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Serotonergic responses in depressed patients with or without a history of alcohol use disorders and healthy controls

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Abstract

Dysfunction of serotonergic neurotransmission has been implicated in the etiopathogenesis of major depression (MDD) and alcohol use disorders (AUD). To compare serotonin function in MDD with co-occurring AUD (MDD/AUD), MDD without co-occurring AUD (MDD only) and healthy controls (HC) we sought to study differences in prolactin responses to fenfluramine administration in patients with MDD/AUD, patients with MDD only and HC. In all, 169 subjects (62 MDD/AUD, 75 MDD only, and 32 HC) were entered into the study. Controlling for gender, prolactin responses were lower in the MDD/AUD group compared to the MDD only or the HC group. Controlling for gender and aggression, prolactin responses in the MDD/AUD group remained significantly lower compared to the HC group but the difference between the MDD/AUD and the MDD only groups disappeared. The difference in prolactin responses between MDD/AUD and MDD only could be attributed to higher aggression scores in the MDD/AUD group compared to the MDD group.

Keywords

Serotonin; Prolactin; Fenfluramine; Depression; Alcohol; Aggression

1. Introduction

Major depression (MDD) affects about 13 million Americans or roughly 5% of the population and is the leading cause of disability in the United States (Williams et al., 2007). Worldwide, MDD affects at least 120 million people (WHO, 2001). Similarly, alcohol abuse and dependence (alcohol use disorders; AUD) are highly prevalent in the U.S. and around the world (NIAAA, 1992; WHO, 2001). In the U.S., prevalence estimates for alcohol abuse and dependence in the general population range between 7% for current and 16–24% for lifetime alcohol problems (NIAAA, 1992; Regier et al., 1990). Recent research indicates that alcohol abuse and dependence are not diagnostically distinct entities, but represent a

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Contributors

Leo Sher, M.D. designed the study, undertook the statistical analysis of clinical and physiological data, managed literature searches, and worked on the manuscript. Maria A. Oquendo, M.D., Thomas B. Cooper, M.A., Kevin M. Malone, M.D., and J. John Mann, M.D. contributed to the implementation of the study and the interpretation of the study results. Maria A. Oquendo, M.D., J. John Mann, M.D. and Barbara H. Stanley, Ph.D. worked on the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

continuum of severity of AUDs (Li et al., 2007). Patients with depression frequently have alcohol problems (Kessler et al., 1997; Regier et al., 1990). One household survey reported a prevalence of 16% for any alcohol diagnosis in depressed patients (Regier et al., 1990). These conditions have been found to coexist in different age, sex, and racial groups (Kessler et al., 1997; Regier et al., 1990). Depressed patients with co-occurring AUD have more chronic impairment than individuals with either diagnosis alone (Cornelius et al., 1996; Cornelius et al., 1995; Sher, in press; Thase et al., 2001). Alcohol problems in depressed patients present diagnostic and management challenges and may adversely affect the course of depression and its response to standard therapies.

Neuroendocrine challenge tests are a widely used research strategy in biological psychiatry and neuropsychopharmacology (D'Souza et al., 1999; Mann et al., 1996; Newman et al., 1998). Their basic premise is that neurotransmitters and receptors which control hormonal release may also be implicated in the pathogenesis and treatment of neuropsychiatric disorders. Putatively, perturbations in the neurotransmitters and receptors which underlie neuropsychiatric disorders and the changes effected by treatment will be reflected in the levels of hormones released by a challenge agent (Coccaro et al., 1996; D'Souza et al., 1999; Malone et al., 1996; Mann et al., 1996; McBride et al., 2004; Newman et al., 1998; O'Keane et al., 1992; Oquendo et al., 2003; Schwartz et al., 1997; Sher et al., 2003). The hormonal response to the serotonin-releasing agent/uptake inhibitor fenfluramine has been widely used as an indicator of central serotonin system function in humans (Mann et al., 1996; Newman et al., 1998; Sher et al., 2003). It has been suggested that the action of fenfluramine involves stimulation of serotonin release from nerve terminals and blockade of its reuptake (Garattini, 1981). This results in a decrease in brain tissue levels of serotonin. A direct effect of D-fenfluramine to increase serotonin release was first shown in vitro in rat brain slices (Laferrere and Wurtman, 1989; Mennini et al., 1985), and subsequently using in vivo microdialysis in rat frontal cortex (Laferrere and Wurtman, 1989) and in lateral hypothalamus (Schwartz et al., 1989). Fenfluramine was first shown to increase prolactin secretion in normal human volunteers in 1983 (Quattrone et al., 1983). The effect was dose-dependent, reached a peak 4 h after administration of the drug, and was blocked by prior administration of metergoline. Prolactin secretion is regulated by an inhibitory input of dopamine and a stimulatory input of serotonin. Serotonergic nerve terminals located in the dorsal raphe nucleus project to the hypothalamus to stimulate prolactin secretion from the pituitary. Thus, serotonin-releasing agents increase prolactin via a central mechanism. Because fenfluramine acts both presynaptically to increase serotonin release and postsynaptically as a receptor agonist, challenge tests using fenfluramine provide an overall indication of the 'net' activity of the serotonergic system, in contrast to other challenge agents where the information which can be derived is limited to an assessment either of serotonin release or of activity at one of the many types of postsynaptic receptors for serotonin. Most studies have been conducted with the racemic formulation that contain approximately equal quantities of fenfluramine's D- and L-isomer (Coccaro et al., 1996). It has been shown that the prolactin response evoked by Dfenfluramine is quantitatively very similar to that evoked by D,L-fenfluramine (Coccaro et al., 1996).

