

Concentration of Neurotransmitter Metabolite 5-hydroxyindoleacetic Acid (5-HIAA) in Cerebrospinal Fluid of Individuals with Suicidal Tendencies: A Meta-Analysis

Ravi Prakash M¹, Sharma R², Bhute AR³, Bastia BK⁴

Abstract

Review of 28 research articles on the cerebrospinal fluid levels of neurotransmitter metabolites involving 1942 psychiatric patients found a strong evidence of involvement of serotonin system in suicidal behavior. All the individuals who attempted suicide, especially those using violent methods, had lower levels of CSF 5-hydroxyindoleacetic acid (5-HIAA) as compared to those in the controls. The Meta-analysis attempts to draw more reliable conclusion than did each individual study alone.

Keywords: Cerebrospinal fluid; Neurotransmitter metabolites; 5-HIAA.

How to cite this article:

Ravi Prakash M, Sharma R, Bhute AR *et al.* Concentration of Neurotransmitter Metabolite 5-hydroxyindoleacetic Acid (5-HIAA) in Cerebrospinal Fluid of Individuals with Suicidal Tendencies: A Meta-analysis. *Indian J Forensic Med Pathol.* 2019;12(3):173-178.

Introduction

In year 2016, there were estimated 7,93,000 suicidal deaths worldwide. This indicates an annual global age-standardized suicide rate of 10.5 per 100000 populations.¹ Suicide is one of the most significant public health issue—globally. Individuals having clinical depression are at higher risk of completed suicide. However, the number of completed suicide is much smaller than that of attempted suicide in individuals with depression. An indicator that can

point to a high suicidal risk can be an aid for the prevention of completed suicide. Such an indicator would benefit the community to categorize persons with higher risk. The more knowledge we have about our cognitive and neurological processes that lead to suicidal behavior, the better equipped we would be to search for the right treatment and proper medication that can match up to the disease. Currently, suicidal tendency is being searched for in sociological and psychological realm, that offers vague prediction for clinical utility.

Recently, there has been a renewed interest in role of neurotransmitters like serotonin, dopamine and norepinephrine in etiology of suicidal behavior, with special focus on neurotransmitters in cerebrospinal fluid (CSF), serum and urine. This biochemical realm seems to be a more promising approach to identify high-risk group that may complete suicide. 5-HT is the main principal metabolite associated with depression. Hypothesis for CSF studies is that levels of the breakdown products in CSF reflect neurotransmitter turnover in brain rather than that in spinal cord². This hypothesis was reinforced from association between levels of 5-HIAA in CSF and in cerebral cortex in post-mortem studies.³ Analyses of

Authors Affiliation: ^{1,3}Assistant Professor, ²PhD Scholar, ⁴Professor and Head, Department of Forensic Medicine and Toxicology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand 249203, India.

Corresponding Author: Sharma R, PhD Scholar, Department of Forensic Medicine and Toxicology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand 249203, India.

E-mail: sharmarishi1991@yahoo.com

Received on 13.05.2019, **Accepted on** 08.06.2019

CSF are much simpler to conduct, than that on brain tissue. However, various Research point out that the CSF levels of metabolites such as 5-HIAA are affected by gender (lower in males), age and height (lower in taller individuals).⁴ Other factors include diet, medication, physical movement, position of subject during lumbar puncture, amount of CSF drawn and analytical method used.⁵ Many studies pertaining to this literature has been published in past and one researcher attempted a comprehensive meta-analysis of individual studies.^{6,7} Purpose of this article is to review the studies for variations in concentration of 5-HIAA in CSF amongst suicidal and non-suicidal individuals and further in those with violent and non-violent methods of suicidal attempt.

Materials and Methods

An extensive literature search for eligible studies published before 08th June 2018 was done in the

PubMed, EMBASE and Google Scholar databases. Following combinations of main keywords and MeSH term were used alone or in combinations: '5-HIAA', 'suicide', 'suicide attempters and Suicid'. We then reviewed reference lists of published studies for additional reports not identified by electronic search.

Only studies that reported sample size, mean scores and standard deviations (or standard errors of mean) for each group were included in our systematic review.

