A Review of Prospective Studies of Biologic Predictors of Suicidal Behavior in Mood Disorders

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Predicting suicide is difficult due to the low base rate, even in high-risk groups, and the multi-causal nature of suicidal behavior. Clinical predictors have shown low specificity. Retrospective and cross-sectional studies have identified a number of biologic anomalies associated with suicide and suicide attempt. Prospective studies provide estimates of the predictive utility of biologic measures. Here we review prospective studies of suicidal behavior and serotonergic, noradrenergic, dopaminergic and hypothalamic-pituitary-adrenocortical axis function in mood disorders. The most promising biologic predictors are low CSF 5-HIAA and HPA axis dysfunction as demonstrated by dexamethasone non-suppression that are each associated with about 4.5 fold greater risk of suicide.

Keywords biologic predictors, biological studies, suicide

INTRODUCTION

Individuals with mood disorders have an elevated risk for suicide and suicide attempt. Identifying individuals at imminent risk for suicidal behavior is a major challenge for clinicians. However, prediction of suicidal behavior is difficult due to the relative rarity of the event as well as the multi-determined cause of such behavior. Cross-sectional and retrospective studies have identified numerous clinical risk factors for suicidal behavior including mood disorder, alcohol, and substance use disorders, cluster B category personality disorders, aggressive and impulsive traits, pessimism, and cigarette smoking (see Oquendo, Galfalvy, Russo et al. 2004 for a review). While such studies may assist in identification of individuals with elevated risk for suicidal behavior, by design they cannot address causal pathways. Nor are they directly informative with respect to predicting who is likely to engage in suicidal behavior in the future. Prospective, or follow-up, studies are better designed to develop and test predictive models (Kraemer, Gullion, Rush et al., 1994). Prospective clinical studies have identified a number of risk factors for suicidal behavior in mood disorders, however efforts to develop predictive models that are both sensitive and specific based on those factors have met with little success (see Pokorny, 1993 and Goldstein, Black, Nasrallah et al. 1991 for reviews). One possibility is that the addition of biologic predictors would enhance the predictive power of clinical models.
Biologic abnormalities in a number of systems including serotonergic, dopaminergic, noradrenergic, and the hypothalamic-pituitary-adrenal (HPA) axis have been investigated with respect to suicidal behavior (Mann, 1998). There have been fewer prospective, or follow-up, studies of biological risk factors and thus their predictive utility remains to be established. This chapter reviews prospective studies of the serotonergic and dopaminergic systems, the hypothalamic-pituitary-adrenal axis, and other neurobiological systems in relation to suicidal behavior in mood disorders, to assess the potential of biologic measures for improving the prediction of suicidal behavior.

METHODS

We searched MEDLINE, Cochrane, PsycINFO, for English language reports from 1966 to the present, using the following identifiers either alone or in combination; “prospective,” “follow-up,” “CSF 5-HIAA,” “serotonin,” “HPA axis,” “dexamethasone,” “CSF HVA,” “MHPG,” “suicide,” and “suicide, attempted.” We then reviewed reference lists of published studies for additional reports not identified by the electronic search. The search was restricted to publications in English. We included both register based studies and prospective studies using follow-up interviews. Studies included had to comprise primarily mood disorder samples or, if suicide attempter or mixed diagnosis samples, provide data on mood disorder cohorts within the sample. Where multiple reports have been published on the same cohort at different time points we included each report separately only where additional information is provided.

SEROTONERGIC SYSTEM

Over 25 years ago, Åsberg and colleagues (1976a) observed a bimodal distribution of CSF 5-hydroxyindoleacetic acid (5-HIAA) in depressed individuals. The low CSF 5-HIAA group had a higher proportion of individuals who either eventually committed suicide or had previously attempted suicide by violent means. Since this initial observation more than 20, mostly retrospective, studies have examined the relationship between CSF 5-HIAA and suicidal behavior in mood disorders (see Asberg, 1997 for a review). Fewer prospective studies have examined the relation between serotonergic function and future suicidal behavior in mood disorders.

