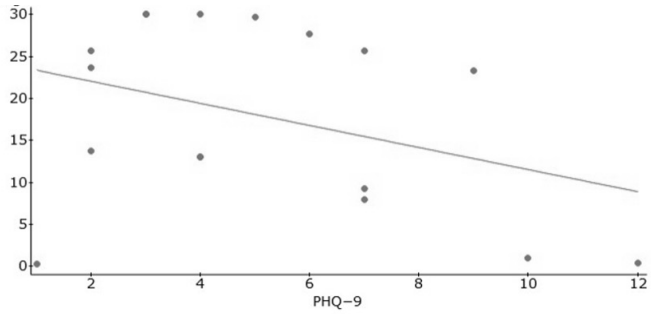

Figure 4. Correlation of the PHQ-9 Scores and PLST on right nostrils among male subjects. Data points represent the PHQ-9 scores (x-axis) and POC-MON assessments for the right nostril in centimeters (y-axis) among male subjects (n=17). Similar linear regression demonstrated a correlation of 14% (SE=10.737636, p=0.1459) for right nostril among male subjects.

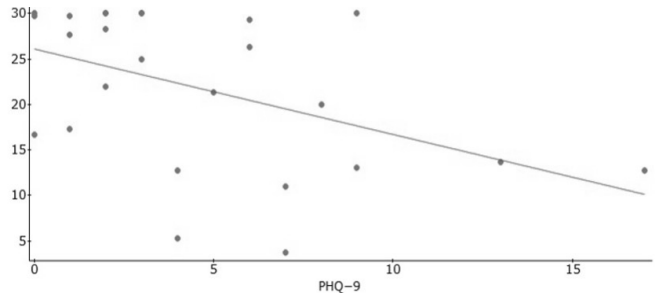

Figure 5. Correlation of the PHQ-9 Scores and PLST on left nostrils among female subjects. Data points represent the PHQ-9 scores (x-axis) and POC-MON assessments for the left nostril in centimeters (y-axis) among female subjects (n=25). Similar linear regression conveyed a correlation of 21% (SE=7.769559, p=0.0198) for the left nostril among female subjects.

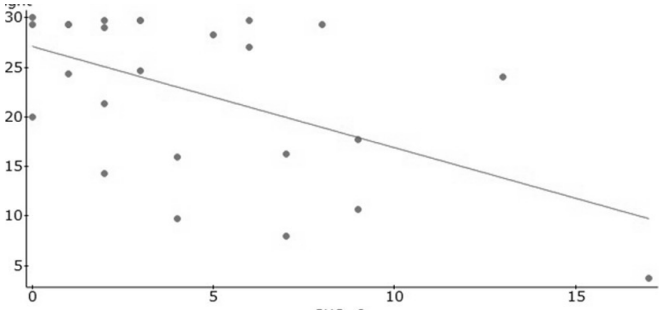

Figure 6. Correlation of the PHQ-9 Scores and PLST on right nostrils among female subjects. Data points represent the PHQ-9 scores (x-axis) and POC-MON assessments for the right nostril in centimeters (y-axis) among female subjects (n=25). Similar linear regression demonstrated a correlation of 28% (SE=7.0820591, p=0.0066) for the right nostril among female subjects.

Smell Identification Test (UPSIT), a self-administered 10-15 minutes olfactory test used in academic, industrial, and clinical settings. In clinical trials for UPSIT, subjects were asked to complete PHQ-9, a brief, patient-rated tool for screening, diagnosing, monitoring, and measuring severity of depression most commonly used in clinical settings, after three trials in each nostril (16). PHQ-9 was used over the other screening tools mainly because it has the shortest administration time. Like in the UPSIT trial, we used PHQ-9 to assess the accuracy of the pocket lemon (POC-MON) sniff test when it comes to presence of depression and its severity. Our POC-MON sniff test may offer an advantage over UPSIT because it is a brief, portable, inexpensive, and user-friendly screening tool that may have direct implications on patient safety, independent functioning, and quality of life.

The rationale of this study is based on the strong link between the loss of olfactory function and depressive behavior based on previous clinical trials; the rise of depression and suicide rates, particularly in teens; and the lack of inexpensive and quick screening tools in detecting early phase of depression. Our study hypothesized that failure of individuals to detect odor by lemon sniff test may correlate to presence of major depressive disorder.