Results of each study thus located were then examined for relevant data: sample size, mean concentrations of the metabolite of interest (5-HIAA). All the data was converted to a standard form: mean, standard deviation instead of standard error, and *nmol/l* against *ng/mL*. Our study also included a control group (psychiatric patients) that roughly matched the study sample. Studies which compared suicidal individuals with healthy controls were not included since these studies failed to account for presence of psychiatric disorders.

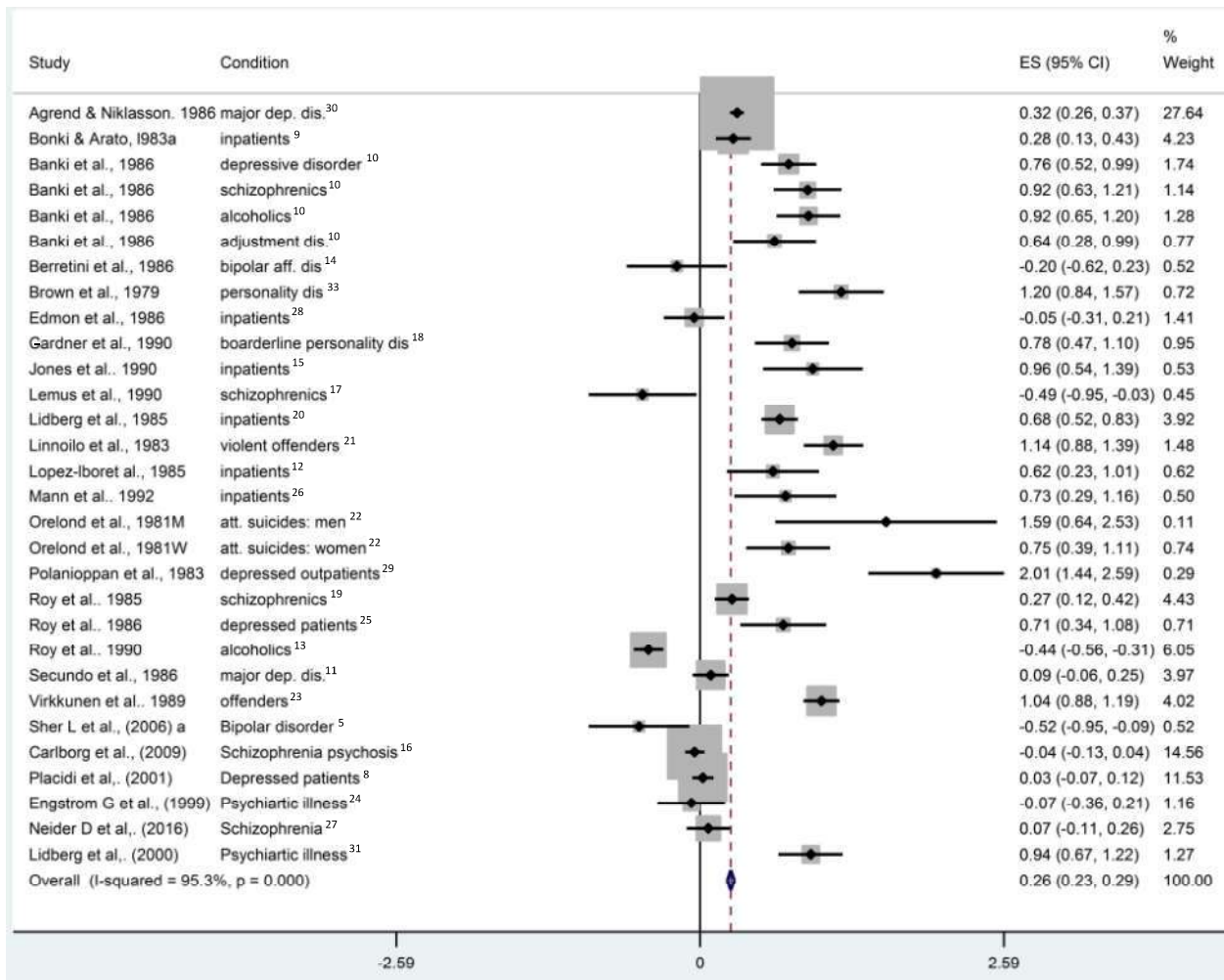


Fig. 1: Forest Plot of attempted suicide v/s Psychiatric control

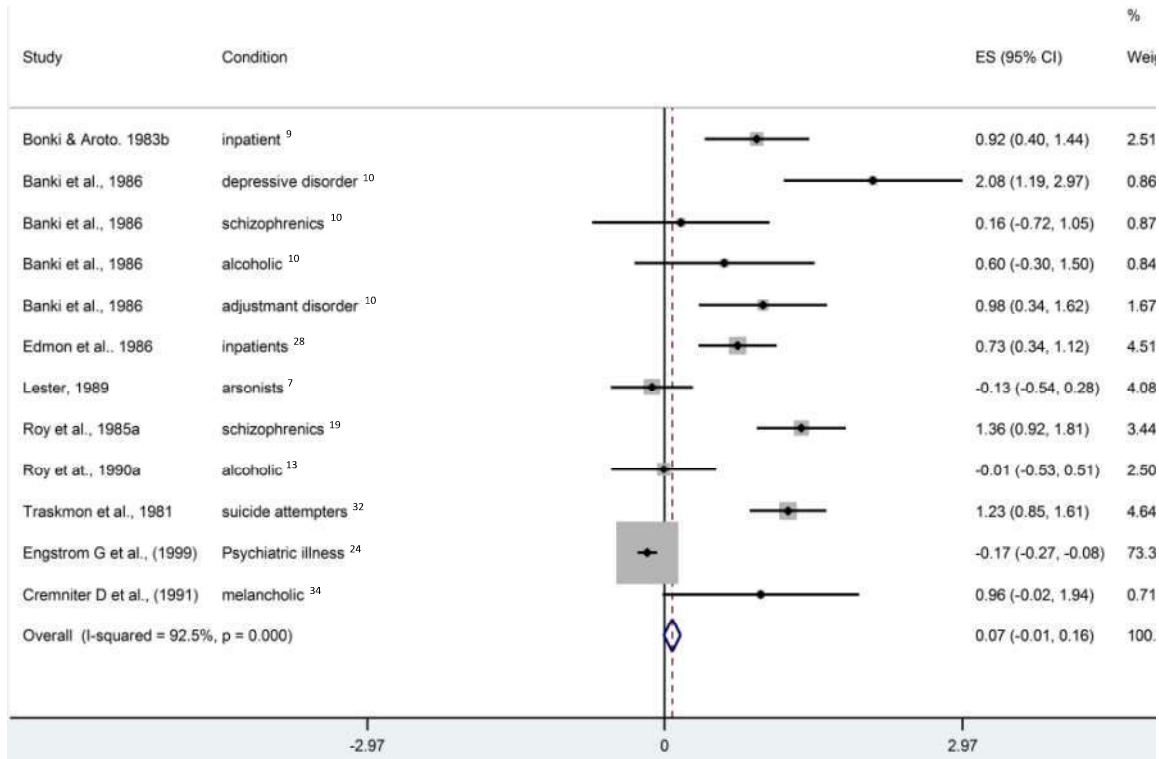


Fig. 2: Forest Plot of Violent v/s Non-Violent Suicide attempters

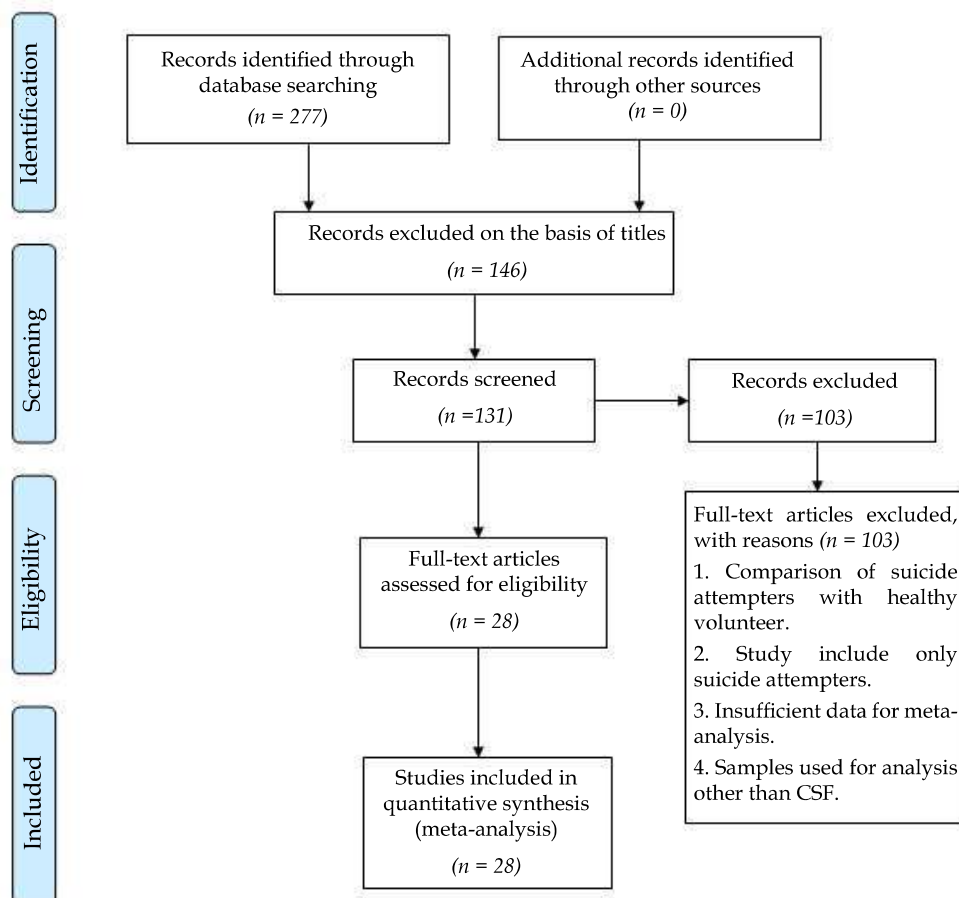


Fig. 3: Prisma flowchart for CSF 5-HIAA describing the process of study selection and exclusion.

All these studies used parametric statistical tests to analyze data in their published reports. Raw data was not available to us and it was also not possible to check whether the data met the criteria for parametric statistical tests. Since only means and standard deviations were available to us, we used parametric statistical tests for analysis. Standardized mean difference (SMD) was calculated for each study.