Dysfunction of central serotonergic neurotransmission has been implicated in the etiopathogenesis and maintenance of alcohol dependence (Fromme and D'Amico, 1999; Mann et al., 1999; Ratsma et al., 2002). Several lines of evidence point to a relationship between serotonergic dysfunction, negative mood states, and excessive alcohol intake (Fromme and D'Amico, 1999; Heinz et al., 2001). Because the serotonergic system is involved in the etiopathogenesis of both depression and alcoholism, the fenfluramine administration is an important research tool in research on depressive and alcohol use disorders. Patients with major depressive episode and co-occurring AUD (MDD/AUD) may

have more profound serotonergic abnormalities compared to patients with major depression without a history of alcohol dependence (MDD only) (Heinz et al., 2001; Sher, in press).

To compare serotonin function in MDD/AUD, MDD only and healthy controls (HC) we sought to study differences in prolactin responses to fenfluramine administration in patients with MDD/AUD, in patients with MDD only and in HC. We hypothesized that prolactin responses to fenfluramine administration will be lower in MDD/AUD individuals compared to MDD only, and higher in HC compared to the MDD only or MDD/ AUD groups. To our knowledge, this is the first such study.

2. Methods

2.1. Subjects

In all, 169 subjects were entered into the study after giving written informed consent as required by the Institutional Review Board. The MDD/AUD group consisted of 62 patients (34 males and 28 females), the MDD only group consisted of 75 patients (27 males and 48 females), and the HC group consisted of 32 subjects (19 males and 13 females). All subjects were diagnosed using a structured clinical interview (SCIDI for DSM III-R) (Spitzer et al., 1992). Healthy volunteers were free from any Axis I disorders based on SCID-NP. All subjects were free from any substance or alcohol dependence for at least 6 months and free from any substance or alcohol abuse for at least 2 months. The duration of the drug-free status of the subjects was established by a combination of urine and blood toxicological screenings, observation in hospital, and a history obtained from the participant, the participant's family and the referring physician. Some participants included in this sample have been the subject of other reports (Malone et al., 2003; Oquendo et al., 2005; Sher et al., 2007; Sher et al., 2003).

Depressed patients had a score of 16 or more on the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Depressive symptoms were also assessed with the Beck Depression Inventory (Beck et al., 1961). Aggression and impulsivity were assessed with the Aggression History Scale (Brown-Goodwin, revised) (Brown and Goodwin, 1986) and the Barratt Impulsivity Scale (Barratt, 1965), respectively. A lifetime history of all suicide attempts was recorded on the Columbia Suicide History Form (Oquendo et al., 2003).

All subjects had been free of antidepressants, anti-psychotics and other medication known to affect serotonergic function for at least two weeks (4 weeks for oral anti-psychotics, 6 weeks for fluoxetine). Presence of significant medical or neurological illness was determined by medical history, physical examination, and routine laboratory testing, and such subjects were excluded. During the drug-free period subjects were closely monitored by experienced psychiatrists and psychologists. Subjects were admitted to the inpatient unit when necessary.

2.2. Procedure

Subjects were administered 0.8 mg/kg of D,L-fenfluramine orally at 9 am. All subjects fasted from midnight prior to the test and had an intravenous catheter placed at about 8 am. Blood samples were drawn 15 min before capsule administration (time — 15), at time of administration of the capsule (time 0) and then hourly for 5 h. Blood samples were analyzed for prolactin, fenfluramine, and norfenfluramine levels (Malone et al., 1996). The study was single-blind. The subjects were told that they will receive either the active drug or placebo.

2.3. Statistical analysis

All data are reported as mean+SD unless otherwise indicated. Demographic and clinical variables were compared using Student's *t*-test for continuous variables and chi-square test

for categorical variables. The prolactin response and fenfluramine and norfenfluramine levels were expressed as area under the curve. We used log transformations of the prolactin levels to insure a normal distribution of the values. Comparisons between the three groups on the prolactin response and the fenfluramine and norfenfluramine levels were analyzed using general linear model controlling for gender. Comparison between the three groups on the prolactin response was also analyzed using general linear model controlling for gender and aggression scores. Relationships between behavioral measures and prolactin responses were assessed using Pearson's correlations.

3. Results

3.1. Demographic data

Demographic parameters of the 3 groups are presented in Table 1. There were no differences with regard to age and marital status between the 3 groups. There were less males in the MDD only group compared to the two other groups. HC subjects had more years of education compared to the MDD/AUD or MDD only subjects.

3.2. Clinical data

Clinical characteristics of the 3 groups are presented in Table 2. As expected, the HC group had lower Hamilton Depression Rating Scale, Beck Depression Inventory, Brown-Goodwin Aggression Scale, and Barratt Impulsivity Scale scores compared to the MDD/ AUD or MDD groups. MDD/AUD subjects had higher aggression scale scores and higher prevalence of antisocial and borderline personality disorders compared to MDD only subjects. There were no differences between the two patient groups with regard to suicide attempt status, age of onset of the first major depressive episode, number of previous major depressive episodes, and number of previous hospitalizations. We found no difference between the three groups with regard to the body weight.