RESULTS

All subjects included in this study were psychiatrically healthy with ages between 13 and 83. Subjects with primary olfactory dysfunction, neurocognitive or neuropsychiatric disorders such as dementia, or sinus problems at the time of testing, as well as those with a history of lemon allergy, were excluded from the study. Any active MDD diagnoses among participants were not disclosed during the test. To determine the correlation between olfaction and depression, the subjects underwent the POC-MON Assessment, in which each subject was asked to detect the lemon odor using the right and left nostrils at different distances, and the initial distance for scent detection was measured in centimeters with a ruler, followed by completion of the PHQ-9 questionnaire.

Based on their PHQ-9 scores, 3 (mean scores, M = 0), 21 (M = 2.52), 14 (M = 7), 3 (M = 11.7), and 1 (M = 17) subject(s) were identified as none, minimal, mild, moderate, and moderately severe, respectively (Table 1). After conducting three trials for each nostril, the mean distances in centimeters when odor was first detected from the left (L) versus right (R) were 25.5 (L)/26.4 (R), 21.8 (L)/22.2 (R), 18.8 (L)/20.8 (R), 5.01 (L)/8.44 (R), and 12.7 (L)/3.7 (R) among the none, minimal, mild, moderate, and moderately severe depressed subjects,

respectively (Table 1). POC- MON and PHQ-9 scores yielded a correlation of 18% (SE=9.2271272, p=0.0052) and 20% (SE=8.7261902, p=0.003) for the left and right nostrils, respectively (Figures 1-2). These results had shown more decline in olfaction with the right nostrils compared with left nostrils. Previous published studies suggest impairment in right nostrils indicate presence of depression.

Our study also demonstrated that no (0%), minimal (53%, n=9), mild (35%, n=6), moderate (12%, n=2), and moderately severe depression (0%) were observed among male subjects; while no (12%, n=3), minimal (48%, n=12), mild (32%, n=8), moderate (4%, n=1), and moderately severe depression (4%, n=1) were observed among female subjects (Table 1). Among male (n=17) subjects, the average distance of POC-MON and PHQ-9 scores produced a correlation of 16% (SE=10.82, p=0.1136) and 14% (SE=10.74, p=0.1459) for the left and right nostrils, respectively (Figures 3-4). Meanwhile, females (n=25) demonstrated a correlation of 21% (SE=7.77, p=0.0198) and 28% (SE=7.08, p=0.0066) for the left and right nostrils, respectively (Figures 5-6). Results of these data suggest females had shown more presence of depression versus male subjects.

Based on the POC-MON and PHQ-9 scores, the mean average age of subjects identified with absent, minimal, mild, moderate, and moderately severe depression are 66, 44, 26, 16, and 29 years, respectively (Table 1), with the correlation of 29% (SE=2.7154041, p=0.0248) among males (n=17) and 20% (SE=3.8594728, p=0.0252) among female (n=25) subjects (Figure 7). Except for severe depression, the severity of depression increases as the age in years decreases.

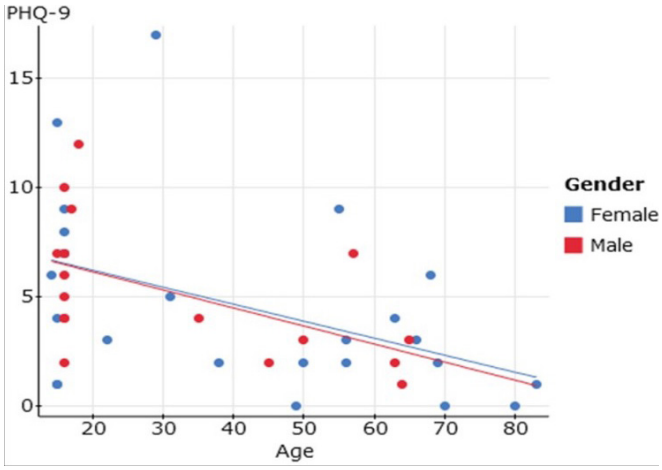

Figure 7. Correlation of the PHQ-9 Scores and PLST on age among subjects. This figure includes the subjects' ages (x-axis) and their corresponding PHQ-9 scores and POC-MON assessments (y-axis). Similar linear regression produced a correlation of 23% (SE=3.3671701, p=0.0014) among subjects (n=42). For male (n=17, red) subjects, there was a correlation of 29% (SE=2.7154041, p=0.0248). Meanwhile, female (n=25, blue) subjects conveyed a correlation of 20% (SE=3.8594728, p=0.0252).

DISCUSSION

The correlation between olfactory dysfunction and depression in patients has been demonstrated in major studies (7-10). Currently available assessment instruments in diagnosing depression consist of physician-administered or patient self-administered interview forms that can be intimidating to answer and may take 20-30 minutes to complete. The rise of unrecognized and undiagnosed depression, particularly in its early stage, is a major health concern. Therefore, development of a novel, brief, and user-friendly screening instrument to detect depression may improve current management and treatment modalities.