Effect size for psychiatric control and suicidal patient was calculated as difference of mean level of CSF 5-HIAA divided by combined standard deviation. Effect size for non-violent and violent patient was calculated as difference of mean level of CSF 5-HIAA divided by combined standard deviation.

Results

In figure-1, 32 studies were pooled together. Thirteen studies out of 32 (41%) had a very small confidence interval depicting larger sample size. Small-pooled effect size of 0.26 was found and is significant.

In figure-2, 12 studies were pooled together for analysis. In all the studies except one, the result was not precise with a larger confidence Interval depicting either a smaller sample size or a bias. Final pooled effect size is 0.07 and not significant. I square is 95%, so the studies are highly heterogeneous in nature and so the pooling of result may be biased.

Discussion

This review of CSF studies of 5-HIAA has clarified the findings of various researches. First, there is strong evidence that those who have attempted suicide have lower levels of CSF 5-HIAA than the psychiatric controls. Second, the serotonin system seems to be most clearly implicated in attempted suicides.

Analysis of violent and non-violent suicide attempters revealed no association between levels of CSF 5-HIAA in violent attempters compared to that in non-violent attempters.

All two sets of analyses point towards evidence for the involvement of serotonin system in those making suicide attempts, especially violent attempters, and in those engaging in subsequent completed suicide. Although there has been some speculation that lower levels of 5-HIAA in CSF of individuals with suicidal tendency might be found only in some psychiatric patients. Individual studies

observed lower levels of 5-HIAA in attempted suicide with diagnoses of alcoholism, depressive disorders, personality disorders and schizophrenia and in offenders. Thus, psychiatric diagnosis does not appear to play a major role in the association.

It should be noted that, since majority of subjects in the studies reviewed were psychiatric patients, some may have been on medication. Therefore, data from these reports were not sufficiently detailed to take this factor into account. Furthermore, different investigators may have had differences in the techniques utilized for estimating the concentration of CSF neurotransmitter metabolites. In spite of these limitations, consistency in the findings of levels of CSF 5-HIAA are more note worthy.