3.3. Physiological data

Physiological parameters are presented in Table 3. When we compared the three groups controlling for gender, we found that prolactin responses were lower in the MDD/AUD group compared to the MDD only or the HC group (Table 3 and Fig. 1). There was a trend ($p=0.068$) towards lower prolactin responses in the MDD only group compared to the HC group. When we fit the general linear model controlling for gender and aggression, prolactin responses in the MDD/AUD group remained significantly lower compared to the HC group, the difference between the MDD/AUD and the MDD only groups disappeared, and the difference between MDD only and HC subjects became significant. In our sample, aggression scores negatively correlated with prolactin responses to fenfluramine administration although the relationship was modest ($r=-0.21$, $p=0.01$). Prolactin responses did not correlate with other behavioral measures (data not shown). There were no differences in fenfluramine or norfenfluramine levels between the three groups.

4. Discussion

4.1. Demographic data

Higher prevalence of males among AUD/MDD subjects is consistent with reports showing that alcohol use disorders are more common in men (Grant, 1994; Harford et al., 2005). The fact that HC subjects are more educated compared to the subjects in the two patient groups is consistent with reports suggesting that persons with lower education are more frequently depressed compared to individuals with better education (Francis et al., 2007; Ross and Mirowsky, 2006; Weiss et al., 2006).

4.2. Clinical and biological data

MDD/AUD subjects had higher aggression scores and a higher prevalence of antisocial and borderline personality disorders compared to MDD subjects. We found that serotonergic responses in the MDD/AUD group were lower compared to the MDD or HC group. The difference between the MDD/AUD and MDD group disappeared after including aggression scores in the model. HC had higher prolactin responses compared to MDD/AUD subjects and, controlling for aggression, compared to MDD subjects.

4.3. Prolactin responses in the MDD/AUD group

The observation that MDD/AUD subjects have the lowest prolactin responses among the three groups is consistent with reports that dysregulation of serotonin function may contribute to the development of comorbid MDD and AUD (Heinz et al., 1998; Sher et al., 2007). Alcohol has complex actions in the brain through several serotonin receptors (Swift, 1999). Serotonin 5-HT_{1A} receptors may be associated with alcohol consumption and the development of tolerance, 5-HT₂ receptors may contribute to reward and 5-HT₃ receptors may contribute to the development of reinforcement through synaptic projections on the mesolimbic dopamine system (Lovinger, 1997; McBride et al., 2004). Serotonin and other monoaminergic neurotransmitter systems have a modulating influence on excitatory (e.g. glutamatergic) and inhibitory (e.g. GABAergic) neurons of the CNS. Studies of the serotonergic system show that compared to non-alcoholics, alcoholics and experimental animals that chronically consume large amounts of alcohol exhibit deficits in serotonin levels (Fromme and D'Amico, 1999; Heinz et al., 2001). A brain imaging study of abstinent alcoholics supported the hypothesis that serotonergic dysfunction may be associated with negative mood states, such as depression and anxiety (Heinz et al., 1998). Among male alcoholics who had abstained from alcohol for more than four weeks, serotonin transporters in the raphe area of the brainstem were significantly reduced compared with healthy control subjects. The reduction in raphe serotonin transporters correlated with the amount of lifetime alcohol intake, indicating that the reduced serotonin transporter availability may be the consequence of chronic alcohol intoxication. Alternatively, the reduced serotonin transporter availability could predispose to chronic alcohol consumption. In some other studies, serotonergic dysfunction was associated with a low alcohol response (Doudet et al., 1995; Heinz et al., 1998; Schuckit et al., 1999). Individuals with a certain genetic constitution of the serotonin transporter and a GABA-A receptor sub-unit display a low level of response to acute alcohol intoxication and an increased risk for excessive alcohol intake (Hinckers et al., 2006). A recent study found an anterior medial prefrontal cortical area where MDD/AUD subjects had more severe hypofrontality than MDD only patients as measured by a positron emission tomography study (Sher et al., 2007). This area encompassed the left medial frontal and left and right anterior cingulate gyri. This group difference disappeared after fenfluramine administration. The fact that the observed group difference disappeared after the fenfluramine challenge suggests that serotonergic mechanisms play a role in the observed differences between the groups.

4.4. Prolactin responses, aggression, and AUD

In our sample prolactin responses to fenfluramine administration correlated with aggression history scores. This is consistent with reports suggesting that blunted prolactin responses are associated with aggression (New et al., 2004). Other studies also suggest that abnormalities in central serotonergic activity are associated with measures of aggression (Coccaro, 1989; O'Keane et al., 1992; Siever and Trestman, 1993). For example, reductions of serotonergic activity as reflected in diminished cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) concentrations have been associated with impulsive aggression in depressed patients, violent alcoholic offenders, mentally ill violent offenders, patients with personality disorders and normal controls (Lidberg et al., 2000; Linnoila et al., 1989; Linnoila et al., 1994; Roy

and Linnoila, 1988; Stanley et al., 2000; Traskman-Bendz et al., 1986; Virkkunen et al., 1994).

Our finding of higher lifetime aggression scale scores in the MDD/AUD patients compared to MDD only subjects is consistent with reports linking aggression and AUD (Chermack and Taylor, 1995; Gudlaugsdottir et al., 2004; Wells et al., 2000). Association between aggression and heavy alcohol use has been documented in various populations and settings, including surveys in the general population (Gudlaugsdottir et al., 2004; Wells et al., 2000), in patients with alcohol-related problems (Fals-Stewart and Kennedy, 2005; Liebschutz et al., 2005; Mann et al., 1998; Steadman et al., 1998) and in experimental studies (Chermack and Taylor, 1995). For example, a recent study reported that aggression levels in subjects with severe alcohol problems are substantially higher than in the general population (Gerevich et al., 2007). As noted above, including aggression scores in the model eliminated the difference between the MDD only and MDD/AUD groups. Chronic alcohol intake may lead to a state of lowered central serotonergic functioning characterized by a propensity towards disinhibited behavior, thus increasing the potential for aggressive behavior. Serotonin is an important modulator within the so-called behavioral inhibition system (Gray, 1982). It has been suggested that low serotonin turnover leads to behavioral disinhibition, alcoholism, and aggression (Cloninger, 1987; Kruesi et al., 1990; Linnoila et al., 1983; Virkkunen et al., 1994). This idea is also supported by pharmacobehavioral studies in rodents relating serotonin to irritable aggression and excessive alcohol intake (Crabbe et al., 1996; Saudou et al., 1994).