Prospective studies of suicide completion and the serotonergic system uniformly report that low CSF 5-HIAA levels and a history of attempting suicide predict elevated risk for suicide. An early prospective study of CSF 5-HIAA and suicidal behavior from the Karolinska Institute reported that, in a sample of 68 depressed subjects, the two who completed suicide shortly after discharge from index hospitalization had lower levels of CSF-5HIAA and had made previous suicide attempts (Åsberg, Träskman, & Thorén 1976b). Three subsequent studies from that group, drawing on sometimes overlapping samples of suicide attempters, also observed a higher incidence of suicide completion during the follow-up period amongst those with low CSF 5-HIAA at index admission, compared with the high to normal CSF 5-HIAA group (Åsberg, Nordström, & Träskman-Bendz, 1986; Nordström, Samuelsson, Åsberg et al., 1994; Träskman, Åsberg, Bertilsson et al., 1981). They found that the risk of suicide was most acute in the first year following discharge from index hospitalization, documenting mortality rates from suicide of 17%–21% in the low CSF 5-HIAA group compared with 2–7% in the normal-high CSF 5-HIAA group in the first year of follow-up. Other studies likewise report that lower baseline CSF 5-HIAA in mood disorder subjects with a history of attempting suicide predict those who go on to
complete suicide (Roy, De Jong, & Linnoila 1989; Samuelsson, Jokinen, Nordstrom et al., 2006; Träskman-Bendz, Alling, Oreland et al., 1992a).

Whereas prospective studies largely concur that those with a history of attempting suicide and who have low CSF 5-HIAA are at higher risk for subsequently completing suicide, the association between CSF 5-HIAA and unsuccessful suicide attempts is less clear (see Mann, Malone, Sweeney et al. 1996 for a review). Roy et al. (1986a) despite finding no difference in baseline CSF 5-HIAA between depressed subjects who had previously attempted suicide, depressed subjects who had not made a previous attempt, and controls, found lower CSF 5-HIAA in subjects who reattempted suicide over the four year follow-up period (Roy, De Jong, & Linnoila, 1989). However the inclusion of completed suicides in the reattempting group precluded detecting a potential association between future nonfatal reattempts and low CSF 5-HIAA levels.

The Karolinska group, in two separate studies (Åsberg, Träskman, & Thorén, 1976b; Träskman, Åsberg, Bertilsson et al., 1981), observed that baseline CSF 5-HIAA of suicide completers was in the same range as those who had previously made violent attempts, or went on to make violent attempts in the follow-up period. They suggest that the association between the serotonergic system and suicidal behavior might be related to the association of low CSF 5-HIAA and poor impulse control and hence to self-directed aggression (Träskman, Åsberg, Bertilsson et al., 1981). That suggestion is consistent with reports that low CSF 5-HIAA predicts recidivism in arsonists and murderers (Virkkunen, Eggert, Rawlings et al., 1996). (See below for more discussion of this relationship). However, a more recent prospective study (Engstrom, Alling, Blennow et al., 1999) failed to replicate these results, finding no significant differences in CSF 5-HIAA levels between violent or non-violent suicide attempters, or between suicide attempters and completers (Engstrom, Alling, Blennow et al., 1999). However, only 26 of 120 attempts were rated violent in this sample, which might not have provided enough statistical power to detect a difference.

Cross-sectional and retrospective studies find little evidence for a relationship between violent method and CSF 5-HIAA (Mann & Malone, 1997). Rather, we found that both greater planning and lethality of the suicide attempt correlate with lower CSF 5-HIAA (Mann & Malone, 1997; Oquendo, Placidi, Maloney et al., 2003b; Placidi, Oquendo, Malone et al., 2001). We have suggested that the choice of a violent method has more to do with what methods are most readily available or commonly used in a society than some biologic factor that regulates suicide intent. That the time between sampling CSF and the suicide attempt did not affect the relationship to lethality (Mann & Malone, 1997) implies that CSF 5-HIAA is a biochemical trait that may predict prospectively not only suicide but also lethality of nonfatal suicidal behavior.

