

# Can biological tests assist prediction of suicide in mood disorders?

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## Abstract

Predicting suicide is difficult due to its low base-rate and the limited specificity of clinical predictors. Prospective biological studies suggest that dysfunctions in the serotonergic system and hypothalamic–pituitary–adrenal axis have some predictive power for completed suicide in mood disorders. A prediction model that incorporates biological testing to increase specificity and sensitivity of prediction of suicide is of potential clinical value. Meta-analyses of prospective biological studies of suicide and cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) and suicide and the dexamethasone suppression test (DST) in mood disorders using the penalized quasi-likelihood (PQL) and bootstrap method yield odds ratios for prediction of suicide of 4.48 and 4.65 respectively. Two combinatory prediction models, the first requiring positive results on more than one test, and the second requiring a positive result on either one of two tests, were tested to assess their sensitivity, specificity, and predictive power using biological data from published and unpublished studies. The prediction model that requires both DST and CSF 5-HIAA tests to be positive results in 37.5% sensitivity, 88% specificity, and has a positive predictive value of 23%. The prediction model that requires either DST or CSF 5-HIAA tests to be positive results in 87.5% sensitivity, 28% specificity, and has a positive predictive value of 10%. Thus, models attempting to predict a lethal outcome that is uncommon perform very differently making model choice of major importance. Further work on refining biological predictors and integration with clinical predictors is needed to optimize a model to predict suicide in the clinic.

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## Background

Suicide is a major cause of mortality worldwide and the leading cause of death in young people in several countries (WHO, 2001). Mood disorders are associated with ~60% of suicides. However, even in higher risk groups such as major depression the incidence of completed suicide is low, making prediction in individual patients difficult. Retrospective and cross-sectional studies can identify correlations between clinical and biological factors and suicidal behaviour, but such a study design cannot test predictive properties or ascertain causal relationships. Prospective studies offer the most effective means of testing the predictive

power of such correlations (Kraemer et al., 1994). Prospective clinical studies have identified a number of risk factors for suicidal behaviour in mood disorders, however, efforts to develop a sensitive and specific predictive model based on those factors have met with little success (see Goldstein et al., 1991 and Pokorny, 1983, 1993 for reviews).

One difficulty in predicting suicide is that most suicide risk factors, when viewed as screening tests, have low specificity (Cohen, 1986). Because suicide is lethal it is important to maximize sensitivity to avoid missing as few cases as possible, however, that risks inclusion of an overwhelming number of non-suicides unless specificity is very high. Low specificity combined with the low base-rate of suicide makes the positive predictive value (PPV) (the proportion of individuals who test positive and actually complete suicide) of individual risk factors low. The problem of lack of specificity of individual risk factors might be

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reduced if risk factors could be used in combinations such that each additional risk factor introduces significant new risk information and updates risk estimates (known as sequential Bayesian updating of priors). To accomplish this the risk factors chosen need to be somewhat independent of each other. The stress-diathesis model of suicidal behaviour is compatible with such an approach insofar as the distribution of the stressor risk factors in the population is believed to be largely independent of the diathesis risk factors (Mann, 2003), and thus, overall risk is factored into (largely) independent risk categories. Candidate biological markers have been proposed for each of those categories; serotonergic dysfunction as a marker of the presence of the diathesis, and hypothalamic–pituitary–adrenal (HPA) axis dysfunction as a marker of acute stress response (Mann, 2003).

Prospective studies of the serotonergic system using measures of 5-hydroxyindoleacetic acid in cerebrospinal fluid (CSF 5-HIAA) uniformly report that the majority of subjects who complete suicide during the follow-up period have CSF 5-HIAA levels below the median, which ranges between studies from <78 pmol/ml to <96 pmol/ml (Åsberg et al., 1976, 1986; Nordström et al., 1994; Roy et al., 1989; Träskman et al., 1981; Träskman-Bendz et al., 1992). Meta-analysis of 27 reports, both prospective and retrospective, by Lester (1995) found suicide attempters, particularly those who use violent methods, had low CSF 5-HIAA compared to psychiatric controls. Moreover, prospective (Faustman et al., 1993; Virkkunen et al., 1989, 1996), and other (Baca-Garcia et al., 2001; Brown et al., 1982; Coccaro et al., 1989; Placidi et al., 2001; Oquendo and Mann, 2000; Oquendo et al., 2003) studies, have reported associations between serotonergic dysfunction and aggressive and impulsive traits that are thought to be a clinical aspect of the diathesis for suicidal behaviour (Mann et al., 1999). CSF 5-HIAA is relatively stable and under substantial genetic control (Rogers et al., 2004). As such, it is a biochemical trait that can potentially predict both aggressive and suicidal behaviour. Post-mortem studies have also demonstrated a role for serotonergic dysfunction in completed suicide (Mann, 2003; Stanley et al., 1983).