Our results indicate that the difference in prolactin responses could be attributed to higher aggression scores in the MDD/AUD group compared to the MDD group. The inclusion of aggression scores in the model eliminates the difference between MDD only and MDD/AUD because aggression scores negatively correlate with prolactin responses which reflects a link between serotonin function and aggression. Given the evidence linking low serotonergic activity separately to aggression, depression and AUD, low serotonergic activity may underlie all three conditions. Low serotonergic activity may mediate genetic and developmental effects on aggression, depression and AUD. Two causal links between aggression and AUD have been proposed: (1) individuals who develop AUD possess higher premorbid levels of aggression than those who do not develop AUD, and (2) aggression differentiates both populations, because it develops as a consequence of alcoholism (Ketzenberger and Forrest, 2000). Most likely, we observe a vicious cycle: abnormal serotonin function and increased aggression contribute to the development and maintenance of AUD and chronic heavy alcohol intake further impairs the serotonergic system and increases aggression.

Our findings of a higher prevalence of antisocial and borderline personality disorders in the MDD/AUD group compared to their counterparts are consistent with studies suggesting that antisocial and borderline personality disorders are related to a lifetime substance abuse diagnosis of either abuse or dependence (Brooner et al., 1997; Darke et al., 2004; Feske et al., 2006; Grilo et al., 1998; Morgenstern et al., 1997; Skodol et al., 1999; Zanarini et al., 1998). These results were obtained across different types of substance misuse (i.e., any alcohol or substance abuse). Several previous studies demonstrated a relationship between borderline personality disorder and substance use disorders in treatment-seeking populations with drug and/or alcohol use diagnoses (Brooner et al., 1997; Darke et al., 2004; Morgenstern et al., 1997).

We did not find a difference between the groups in the impulsivity scale. It is possible that the scale that we used is not sensitive enough to detect differences between the groups. We cannot rule out a possibility that the results of our study are influenced by group differences

in nicotine and caffeine consumption, nutrition and other factors for which we did not account.

Our study supports previous observations suggesting that MDD/AUD patients are psychobiologically distinct from MDD individuals and may need to be studied as a separate diagnostic group.

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References

- Barratt ES. Factor analysis of some psychometric measures of impulsiveness and anxiety. *Psychol. Rep.* 1965; 16:547–554. [PubMed: 14285869]
- Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch. Gen. Psychiatry.* 1961; 4:561–571. [PubMed: 13688369]
- Broner RK, King VL, Kidorf M, Schmidt CW Jr, Bigelow GE. Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. *Arch. Gen. Psychiatry.* 1997; 54:71–80. [PubMed: 9006403]
- Brown GL, Goodwin FK. Human aggression and suicide. *Suicide Life Threat. Behav.* 1986; 16:223–243. [PubMed: 2428140]
- Chermack ST, Taylor SP. Alcohol and human physical aggression: pharmacological versus expectancy effects. *J. Stud. Alcohol.* 1995; 56:449–456. [PubMed: 7674681]
- Cloninger CR. A systematic method for clinical description and classification of personality variants. A proposal. *Arch. Gen. Psychiatry.* 1987; 44:573–588.
- Coccaro EF. Central serotonin and impulsive aggression. *Br. J. Psychiatry Suppl.* 1989;52–62. [PubMed: 2692640]
- Coccaro EF, Kavoussi RJ, Cooper TB, Hauger RL. Hormonal responses to d- and d,l-fenfluramine in healthy human subjects. *Neuropsychopharmacology.* 1996; 15:595–607. [PubMed: 8946434]
- Cornelius JR, Salloum IM, Day NL, Thase ME, Mann JJ. Patterns of suicidality and alcohol use in alcoholics with major depression. *Alcohol Clin. Exp. Res.* 1996; 20:1451–1455. [PubMed: 8947324]
- Cornelius JR, Salloum IM, Mezzich J, Cornelius MD, Fabrega H Jr, Ehler JG, Ulrich RF, Thase ME, Mann JJ. Disproportionate suicidality in patients with comorbid major depression and alcoholism. *Am. J. Psychiatry.* 1995; 152:358–364. [PubMed: 7864260]
- Crabbe JC, Phillips TJ, Feller DJ, Hen R, Wenger CD, Lessov CN, Schafer GL. Elevated alcohol consumption in null mutant mice lacking 5-HT1B serotonin receptors. *Nat. Genet.* 1996; 14:98–101. [PubMed: 8782828]
- D’Souza DC, Berman RM, Krystal JH, Charney DS. Symptom provocation studies in psychiatric disorders: scientific value, risks, and future. *Biol. Psychiatry.* 1999; 46:1060–1080. [PubMed: 10536743]
- Darke S, Williamson A, Ross J, Teesson M, Lynskey M. Borderline personality disorder, antisocial personality disorder and risk-taking among heroin users: findings from the Australian TreatmentOutcome Study(ATOS). *Drug Alcohol Depend.* 2004; 74:77–83. [PubMed: 15072810]
- Doudet D, Hommer D, Higley JD, Andreason PJ, Moneman R, Suomi SJ, Linnoila M. Cerebral glucose metabolism, CSF 5-HIAA levels, and aggressive behavior in rhesus monkeys. *Am. J. Psychiatry.* 1995; 152:1782–1787. [PubMed: 8526246]
- Fals-Stewart W, Kennedy C. Addressing intimate partner violence in substance-abuse treatment. *J. Subst. Abuse Treat.* 2005; 29:5–17. [PubMed: 15979527]