Suicidal acts are associated with aggressive and impulsive traits that are also associated with serotonergic dysfunction (Baca-Garcia, Diaz-Sastre, Basurte et al., 2001; Oquendo & Mann, 2000; Oquendo, Placidi, Malone et al., 2003b; Placidi, Oquendo, Malone et al., 2001). Lower levels of CSF 5-HIAA predict future aggression against property or homicide in prospective studies of alcoholic fire setters and violent offenders (Virkkunen, De Jong, Bartko et al., 1989; Virkkunen, Eggert, Rawlings et al., 1961). Moreover, a 15 year prospective study of army veterans (Faustman, Ringo, & Faull, 1993), supports the association between suicide, aggression and lower CSF 5-HIAA insofar as it found that those under 40 years of age who died by suicide, accident, or homicide, had significantly lower CSF 5-HIAA (and homovanillic acid or HVA) than living controls.
Two prospective biological studies investigating suicidal behavior and behavioral traits such as aggression and impulsivity found limited evidence of an association with platelet serotonergic markers. Verkes et al. (1997), examining the relationship between levels of platelet serotonin (5-HT) and clinical measures of mood among repeat suicide attempters with mood disorders, reported that within-subject variations of mood, self-depreciation and anger negatively correlated with platelet 5-HT. This concurs with non-prospective findings in which platelet 5-HT content correlates with past aggression severity in mood disordered subjects (McBride, Brown, De Meo et al., 1994). However, not all studies show consistent results. A 14 year follow-up study found that impulsivity, aggression, or anxiety did not distinguish future suicide attempters or suicides (Nordstrom, Gustavsson, Edman et al., 1996), and did not correlate with CSF 5-HIAA. In contrast, in the short term (3 years following index evaluation) survival time correlated negatively with anxiety and impulsivity and positively with socialization and CSF 5-HIAA, suggesting that greater anxiety and impulsivity, and low socialization and low CSF 5-HIAA, predict greater short-term suicide risk (Nordström, Schalling, & Åsberg, 1995).

The relationships between impulsivity, aggression, the serotonergic system and suicidal behavior are complex. In non-prospective studies we have found lower CSF 5-HIAA and more highly lethal suicidal behavior associated with greater planning and less impulsivity (Placidi, Oquendo, Malone et al., 2001), while low lethality attempts involve less planning and CSF 5-HIAA levels comparable to nonattempters with major depression (Mann, Malone, Sweeney et al., 1996; Träskman-Bendz, Alling, Oreland et al., 1992a). Lower CSF 5-HIAA was also associated with severity of lifetime aggressivity and a history of higher lethality suicide attempt (Mann, Malone, Sweeney et al., 1996; Placidi, Oquendo, Malone et al., 2001; Träskman-Bendz, Alling, Oreland et al., 1992a). Prospective studies of these associations would be instructive. It is likely that our definitions of impulsiveness and aggressive traits need to be refined. Perhaps greater suicide intent correlates with greater aggressive intent, but inversely with impulsiveness. This would imply that the serotonin system deficiency is related to the intent rather than the impulsiveness, or that different parts of the serotonin system modulate intent and impulsiveness, as we have reported in depressed suicide attempters using positron emission tomography, or PET, scanning (Oquendo, Placidi, Malone et al., 2003b). The causal relationship between lower serotonin function and aggressive or impulsive behaviors is demonstrated by the increase in aggressiveness and impulsiveness following lowering serotonin function transiently by acute tryptophan depletion in healthy male volunteers (Cleare & Bond, 1995; Moeller, Dougherty, Swann et al., 1996; Salomon, Mazure, Delgado et al., 1994). Clearly the same kind of study would be unethical in those at risk for suicidal behavior.

Clinical prospective studies have suggested that risk for suicidal acts might be associated with phases of depressive episodes or subtype of depressive disorder (Berglund & Nilsson, 1987; Brinkman-Sull, Overholser, & Silverman, 2000; Coryell, Haley, Endicott et al., 2002; Leon, Keller, Warshaw et al., 1999). The finding of a serotonergic abnormality in euthymic patients with a history of major depression, as shown by a depressive response to tryptophan depletion (Delgado, Price, Miller et al., 1994; Heninger, Delgado, Charney et al., 1992; Moreno, Gelenberg, Heninger et al., 1999; Price et al., 1991; Smith, Morris, Friston et al., 1999) and a blunted prolactin response to serotonin release by fenfluramine during remission (Flory, Mann,
Manuck et al., 1998; Smith, Morris, Friston et al., 1999), suggests that an abnormality in serotonergic function may underlie the predisposition to recurrent episodes of major depression. A prospective study of CSF 5-HIAA across the course of depressive illness found that, while it increases on recovery, levels remained lower in subjects who showed the lowest levels during a depressive episode compared to those with higher levels during a depressive episode who recovered to the same degree as healthy volunteer controls (Träskman-Bendz, Åsberg, Bentilsson et al., 1984). It is critical to note that the abnormalities in serotonergic function associated with suicidal behavior can be distinguished from those of a major depressive episode = disorder (Mann, Huang, Underwood et al., 2000). Thus, those that have mood disorders have a widespread abnormality in serotonin function affecting most of the prefrontal cortex and many other cortical and subcortical areas (Milak, Parsey, Keilp et al., 2005). In contrast, the abnormality in post-mortem brain tissue from suicides, or in depressed suicide attempters identified by PET, is localized to parts of the prefrontal cortex, perhaps reflecting those brain regions involved in suicide intent, decision-making, and impulse regulation (Oquendo, Placidi, Malone et al., 2003b). The generalizability of this localized serotonin system deficit and suicidal behavior is demonstrated by low CSF 5-HIAA characterizing suicide attempters with schizophrenia or personality disorders compared to psychiatric controls (Brown, Ebert, Goyer et al., 1982; Cooper, Kelly, & King, 1992; Gardner, Lucas, & Cowdry, 1990; Ninan, van Kammen, Scheinin et al., 1984).