In this study, we administered an olfactory threshold test, the lemon peel sniff test, and compared the threshold measurements with PHQ-9 scores. The data support a model where individuals with reduced olfactory performance had depression. Of the 42 subjects included in the study, 39 were identified as depressed based on their PHQ-9 scores. However, no subjects were scored as severely depressed in both POC-MON and PHQ-9. The POC-MON and PHQ-9 scores of the subjects were utilized to compare their left nostrils with their right nostrils, and yielded correlations of 18% and 20%, respectively. The average distance of POC-MON and PHQ-9 scores produced a higher correlation for the right versus the left nostrils in both genders. Our study also showed that depression was identified more often in female than in male subjects. Although data support that age is not an indicator of the severity of depression, the correlation of POC-MON and PHQ-9 scores on ages among subjects was higher in female versus male subjects. These results are consistent with previous published findings, which showed that decreased olfactory function may indicate depressive disorder (7-14).

The primary source of error in the study was the subjects' responses with the POC-MON and PHQ-9 assessments. Three trials for each nostril, as well as intervals of resting in between were implemented as measures to eliminate as much error as possible. However, there was still a possibility that many of the subjects weren't entirely honest or confident with their responses. Another measure against error was that the subjects were asked to close their eyes during testing; otherwise, a false positive effect might have occurred. Despite these measures, many of the subjects may have been confused in determining the furthest distance they were able to smell the lemon because they struggled in identifying the lemon odor or mistook it for other smells, such as body odor or clothing. Another source of error that may have affected the results is the cofounding symptoms between depression and other neurological or psychiatric disorders. Participants' MDD diagnoses were not disclosed during the test. Therefore, participants who were diagnosed with MDD and were receiving antidepressant treatments may not have provided the most accurate results. To better examine whether POC-MON has the ability to detect depression, a similar experiment could be conducted with clinical cases presenting with mixed affective and cognitive symptoms, as well as various types

of dementia. This will allow for differential diagnosis among neurological and psychiatric disorders to avoid misdiagnosis and inappropriate pharmacotherapies. Moreover, to fully confirm that decreased olfaction occurred as a result of the increase in severity of depression and the accurate detection of lemon peels, the study should have included a larger sample size to allow for better statistical significance. However, due to time constraints, only 42 subjects were tested. Despite this, the data suggests that POC-MON demonstrated that a deficit in olfactory function may be a useful marker for detecting depression. Although there are conflicting studies in which nostril serves as an indicator of depression, this study showed that the right nostril was more affected in olfactory dysfunction among depressed people. Additional limitation of the study was the inability to differentiate the effect of initiating the sniff test using the left versus the right nostril among participants. Future studies should include a larger sample size and also follow patients longitudinally, with or without antidepressant treatments, to assess POC-MON performance. Further investigation should also identify a standard or cut-off distance at which limonene can be detected at various stages of depression. Newer diagnostic methods including those that utilize genomics, proteomics, and metabolomics, can be technically sophisticated and costly. POC-MON is a promising alternative instrument although further evaluation of this method is needed to fully demonstrate its clinical value and accuracy.

POC-MON may be a quick, inexpensive, and patient-friendly screening tool that may aid in defeating the alarming increase of depression and suicide rates among adults and teens. Awareness of the presence of depression in its earliest stage will allow healthcare professionals for early intervention and alleviate disease burden.

METHODS:

In preparation of POC-MON materials, fresh lemons were washed with water and then cut into four equal, longitudinal slices with a knife. Using a vegetable peeler, the white bitter pith of the lemon slices was removed to obtain the rinds. Lemon peels were placed on a cookie sheet with aluminum foil and oven-dried for 10 to 15 minutes at 95 degrees Fahrenheit to obtain limonene.

If the lemon peels were still able to bend when taken out of the oven, they were placed in the oven again and checked periodically until they were no longer malleable, avoiding browning of the peels. The oven-dried peels were stored in a ziploc bag at room temperature until needed for the POC-MON procedure.

POC-MON Assessment

Prior to the study, each subject completed the Human Participant Consent Form. During the POC-MON procedure, the subject was then asked to sit down, close his or her eyes and mouth, and cover the right nostril with one hand to prepare the left nostril for the sniff test. The lemon peel was placed next to the ruler, and the subject was asked to start sniffing as the lemon peel moved up and down towards the subject, until the subject was able to detect the lemon odor (threshold) for the first time. This distance was measured with a ruler in centimeters away from the nostril. The procedure was repeated for the right nostril with an interval of one to three minutes in between alternating nostrils. POC-MON assessment for both nostrils was administered three times. Then, the subject was asked to proceed for depression screening as administered by the student investigator.