- Feske U, Tarter RE, Kirisci L, Pilkonis PA. Borderline personality and substance use in women. *Am. J. Addict.* 2006; 15:131–137. [PubMed: 16595350]
- Francis L, Weiss BD, Senf JH, Heist K, Hargraves R. Does literacy education improve symptoms of depression and self-efficacy in individuals with low literacy and depressive symptoms? A preliminary investigation. *J. Am. Board Fam. Med.* 2007; 20:23–27. [PubMed: 17204731]
- Fromme, K.; D'Amico, EJ. Neurobiological bases of alcohol's psychological effects. In: Leonard, KE.; Blane, HT., editors. *Psychological Theories of Drinking and Alcoholism*. New York: Guilford; 1999. p. 422–455.
- Garattini S. Central mechanisms of fenfluramine and related anorectic drugs. *Jpn. J. Pharmacol.* 1981; 31(Suppl):29P–35P.
- Gerevich S, Bacskai E, Czobor P. Aggression levels in treatment seeking inpatients with alcohol-related problems compared to levels in the general population in Hungary. *J. Nerv. Ment. Dis.* 2007; 195:669–672. [PubMed: 17700299]
- Grant BF. Alcohol consumption, alcohol abuse and alcohol dependence. The United States as an example. 1994; 89:1357–1365. *Addiction*.
- Gray, J. *The Neuropsychology of Anxiety: An Inquiry Into the Function of the Septo-Hippocampal System*. New York: Oxford University Press; 1982.
- Grilo CM, McGlashan TH, Quinlan DM, Walker ML, Green-feld D, Edell WS. Frequency of personality disorders in two age cohorts of psychiatric inpatients. *Am. J. Psychiatry.* 1998; 155:140–142. [PubMed: 9433356]
- Gudlaugsdottir GR, Vilhjalmsdottir R, Kristjansdottir G, Jacobsen R, Meyrowitsch D. Violent behaviour among adolescents in Iceland: a national survey. *Int. J. Epidemiol.* 2004; 33:1046–1051. [PubMed: 15319410]
- Hamilton M. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry.* 1960; 23:56–62. [PubMed: 14399272]
- Harford TC, Grant BF, Yi HY, Chen CM. Patterns of DSM-IV alcohol abuse and dependence criteria among adolescents and adults: results from the 2001 National Household Survey on Drug Abuse. *Alcohol Clin. Exp. Res.* 2005; 29:810–828. [PubMed: 15897727]
- Heinz A, Mann K, Weinberger DR, Goldman D. Serotonergic dysfunction, negative mood states, and response to alcohol. *Alcohol Clin. Exp. Res.* 2001; 25:487–495. [PubMed: 11329486]
- Heinz A, Ragan P, Jones DW, Hommer D, Williams W, Knable MB, Gorey JG, Doty L, Geyer C, Lee KS, Coppola R, Weinberger DR, Linnoila M. Reduced central serotonin transporters in alcoholism. *Am. J. Psychiatry.* 1998; 155:1544–1549. [PubMed: 9812115]
- Hinckes AS, Laucht M, Schmidt MH, Mann KF, Schumann G, Schuckit MA, Heinz A. Low level of response to alcohol as associated with serotonin transporter genotype and high alcohol intake in adolescents. *Biol. Psychiatry.* 2006; 60:282–287. [PubMed: 16497275]
- Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Arch. Gen. Psychiatry.* 1997; 54:313–321. [PubMed: 9107147]
- Ketzerberger KE, Forrest L. Impulsiveness and compulsiveness in alcoholics and nonalcoholics. *Addict. Behav.* 2000; 25:791–795. [PubMed: 11023021]
- Kruesi MJ, Rapoport JL, Hamburger S, Hibbs E, Potter WZ, Lenane M, Brown GL. Cerebrospinal fluid monoamine metabolites, aggression, and impulsivity in disruptive behavior disorders of children and adolescents. *Arch. Gen. Psychiatry.* 1990; 47:419–426. [PubMed: 1691910]
- LaFerrere B, Wurtman RJ. Effect of D-fenfluramine on serotonin release in brains of anaesthetized rats. *Brain Res.* 1989; 504:258–263. [PubMed: 2480833]
- Li TK, Hewitt BG, Grant BF. The alcohol dependence syndrome, 30 years later: a commentary. the 2006 H. David Archibald lecture. *Addiction.* 2007; 102:1522–1530. [PubMed: 17680851]
- Lidberg L, Belfrage H, Bertilsson L, Evenden MM, Asberg M. Suicide attempts and impulse control disorder are related to low cerebrospinal fluid 5-HIAA in mentally disordered violent offenders. *Acta Psychiatr. Scand.* 2000; 101:395–402. [PubMed: 10823300]
- Liebschutz JM, Geier JL, Horton NJ, Chuang CH, Samet JH. Physical and sexual violence and health care utilization in HIV-infected persons with alcohol problems. *AIDS Care.* 2005; 17:566–578. [PubMed: 16036243]