In a recent longitudinal genetic study, Caspi et al. (2003) found a functional polymorphism in the promoter region of the serotonin transporter (5-HTT) was associated with the likelihood of developing major depression and suicidality in relation to stressful life events. Individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism had a higher incidence of depression and suicidality in relation to recent stressful life events than individuals homozygous for the long allele. Moreover, childhood maltreatment predicted adult depression only among those carrying the short allele. Thus, the role of the serotonergic system in suicidal behavior as well as mood disorders may be mediated by genetic and environmental factors. More recent studies have mostly replicated the findings related to mood disorders but not suicidal behavior (see Zalsman, 2002, for a review).

**Dopaminergic System**

Abnormality in the dopaminergic system has been documented in major depression (for reviews see Mann & Kapur, 1995, and Dailly et al., 2004), however post-mortem and retrospective studies of dopaminergic function and suicidal behavior are few and inconclusive (see Mann, 2003).

Prospective studies of dopaminergic system function and the prediction of suicidal behavior have also produced divergent findings. Roy and colleagues, in two separate studies, found that those with a history of attempting suicide had lower CSF homovanillic acid (HVA), a dopamine metabolite, (Roy, Ågren, Pickar et al., 1986a), and urinary HVA (Roy, Karoum, & Pollack, 1992) output at baseline compared with those who had never attempted and controls. Additionally, lower urinary dihydroxyphenylacetic acid (DOPAC) and dopamine were found in those who had previously attempted suicide. On follow-up 5 years later, those with prior attempts who reattempted or completed suicide, had lower baseline CSF HVA (Roy, De Jong, & Linnoila, 1989), urinary HVA, DOPAC and dopamine levels (Roy, Karoum, & Pollack, 1992) compared to those who made no further attempts, had
never attempted, and controls. The association between HVA and 5-HIAA in CSF is addressed below.

Other prospective studies do not find CSF HVA predicts suicide (Engstrom, Alling, Blennow et al., 1999; Nordström, Samuelsson, Åsberg et al., 1994) or correlates with clinical factors related to suicide such as depression, aggression or impulsivity. Repeating lumbar punctures to record monoamine levels across the course of illness, Traskman-Bendz et al. (1984) found no significant difference in CSF HVA within subjects between depressed and recovered states suggesting that CSF HVA is a mood state independent biochemical trait.

Prospective studies have not found compelling evidence of a relation between aggression and low CSF HVA. Virkkunen (1996) found low CSF HVA associated with paternal violence and alcoholism in a sample of male alcoholic violent offenders and fire setters, while Soderstrom and colleagues (2001) reported high CSF HVA correlated with measures of psychopathic violence and aggression, although in that and a later study, the ratio of CSF HVA\(\div\)5-HIAA presented the strongest correlation (Soderstrom, Blennow, Manhem et al., 2001; Soderstrom, Blennow, Sjödin et al., 2003). No correlation of CSF HVA with life-time severity of aggression or impulsivity has been observed in non-prospective studies (Placidi, Oquendo, Malone et al., 2001).

**CSF HVA/5-HIAA RATIO**

Monoamine studies have found, in some cases, that the ratio between metabolites shows a stronger association with suicidal behavior, although the predictive value of these ratios is unclear. Such a ratio factors out common variance due to characteristics such as the shared CSF transport system and effects on monoamine metabolites levels related to CSF gradient due to variation in length of the spinal canal.