Depression Screening

The PHQ-9 was distributed to the subject after completing POC-MON assessment. The subject was then asked to answer all the questions to the best of his or her ability. Each question from PHQ-9 has a maximum of 3 points, 3 indicating a problem occurring nearly every day, whereas 2 points and 1 point represent more than half the days and several days, respectively. Total PHQ-9 scores indicate the severity of depression: 1-4 range indicates minimal, 5-9 is mild, 10-14 is moderate, 15-19 is moderately severe, and 20-27 is severe (16).

Data Statistical Analysis

Statistical analyses such as Pearson correlation coefficient and standard error (SE) were provided by the computer program StatCrunch.

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REFERENCES

1. “Depression.” World Health Organization, www.who.int/news-room/fact-sheets/detail/depression. Accessed 30 June 2019.
2. Marcus, Marina, et al. “Depression: A Global Public Health Concern.” PsycEXTRA Dataset, 2012, doi:10.1037/e517532013-004.

3. "2017 National Survey on Drug Use and Health (NSDUH)", National Institute of Mental Health, https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.htm#tab9-6A. Accessed 30 June 2019.
4. Garland, E. Jane, et al. "Early detection of depression in young and elderly people." British Columbia Medical Journal, vol. 44, no. 9, November 2002, pp. 469-472.
5. "Diagnostic and Statistical Manual of Mental Disorders. 5th ed.", American Psychiatric Association 2013, https://doi.org/10.1176/appi.books.9780890425596. Accessed 25 June 2019.
6. Hoflich, A., et al. "Imaging treatment effects in depression." Reviews in the Neurosciences, vol. 23, no. 3, 2012, pp. 227-252. PubMed, doi: 10.1515/revneuro-2012-0038.
7. Masini, C.V., et al. "Dopamine overflow is increased in olfactory bulbectomized rats: an in vivo microdialysis study." Physiology and Behavior, vol. 81, no. 1, March 2004, pp. 111-119. PubMed, doi: 10.1016/j.physbeh.2004.01.003.
8. Kelly, J.P., et al. "The olfactory bulbectomized rat as a model of depression: an update." Pharmacology and Therapeutics, vol. 74, no. 3, 1997, pp. 299-316.
9. Leonard, B.E. "The olfactory bulbectomized rat as a model of depression." Polish Journal of Pharmacology and Pharmacy, vol. 35, no. 5, 1984, pp. 561-569.
10. Song, C., and B.E. Leonard. "The olfactory bulbectomised rat as a model of depression." Neuroscience and Biobehavioral Reviews, vol. 29, no. 4-5, 2005, pp. 627-647. PubMed, doi: 10.1016/j.neubiorev.2005.03.010.
11. Atanasova, B., et al. "Olfactory anhedonia and negative olfactory alliesthesia in depressed patients." Psychiatry Research, vol. 176, no. 2-3, 2010, pp. 190-196. PubMed, doi: 10.1016/j.psychres.2008.11.016.
12. Negoias, S., et al. "Reduced olfactory bulb volume and olfactory sensitivity in patients with acute major depression." Neuroscience, vol. 169, no. 1, 2010, pp. 415-421. PubMed, doi: 10.1016/j.neuroscience.2010.05.012.
13. Pause, B.M., et al. "Convergent and divergent effects of odors and emotions in depression." Psychophysiology, vol. 40, no. 2, 2003, pp. 209–225.
14. Van Hartevelt, T., et al. The Human Nervous System. 3rd ed., Academic Press, 2012, pp. 1219–1238.
15. Stamps, J., et al. A brief olfactory test for Alzheimer's disease. Journal of the Neurological Sciences. Vol. 333, issue 1-2, pp 19-24. October 15, 2013.
16. Doty, Richard L., et al. Trigeminal Chemosensation. 2003, pp. 8-46. U of Pennsylvania and U of California, PhD dissertation. eScholarship, https://escholarship.org/content/qt5wm4g2gq/qt5wm4g2gq.pdf?t=oxxxcd&nosplash=121f602ba739c1d01127e80f8c524aed. Accessed 26 August 2019.
17. "Depression Screening Tools." 2019, SAMHSA-HRSA Center for Integrated Health Solutions, https://www.integration.samhsa.gov/clinical-practice/screening-tools#sample%20screening%20forms. Accessed 13 August 2019.

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