Furthermore, although researches so far has been conducted on samples of patients with a variety of psychiatric diagnoses and the results do not at present appear to depend upon diagnosis, future researches should focus in a more systematic manner for possible mediating impact of psychiatric diagnosis on level of CSF 5-HIAA.

The studies reviewed in this paper typically employed small sample sizes, and only by examining the data from all of the studies, trend could be identified. It is suggested that future investigators should involve large number of samples, so that not only will their results be more reliable, but also they can investigate the role of factors other than suicidal status *viz*, gender, age, height, diet, medication etc., that affect the CSF levels of these metabolites.

References

1. https://www.who.int/gho/mental_health/suicide_rates/en.
2. Asberg M. Biochemical aspects of suicide. *Clin Neuropharmacol*. 1986;9(4):374-76.
3. Cowns I. John W. Creswell Research Design Qualitative, Quantitative, and Mixed Methods Approaches SAGE Publications Inc. 2013 (cited 2019 May 10); Available from: https://www.academia.edu/29332705/John_W._Creswell_Research_Design_Qualitative_Quantitative_and_Mixed_Methods_Approaches_SAGE_Publications_Inc._2013_.
4. Haidich AB. Meta-analysis in medical research. *Hippokratia*. 2010;14(Suppl 1):29-37.
5. Sher L, Carballo JJ, Grunebaum MF, *et al.* A prospective study of the association of cerebrospinal fluid monoamine metabolite levels with lethality of suicide attempts in patients with bipolar disorder. *Bipolar Disord*. 2006 Oct 8 (5):543-50.