Engstrom et al. (1999) found lower HVA/5-HIAA and HVA/MHPG ratios in past suicide attempters compared with surgical controls at baseline, although no differences were apparent on follow-up between attempters and those who completed suicide. Roy, Ågren, Pickar et al. (1986a) also found lower baseline CSF HVA/5-HIAA ratio in depressed subjects compared to controls. Moreover, among depressed subjects who had made prior suicide attempts, dexamethasone suppression test (DST) non-suppressors had a significantly lower mean CSF HVA/5-HIAA ratio than suppressors. They suggest that depressed patients who attempt suicide may have a more marked imbalance between the turnover of dopamine and serotonin in terms of relatively lower dopaminergic activity or turnover. Non-prospective studies of violent offenders have reported significant correlations between CSF HVA/5-HIAA ratio and psychopathic traits of aggression and violence, likewise suggesting dysfunction in the relative activity of the two systems (Soderstrom, Blennow, Manhem et al., 2001; Soderstrom, Blennow, Sjödin et al., 2003).

**Noradrenergic System**

Abnormal functioning in the noradrenergic system has been associated with both major depression and suicidal behavior. Post-mortem studies of the noradrenergic system have observed fewer noradrenergic neurons in the locus coeruleus in the brainstem in depressed suicide victims (Arango, Underwood, & Mann, 1996), along with indications of cortical noradrenergic overactivity such as lower alpha and high affinity beta1-adrenergic receptor binding (Arango, Ernsberger, Sved et al., 1993). While data are limited on the role of the noradrenergic system in suicidal behavior (see Mann, 2003), severe anxiety or agitation increase suicide risk and are associated with noradrenergic overactivity (Fawcett, Busch, Jacobs et al., 1997).
Prospective studies of noradrenergic function in suicidal behavior have examined CSF 3-methoxy-4-hydroxyphenylglycol (MHPG), a major metabolite of norepinephrine. Two studies (Engstrom, Alling, Blennow et al., 1999; Nordström, Samuelsson, Åsberg et al., 1994) found no predictive value for CSF MHPG in terms of identifying previous attempters at risk of eventual suicide completion. Other studies suggest that higher CSF MHPG may predict future risk. Träskman-Bendz et al. (1992a) reported that all four completers, in a group of 61 previous attempters, had baseline CSF MHPG higher than the median. Violent attempts were associated with CSF MHPG above the median and a statistically nonsignificant trend towards higher levels in those with repeat attempts after index evaluation was observed. The possibility that increased noradrenergic activity may predict suicidal behavior is supported by the outcome of a treatment study of a noradrenergic reuptake inhibitor (NRI), maprotiline, demonstrating that those maintained on the NRI after remission of the depressive episode have higher rates of suicidal behavior than those on placebo despite a lower likelihood of relapse (Rouillon, Phillips, Serrurier et al., 1989).

Hypothalamic-Pituitary-Adrenal Axis

Major depression is associated with hyperactivity of the HPA axis (Carroll, Feinberg, & Greden, 1981a), particularly more severe or psychotic or psychomotor agitated depression (Brown, Stoll, Stokes et al., 1988), features that increase suicide risk. Suicidal patients in diagnostically heterogeneous populations exhibit HPA axis abnormalities, most commonly dexamethasone resistance (Brunner, Stalla, Stalla et al., 2001; Bunney, Jr., Fawcett, Davis, 1969; Coryell & Schlesser, 2001; Inder, Donald, Prickett et al., 1997; Melzner, Perline, Tricou et al., 1984; Nemeroff, Owens, Bissette et al., 1988; Roy, 1992; Träskman-Bendz, Ekman, Regnell et al., 1992b; van Heeringen, Audenaert, Vande et al., 2000). Prospective biological studies of suicidal behavior have investigated HPA function using both urinary measures of cortisol and the dexamethasone suppression test (DST).

Dexamethasone Suppression Test

Seven of nine prospective reports on the DST in mood disordered samples, which included both previous suicide attempters and non- attempters, reported that the majority of subjects who completed suicide over the course of the study were DST non-suppressors (Boza, Milanes, Llorente et al., 1988; Carroll, Greden, & Feinberg et al., 1981b; Coryell, 1990; Coryell & Schlesser, 1981; Norman, Brown, Miller et al., 1990; Roy, Ågren, Pickar et al., 1986a; Yerevanian, Olafsdottir, Milanese et al., 1983) while two studies found no relation (Black, Monahan, & Winokur, 2002; Träskman-Bendz, Alling, & Oreland et al., 1992a). Coryell and Schlesser (2001) estimated that DST non-suppressors had a 14 fold higher risk of suicide compared to suppressors, over a 15 year follow-up period. They note that the next most powerful predictor, a prior serious suicide attempt, indicated only a threefold increase in risk.