- Linnoila M, De Jong J, Virkkunen M. Family history of alcoholism in violent offenders and impulsive fire setters. *Arch. Gen. Psychiatry.* 1989; 46:613–616. [PubMed: 2472125]
- Linnoila M, Karoum F, Miller T, Potter WZ. Reliability of urinary monoamine and metabolite output measurements in depressed patients. *Am. J. Psychiatry.* 1983; 140:1055–1057. [PubMed: 6191580]
- Linnoila M, Virkkunen M, George T, Eckardt M, Higley JD, Nielsen D, Goldman D. Serotonin, violent behavior and alcohol. *EXS.* 1994; 71:155–163. [PubMed: 7518265]
- Lovinger DM. Serotonin's role in alcohol's effects on the brain. *Alcohol Health Res. World.* 1997; 21:114–120. [PubMed: 15704346]
- Malone KM, Corbitt EM, Li S, Mann JJ. Prolactin response to fenfluramine and suicide attempt lethality in major depression. *Br. J. Psychiatry.* 1996; 168:324–329. [PubMed: 8833686]
- Malone KM, Waternaux C, Haas GL, Cooper TB, Li S, Mann JJ. Cigarette smoking, suicidal behavior, and serotonin function in major psychiatric disorders. *Am. J. Psychiatry.* 2003; 160:773–779. [PubMed: 12668368]
- Mann JJ, Malone KM, Diehl DJ, Perel J, Nichols TE, Mintun MA. Positron emission tomographic imaging of serotonin activation effects on prefrontal cortex in healthy volunteers. *J. Cereb. Blood Flow Metab.* 1996; 16:418–426. [PubMed: 8621746]
- Mann JJ, Waternaux C, Haas GL, Malone KM. Toward a clinical model of suicidal behavior in psychiatric patients. *Am. J. Psychiatry.* 1999; 156:181–189. [PubMed: 9989552]
- Mann K, Ackermann K, Jung M, Morlock P, Mundle G. Aggressiveness, onset of dependence, and treatment outcome in socially well-adapted alcoholics. *Alcohol Alcohol.* 1998; 33:16–19. [PubMed: 9539171]
- McBride WJ, Lovinger DM, Machu T, Thielen RJ, Rodd ZA, Murphy JM, Roache JD, Johnson BA. Serotonin-3 receptors in the actions of alcohol, alcohol reinforcement, and alcoholism. *Alcohol Clin. Exp. Res.* 2004; 28:257–267. [PubMed: 15112933]
- Mennini T, Garattini S, Caccia S. Anorectic effect of fenfluramine isomers and metabolites: relationship between brain levels and in vitro potencies on serotonergic mechanisms. *Psychopharmacology (Berl).* 1985; 85:111–114. [PubMed: 2984709]
- Morgenstern J, Langenbucher J, Labouvie E, Miller KJ. The comorbidity of alcoholism and personality disorders in a clinical population: prevalence rates and relation to alcohol typology variables. *J. Abnorm. Psychol.* 1997; 106:74–84. [PubMed: 9103719]
- New AS, Trestman RF, Mitropoulou V, Goodman M, Koenigsberg HH, Silverman J, Siever LJ. Low prolactin response to fenfluramine in impulsive aggression. *J. Psychiatr. Res.* 2004; 38:223–230. [PubMed: 15003426]
- Newman ME, Shapira B, Lerer B. Evaluation of central serotonergic function in affective and related disorders by the fenfluramine challenge test: a critical review. *Int. J. Neuropsychopharmacol.* 1998; 1:49–69. [PubMed: 11281946]
- NIAAA. Bethesda, Maryland: National Institute of Alcohol Abuse and Alcoholism; 1992. Prevalence of Alcohol Abuse and Alcohol Dependence.
- O'Keane V, Moloney E, O'Neill H, O'Connor A, Smith C, Dinan TG. Blunted prolactin responses to D-fenfluramine in sociopathy. *Br. J. Psychiatry.* 1992; 160:643–646. Evidence for subsensitivity of central serotonergic function. [PubMed: 1591573]
- Oquendo, M.; Halberstam, B.; Mann, JJ. Risk factors for suicidal behavior: utility and limitations of research instruments. In: MB, F., editor. *Standardized Assessment for the Clinician.* Washington, D.C.: APPI; 2003.
- Oquendo MA, Echavarria G, Galfalvy HC, Grunebaum MF, Burke A, Barrera A, Cooper TB, Malone KM, John Mann J. Lower cortisol levels in depressed patients with comorbid post-traumatic stress disorder. *Neuropsychopharmacology.* 2003; 28:591–598. [PubMed: 12629542]
- Oquendo MA, Kronic A, Parsey RV, Milak M, Malone KM, Anderson A, van Heertum RL, John Mann J. Positron emission tomography of regional brain metabolic responses to a serotonergic challenge in major depressive disorder with and without borderline personality disorder. *Neuropsychopharmacology.* 2005; 30:1163–1172. [PubMed: 15770239]