6. Molcho A, Stanley B, Stanley M, *et al.* Biological studies and markers in suicide and attempted suicide. *Int Clin Psychopharmacol.* 1991;6(2):77-92.
7. Lester D. The concentration of neurotransmitter metabolites in the cerebrospinal fluid of suicidal individuals: a Meta-analysis. *Pharmacopsychiatry.* 1995 Mar;28(2):45-50.
8. Placidi GP, Oquendo MA, Malone KM, *et al.* Aggressivity, suicide attempts, and depression: relationship to cerebrospinal fluid monoamine metabolite levels. *Biol Psychiatry.* 2001 Nov 15;50(10):783-91. PubMed PMID:11720697.
9. Banki CM, Arató M. Amine metabolites and neuroendocrine responses related to depression and suicide. *J Affect Disord.* 1983 Aug;5(3):223-32.
10. Banki CM, Arató M, Kilts CD, *et al.* Aminergic studies and cerebrospinal fluid cations in suicide. *Ann NY Acad Sci.* 1986;487:221-30.
11. Secunda SK, Cross CK, Koslow S, *et al.* Biochemistry and suicidal behavior in depressed patients. *Biol Psychiatry.* 1986 Jul;21(8-9):756-67.
12. López-Ibor JJ, Saiz-Ruiz J, Pérez de los Cobos JC, *et al.* Biological correlations of suicide and aggressivity in major depressions (with melancholia): 5-hydroxyindoleacetic acid and cortisol in cerebral spinal fluid, dexamethasone suppression test and therapeutic response to 5-hydroxytryptophan. *Neuropsychobiology.* 1985;14(2):67-74.
13. Roy A, Lamparski D, De Jong J, *et al.* Cerebrospinal fluid monoamine metabolites in alcoholic patients who attempt suicide. *Acta Psychiatry Scand.* 1990 Jan;81(1):58-61.
14. Berrettini WH, Nurnberger JL, Narrow W, Simmons-Alling S, Gershon ES, *et al.* Cerebrospinal fluid studies of bipolar patients with and without a history of suicide attempts. *Ann NY Acad Sci.* 1986;487:197-201.
15. Jones JS, Stanley B, Mann JJ, *et al.* CSF 5-HIAA and HVA concentrations in elderly depressed patients who attempted suicide. *Am J Psychiatry.* 1990 Sep;147(9):1225-27.
16. Carlborg A, Jokinen J, Nordström A-L, *et al.* CSF 5-HIAA, attempted suicide and suicide risk in schizophrenia spectrum psychosis. *Schizophr Res.* 2009 Jul;112(1-3):80-85.
17. Lemus CZ, Lieberman JA, Johns CA, *et al.* CSF 5-hydroxyindoleacetic acid levels and suicide attempts in schizophrenia. *Biol Psychiatry.* 1990 Apr 15;27(8):926-29.
18. Gardner DL, Lucas PB, Cowdry RW, *et al.* CSF metabolites in borderline personality disorder compared with normal controls. *Biol Psychiatry.* 1990 Aug 1;28(3):247-54.
19. Roy A, Ninan P, Mazonson A, *et al.* CSF monoamine metabolites in chronic schizophrenic patients who attempt suicide. *Psychol Med* 1985 May;15(2):335-40.
20. Lidberg L, Tuck JR, Asberg M, *et al.* suicide and CSF 5-HIAA. *Acta Psychiatry Scand.* 1985 Mar;71(3):230-36.
21. Linnoila M, Virkkunen M, Scheinin M, *et al.* Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from non-impulsive violent behavior. *Life Sci.* 1983 Dec 26;33(26):2609-14.
22. Orelund L, Wiberg A, Asberg M, *et al.* Platelet MAO activity and monoamine metabolites in cerebrospinal fluid in depressed and suicidal patients and in healthy controls. *Psychiatry Res* 1981 Feb;4(1):21-29.
23. Virkkunen M, De Jong J, Bartko J, *et al.* Psychobiological concomitants of history of suicide attempts among violent offenders and impulsive fire setters. *Arch Gen Psychiatry* 1989 Jul;46(7):604-6.
24. Engström G, Alling C, Blennow K, *et al.* Reduced cerebrospinal HVA concentrations and HVA/5-HIAA ratios in suicide attempters. *Monoamine metabolites in 120 suicide attempters and 47 controls.* *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol* 1999 Sep;9(5):399-5.
25. Roy A, Agren H, Pickar D, *et al.* Reduced CSF concentrations of homovanillic acid and homovanillic acid to 5-hydroxyindoleacetic acid ratios in depressed patients: relationship to suicidal behavior and dexamethasone non-suppression. *Am J Psychiatry.* 1986 Dec;143(12):1539-45.
26. Mann JJ, McBride PA, Brown RP, *et al.* Relationship between central and peripheral serotonin indexes in depressed and suicidal psychiatric inpatients. *Arch Gen Psychiatry.* 1992 Jun;49(6):442-46.
27. Neider D, Lindström LH, Bodén R, *et al.* Risk factors for suicide among patients with schizophrenia: a cohort study focused on cerebrospinal fluid levels of homovanillic acid and 5-hydroxyindoleacetic acid. *Neuropsychiatry Dis Treat.* 2016;12:1711-14.
28. Edman G, Asberg M, Levander S, Schalling D, *et al.* Skin conductance habituation and cerebrospinal fluid 5-hydroxyindoleacetic acid in suicidal patients. *Arch Gen Psychiatry.* 1986 Jun;43(6):586-92.
29. Palaniappan V, Ramachandran V, Somasundaram O, *et al.* Suicidal ideation and biogenic amines in depression. *Indian J Psychiatry.* 1983 Oct;25(4):286-92.
30. Agren H, Niklasson F. Suicidal potential in depression: focus on CSF monoamine and purine metabolites. *Psychopharmacol Bull.* 1986;22(3):656-60.
31. Lidberg L, Belfrage H, Bertilsson L, *et al.* Suicide attempts and impulse control disorder are related to low cerebrospinal fluid 5-HIAA in mentally

- disordered violent offenders. *Acta Psychiatry Scand.* 2000 May;101(5):395-402.
32. Träskman L, Asberg M, Bertilsson L, *et al.* Monoamine metabolites in CSF and suicidal behavior. *Arch Gen Psychiatry.* 1981 Jun;38(6):631-36. PubMed PMID: 6166274.
33. Brown GL, Goodwin FK, Ballenger JC, *et al.* Aggression in humans correlates with cerebrospinal fluid amine metabolites. *Psychiatry Res.* 1979 Oct;1(2):131-39. PubMed PMID: 95232.
34. Cremniter D, Jamain S, Kollenbach K, *et al.* CSF 5-HIAA levels are lower in impulsive as compared to non-impulsive violent suicide attempters and control subjects. *Biol Psychiatry* 1999 Jun 15;45(12):1572-9. PubMed PMID: 10376117.