With respect to suicide attempts, consistent with retrospective studies (Brown, Mason, Stoll et al., 1986; Modestin & Ruef, 1987; Secunda, Cross, Koslow et al., 1986), prospective studies have found that DST suppression status and level of post dexamethasone plasma cortisol, do not differentiate between those who will attempt suicide from those who will not (Black, Monahan, & Winokur, 2002; Norman, Brown, Miller et al., 1990; Roy, 1992; Roy, Pickar, Linnoila et al., 1986b).

Three of seven studies found an association between DST non-suppression and seriousness of suicide attempts at baseline (Norman, Brown, Miller et al., 1990; Targum, Rosen, & Capodanno, 1983),
and over the follow-up period (Coryell, 1990). The definition of a serious attempt varied across the studies. Attempts prior to baseline resulting in high medical damage (Norman, Brown, Miller et al., 1990) and necessitating hospitalization (Targum, Rosen, & Capodanno et al., 1983) were designated serious and were associated with DST non-suppression. In the third study, DST non-suppressors were more likely to make a psychologically, rather than medically, serious attempt in follow-up (Coryell, 1990). Three further studies (Carroll, Gredden, & Feinberg, 1981b; Roy, 1992; Träskman-Bendz, Alling, Oreland et al., 1992a) noted baseline associations between violent method in attempts and HPA abnormalities, however, only one achieved statistical significance. In that study Roy (1992) found that previous violent attempters had significantly higher maximum post DST plasma cortisol levels than previous nonviolent attempters at baseline, but no significant differences were observed between attempters, violent or not, and non-attempters during a 5 year follow-up.

A prospective study of DST and suicide attempts found paradoxically that suppressors had a higher rate of suicide attempts both prior to and after entry into the study (Black, Monahan, & Winokur, 2002). This larger study (N = 432), included the early sample of Coryell and Schlesser (2001) that found more suicide completers in DST non-suppressors consistent with that group having made more serious suicide attempts. The reason for the divergent findings between these two studies is unclear. Another study found a twofold higher risk for suicide attempt in non-suppression, however this was only a trend toward significance (Yerevanian, Feusner, Koek et al., 2004). In that study individuals who were DST non-suppressors were also more likely to have been hospitalized for suicidal ideation than DST suppressors, but that could have been related to severity of depression.

Non-suppression on the DST may be associated with suicide because it predicts a failure to respond to antidepressant treatment or a tendency for early relapse such as shortly after discharge. Evidence from prospective studies exists for both possibilities. Two prospective studies (Targum, 1984; Yerevanian, Olafsdottir, Milanese et al., 1983) have noted that non-suppressors, particularly those who fail to normalize over the course of inpatient treatment, have worse outcomes in terms of remission and relapse, circumstances which clinical follow-up studies have suggested elevate risk for future suicidal acts (Oquendo, Kamali, Ellis et al., 2002). Targum et al. (1983) found that MDD subjects who normalized during treatment had the same relapse rate as non-suppressor psychiatric controls, while those who did not normalize had higher incidences of relapse and poorer response to treatment compared to normalizers. Similarly, Yerevanian et al. (1983) reported that of ten MDD non-suppressors who had not normalized by discharge from index hospitalization, two had committed suicide, three required readmission within three weeks, and the remainder still showed RDC diagnoses of Major and Minor Depression after 8 months. In comparison, three of the four subjects who had normalized had no RDC diagnosis after 18 months follow-up.

Other Measures of HPA Function

Bunney et al. (1969) found that of 36 depressed subjects, five of seven suicide completers and two subjects who made further serious attempts all had elevated urinary levels of 17-hydroxycorticosteroids (17-OHCS), > 10 mg/24 hr. in men and > 8 mg/24 hr. in women. Subsequent studies by Fink and Carpenter (1976) and Levy and Hansen (1969) failed to replicate those findings, but their samples included few suicides (N = 2 suicides) and their subjects had mixed diagnoses. A follow-up study
of urinary cortisol in a sample of 20 suicide attempters (Träskman-Bendz, Alling, Oreland et al., 1992a) reported that three of four completed suicides had urinary cortisol levels above the median of 160 nmol/l and also found that reattempters more often had levels below median.