- Quattrone A, Tedeschi G, Aguglia U, Scopacasa F, Drenzo GF, Annunziato L. Prolactin secretion in man: a useful tool to evaluate the activity of drugs on central 5-hydroxytryptaminergic neurones. Studies with fenfluramine. *Br. J. Clin. Pharmacol.* 1983; 16:471–475. [PubMed: 6639832]
- Ratsma JE, Van Der Stelt O, Gunning WB. Neurochemical markers of alcoholism vulnerability in humans. *Alcohol Alcohol.* 2002; 37:522–533. [PubMed: 12414542]
- Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA.* 1990; 264:2511–2518. [PubMed: 2232018]
- Ross CE, Mirowsky J. Sex differences in the effect of education on depression: resource multiplication or resource substitution? *Soc. Sci. Med.* 2006; 63:1400–1413. [PubMed: 16644077]
- Roy A, Linnoila M. Suicidal behavior, impulsiveness and serotonin. *Acta Psychiatr. Scand.* 1988; 78:529–535. [PubMed: 3068956]
- Saudou F, Amara DA, Dierich A, LeMeur M, Ramboz S, Segu L, Buhot MC, Hen R. Enhanced aggressive behavior in mice lacking 5-HT1B receptor. *Science.* 1994; 265:1875–1878. [PubMed: 8091214]
- Schuckit MA, Mazzanti C, Smith TL, Ahmed U, Radel M, Iwata N, Goldman D. Selective genotyping for the role of 5-HT2A, 5-HT2C, and GABA alpha 6 receptors and the serotonin transporter in the level of response to alcohol: a pilot study. *Biol. Psychiatry.* 1999; 45:647–651. [PubMed: 10088053]
- Schwartz D, Hernandez L, Hoebel BG. Fenfluramine administered systemically or locally increases extracellular serotonin in the lateral hypothalamus as measured by microdialysis. *Brain Res.* 1989; 482:261–270. [PubMed: 2468397]
- Schwartz PJ, Murphy DL, Wehr TA, Garcia-Borreguero D, Oren DA, Moul DE, Ozaki N, Snelbaker AJ, Rosenthal NE. Effects of meta-chlorophenylpiperazine infusions in patients with seasonal affective disorder and healthy control subjects. Diurnal responses and nocturnal regulatory mechanisms. *Arch. Gen. Psychiatry.* 1997; 54:375–385. [PubMed: 9107154]
- Sher L, Milak MS, Parsey RV, Carballo JJ, Cooper TB, Malone KM, Oquendo MA, Mann JJ. Positron emission tomography study of regional brain metabolic responses to a serotonergic challenge in major depressive disorder with and without comorbid lifetime alcohol dependence. *Eur. Neuropsychopharmacol.* 2007; 17:608–615.
- Sher L, Oquendo MA, Li S, Ellis S, Brodsky BS, Malone KM, Cooper TB, Mann JJ. Prolactin response to fenfluramine administration in patients with unipolar and bipolar depression and healthy controls. *Psychoneuroendocrinology.* 2003; 28:559–573. [PubMed: 12689612]
- Sher L, Stanley BH, Harkavy-Friedman J, Carballo JJ, Arendt M, Brent D, Sperling D, Lizardi D, Mann JJ, Oquendo MA. Depressed patients with co-occurring alcohol use disorders: a unique patient population. *J. Clin. Psychiatry.* in press.
- Siever L, Trestman RL. The serotonin system and aggressive personality disorder. *Int. Clin. Psychopharmacol.* 1993; 8(Suppl 2):33–39. [PubMed: 8201245]
- Skodol AE, Oldham JM, Gallaher PE. Axis II comorbidity of substance use disorders among patients referred for treatment of personality disorders. *Am. J. Psychiatry.* 1999; 156:733–738. [PubMed: 10327906]
- Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Arch. Gen. Psychiatry.* 1992; 49:624–629. [PubMed: 1637252]
- Stanley B, Molcho A, Stanley M, Winchel R, Gameroff MJ, Parsons B, Mann JJ. Association of aggressive behavior with altered serotonergic function in patients who are not suicidal. *Am. J. Psychiatry.* 2000; 157:609–614. [PubMed: 10739421]
- Steadman HJ, Mulvey EP, Monahan J, Robbins PC, Appelbaum PS, Grisso T, Roth LH, Silver E. Violence by people discharged from acute psychiatric inpatient facilities and by others in the same neighborhoods. *Arch. Gen. Psychiatry.* 1998; 55:393–401. [PubMed: 9596041]
- Swift RM. Medications and alcohol craving. *Alcohol Res. Health.* 1999; 23:207–213. [PubMed: 10890816]
- Thase ME, Salloum IM, Cornelius JD. Comorbid alcoholism and depression: treatment issues. *J Clin Psychiatry.* 2001; 62(Suppl 20):32–41. [PubMed: 11584873]

- Traskman-Bendz L, Asberg M, Schalling D. Serotonergic function and suicidal behavior in personality disorders. *Ann. N. Y. Acad. Sci.* 1986; 487:168–174. [PubMed: 2436531]
- Virkkunen M, Rawlings R, Tokola R, Poland RE, Guidotti A, Nemeroff C, Bissette G, Kalogeras K, Karonen SL, Linnoila M. CSF biochemistries, glucose metabolism, and diurnal activity rhythms in alcoholic, violent offenders, fire setters, and healthy volunteers. *Arch. Gen. Psychiatry.* 1994; 51:20–27. [PubMed: 7506515]
- Weiss BD, Francis L, Senf JH, Heist K, Hargraves R. Literacy education as treatment for depression in patients with limited literacy and depression: a randomized controlled trial. *J. Gen. Intern. Med.* 2006; 21:823–828. [PubMed: 16881941]
- Wells S, Graham K, West P. Alcohol-related aggression in the general population. *J. Stud. Alcohol.* 2000; 61:626–632. [PubMed: 10928735]
- WHO. The world health report 2001 — Mental Health: New Understanding, New Hope. World Health Organization; 2001.
- Williams DR, Gonzalez HM, Neighbors H, Nesse R, Abelson JM, Sweetman J, Jackson JS. Prevalence and distribution of major depressive disorder in African Americans, Caribbean blacks, and non-Hispanic whites: results from the National Survey of American Life. *Arch. Gen. Psychiatry.* 2007; 64:305–315. [PubMed: 17339519]
- Zanarini MC, Frankenburg FR, Dubo ED, Sickel AE, Trikha A, Levin A, Reynolds V. Axis I comorbidity of borderline personality disorder. *Am. J. Psychiatry.* 1998; 155:1733–1739. [PubMed: 9842784]

* Log transformed, adjusted for gender

Figure 1.