In a pre-DST study of plasma cortisol in subjects hospitalized for suicide attempt, threats or ideation, Krieger (1974) observed higher morning plasma cortisol in those who subsequently committed suicide. In other indices of HPA activity, depressed adolescents who attempted suicide during a 10 year follow-up period had elevated pre-sleep cortisol compared to depressed non-attempters and healthy controls (Mathew, Coplan, Goetz et al., 2003). CSF corticotropin-releasing hormone (CRH) level failed to distinguish between suicide attempters, reattempters, and never attempters (Roy, Karowm, & Pollack, 1992), and failed to correlate with clinical improvement (Westrin, Ekman, Ragnéll et al., 2001). CSF somatostatin was found to increase in conjunction with clinical improvement and amongst subjects who made no repeat suicide attempts in the year following index attempt (Westrin, Ekman, Ragnéll et al., 2001). Whether some of the inconsistencies in the ability of HPA axis measures to predict suicidal acts are related to effects of the presence of comorbid PTSD or histories of childhood abuse has recently been raised (Oquendo, Echavarria, Galfalvy et al., 2003a).

**Thyroid Axis**

In one of the two prospective studies of thyroid activity in depressed subjects, Linkowski et al. (1983) followed up 51 females hospitalized for a depressive disorder measuring thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH). At baseline, no differences were observed between those who had or had not made a prior suicide attempt, or those who had made a recent attempt and those who had made a suicide attempt some time ago. However, on follow up, all four suicide completers (three of which used violent methods) had a blunted TSH response to TRH. Reporting on a slightly enlarged group one year later (Linkowski, Van Wettere, Kerkhofs et al., 1984) they found that five of the seven suicide completers had lower TSH response compared with four subjects who died of natural causes. Targum (1984) studying thyroid dysfunction in 86 MDD subjects, found that those who had continuing blunted TSH responses to repeated TRH tests over the course of a 6 month follow-up period were more likely to show a poor response to treatment and a higher relapse rate, than those who normalized, or were normal from the outset. As with the DST, persistence of a blunted TSH response to TRH may predict relapse or poor response of the mood disorder to treatment and hence greater risk of suicidal behavior.

**Other Biological Measures**

To examine the relationship between aggression and abnormal glucose in depressed suicide attempters Verkes et al. (1998) took repeated blood samples from 106 repeat suicide attempters over a one year follow-up period. There was no correlation between fructosamine and intra-subject variations in depressed mood, self-depreciation, and anger. Intra-subject fructosamine levels and platelet serotonin content were positively correlated, however the study did not report on suicidal behavior in relation to that correlation.

Roy (1993) observed no differences at baseline, or after 5 year follow-up between suicide attempters, repeat attempters, and never attempters, all with major depression, in a range of CSF neuropeptides including, neuropeptide Y, somatostatin, dizepam-binding inhibitor, GABA, and CRH.
Biological Markers and the Prediction of Future Suicidal Behavior

Developing sensitive prediction models for suicidal behavior is crucial for prevention but remains a difficult task due to the multiplicity of contributory risk factors and the low base rate of suicidal behavior. Anomalies in several biological systems have been associated with suicidal behavior in mood disorders and prospective biological studies, and, while not yet conclusive, have suggested some potential for prediction based on biological measures. A metaanalysis of prospective studies findings on suicide and CSF 5-HIAA levels and dexamethasone suppression in the HPA axis yielded odds ratios for prediction of suicide of 4.48 and 4.65 respectively (Mann, Currier, Stanley et al., 2006). Given the multi-causal nature of suicidal behavior no one biological index will be adequate to predict suicidal behavior, however multiple biological tests could be included in a prediction model, for example CSF 5-HIAA and dexamethasone response, in order to assess both trait and state related risks (Mann, Currier, Stanley et al., 2006). Using one or more tests is a trade-off of sensitivity (requiring a positive result on any single test) versus specificity (requiring a positive result on more than one test). Therefore, how such biological tests can be integrated into multi-variate predictive models alongside clinical and genetic risk factors to develop still more sensitive and specific predictive models, is a major challenge for this field of research.

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REFERENCES