Effects of fenfluramine administration on prolactin levels in MDD with co-occurring AUD (MDD/AUD), MDD without co-occurring AUD (MDD only) and healthy controls (HC).

Table 1

Demographic characteristics of depressed patients and healthy volunteers

Measure	Healthy controls		MDD only patients		MDD/AUD patients		$F (\lambda^2)$	df	P	Pairwise comparisons/ post hoc test
	Mean (%)	SD (N)	Mean (%)	SD (N)	Mean (%)	SD (N)				
Age (yr)	38.94	15.98	38.05	13.02	35.5	10.98	0.98	2,166	0.38	
Gender (% males)	(59.4%)	(19)	(36.0%)	(27)	(54.8%)	(34)	(7.13)	2	0.028	<i>a,c</i>
Married (% married)	(19.4%)	(6)	(30.7%)	(23)	(17.7%)	(11)	(3.54)	2	0.17	
Total years of education	16.47	2.16	14.68	3.48	13.89	2.49	7.39	2,152	0.001	<i>a,b</i>

^athe HC group is different from the MDD only group at $p < 0.05$,

^bthe HC group is different from the MDD/AUD group at $p < 0.05$,

^cthe MDD/AUD group is different from the MDD only group at $p < 0.05$.

Table 2

Clinical characteristics of depressed patients and healthy volunteers

Measure	Healthy controls		MDD only patients		MDD/AUD patients		$F, t (^2)$	df	P	Pairwise comparisons/ post hoc test
	Mean (%)	SD (N)	Mean (%)	SD (N)	Mean (%)	SD (N)				
Hamilton Depression Rating Scale (HDRS-17) *	1.13	1.71	22.08	5.73	20.61	5.63	183.08	2,162	<0.001	<i>a, b</i>
Beck Depression inventory *	1.97	3.52	27.37	12.06	27.35	12.03	63.08	2,142	<0.001	<i>a, b</i>
Brown-Goodwin Aggression Scale *	14.57	4.33	15.80	4.43	22.07	5.95	30.82	2,154	<0.001	<i>a, b, c</i>
Barratt Impulsivity Scale *	35.48	10.85	47.19	14.52	51.80	15.48	12.07	2,129	<0.001	<i>a, b</i>
Suicide attempt status (% attempters) *	N/A	N/A	(49.3%)	(37)	(59.7%)	(37)	1.66	1,134	0.2	
Age of onset of the first major depressive episode	N/A	N/A	28.26	14.53	24.51	9.98	-1.69	129	0.09	
Number of previous major depressive episodes	N/A	N/A	4.30	6.92	5.88	13.85	0.83	125	0.41	
Number of previous hospitalizations	N/A	N/A	1.93	3.49	2.26	4.17	0.49	130	0.63	
Borderline personality disorder *	N/A	N/A	(24.3%)	(18)	(43.3%)	(26)	5.43	1,131	0.002	
Antisocial personality disorder *	N/A	N/A	(1.4%)	(1)	(21.7%)	(13)	11.24	1,131	0.001	
Body weight (kg) *	72.19	12.47	75.83	18.60	75.21	18.43	1.88	2,158	0.16	

* Controlled for gender.

^a the HC group is different from the MDD only group at $p < 0.001$,

^b the HC group is different from the MDD/AUD group at $p < 0.001$,

^c the MDD/AUD group is different from the MDD only group at $p < 0.001$.

Table 3

Prolactin, fenfluramine, and norfenfluramine levels in depressed patients and healthy volunteers^{*}

Measure	Healthy controls (HC)		MDD only patients		MDD/AUD patients		<i>F</i>	<i>df</i>	<i>P</i>	Pairwise comparisons/ post hoc test
	Mean	SD	Mean	SD	Mean	SD				
Prolactin levels ^{***}	0.41	4.07	0.63	3.85	0.64	3.63	7.23 [*]	2,155 [*]	0.001 [*]	<i>b,c,d</i>
							6.06 ^{**}	2,146 ^{**}	0.003 ^{**}	<i>a,b</i>
Fenfluramine levels ^{***}	5.19	0.33	5.20	0.37	5.067	0.45	1.56 [*]	2,148 [*]	0.21 [*]	
Norfenfluramine levels ^{***}	3.60	0.52	3.72	0.48	3.80	0.44	1.73 [*]	2,143 [*]	0.18 [*]	

^{*} Controlled for gender.

^{**} Both gender and aggression scores are included in the model.

^{***} Log transformed.

^a the HC group is different from the MDD only group at $p < 0.05$,

^b the HC group is different from the MDD/AUD group at $p < 0.05$,

^c the MDD only group is different from the MDD/AUD group at $p < 0.05$,

^d there is a trend towards a difference between the HC group and the MDD/AUD group.