Most (Boza et al., 1988; Carroll et al., 1981; Coryell and Schlessner, 1981, 2001; Norman et al., 1990; Roy et al., 1986; Targum et al., 1983; Yerevanian et al., 1983), but not all (Black et al., 2002; Träskman-Bendz et al., 1992), prospective studies of suicidal behaviour and HPA axis function in mood disorder subjects using the dexamethasone suppression test (DST) found that those who complete suicide during follow-up are

more likely to be DST non-suppressors. A published meta-analysis of DST studies finds non-suppression associated with completed suicide (Lester, 1992). HPA axis dysfunction has been associated with severity and poorer outcome of a major depressive episode, and may be a potential state-dependent marker for unstable mood disorder and suicide risk (see Mann, 2003 for a review). Prospective studies have observed that DST non-suppressors with major depression, particularly those who fail to normalize over the course of in-patient treatment, have worse outcomes in terms of remission and relapse (Targum, 1984; Yerevanian et al., 1983), circumstances which clinical follow-up studies find elevate risk for future suicidal acts (Oquendo et al., 2002).

In this study, we explore the predictive potential of two biological markers through meta-analyses of prospective biological studies of CSF 5-HIAA and the DST. Despite the bi-directional relationship of components of serotonin function and the HPA axis (Meijer and De Kloet, 1998), within the stress-diathesis model of suicidal behaviour we find these indices of the central serotonergic system and HPA axis are relatively independent elements, and therefore, we use them to test a preliminary predictive model that combines multiple orthogonal predictors. Such an approach may better identify individuals in need of closer monitoring and more intensive treatment to prevent suicidal behaviour in the short-term.

## Methods

### Meta-analyses

Relevant primary studies for the meta-analyses were identified through an electronic MEDLINE search using the search terms 'prospective', 'follow-up', 'CSF 5-HIAA', 'serotonin', 'HPA axis', 'dexamethasone', and 'suicide', and by searching reference lists of published studies for reports not identified by the electronic search. The search was restricted to studies of mood disorder subjects and publications in English. We identified 12 prospective reports on CSF 5-HIAA (Åsberg et al., 1976, 1986; Engstrom et al., 1999; Faustman et al., 1993; Nordström et al., 1994, 1995; Roy et al., 1986, 1989; Träskman et al., 1981; Träskman-Bendz et al., 1984, 1992; Virkkunen et al., 1996) and 13 prospective reports on DST (Boza et al., 1988; Black et al., 2002; Carroll et al., 1981; Coryell, 1990; Coryell and Schlessner, 1981, 2001; Norman et al., 1990; Roy, 1992; Roy et al., 1986; Targum, 1984; Targum et al., 1983; Träskman-Bendz et al., 1992; Yerevanian et al., 1983). To be included in the meta-analyses studies had

Table 1. Prospective studies of completed suicide and CSF 5-HIAA levels

Study	Subjects	Follow up	Suicides	Time of suicides	Low CSF 5-HIAA	Suicides low/high CSF 5-HIAA*	Non-suicides low/high CSF 5-HIAA	OR (95% CI)
Åsberg et al. (1976)	<i>n</i> = 68 depressed	Unspecified	<i>n</i> = 2	1 during index, 1 'several months' after index	<78 pmol/ml	2/0	18/48	13.10 (0.6–286)
Åsberg et al. (1986)	<i>n</i> = 45 non-psych. attempters <i>n</i> = 76 psych. attempters	1 yr	<i>n</i> = 8	Within 1 yr of index	<90 pmol/ml	7/1	27/41	10.62 (1.24–91.34)
Nordström et al. (1994)	<i>n</i> = 92 mood disorder <i>n</i> = 27 depressed	14 yr	<i>n</i> = 14	1st yr: 11 suicides	<87 pmol/ml	9/5	37/41	1.99 (0.61–6.49)
Roy et al. (1986) Population	<i>n</i> = 27 depressed	1 yr	<i>n</i> = 4	Within 1 yr of index	<75 pmol/ml	3/1 21/7	10/13 92/140	3.90 (0.35–43.37) 4.48 (1.84–13.6)†

OR, Odds ratio; CI, confidence interval.

\* High/low CSF 5-HIAA group based on individual studies designation of high/low.

† Computed from PQL analysis and bootstrap.

to: (a) be prospective; (b) report completed suicides; and (c) have samples comprised of individuals with mood disorders. Additionally, for the CSF 5-HIAA meta-analysis, reports had to define high and low CSF 5-HIAA groups, and report to which CSF 5-HIAA group non-suicides as well as suicides belonged. Four of the twelve studies met these criteria (Table 1). For inclusion in the DST meta-analysis, reports had to include both suppressors and non-suppressors, and report DST results for both suicides and non-suicides. Seven of the twelve studies met these criteria (Table 2). All studies which met inclusion criteria were included without regard to positive or negative findings. The majority of studies were excluded because they were earlier reports on the same sample or a subsample of an included study (Engstrom et al., 1999; Nordström et al., 1995; Roy, 1989; Targum, 1984; Träskman et al., 1981; Träskman-Bendz et al., 1984, 1992). The remaining studies were excluded because they included insufficient data.

The differing follow-up durations in the source studies initially suggested that the suicide 'rate' in each study would be the variable of interest. However, we observed that where data on time of suicide were reported, the majority of suicides were clustered in a similar time period of within 12 months following index admission (25 of 28 in CSF 5-HIAA studies, and 5 of 6 in the DST studies) (see Tables 1 and 2). As the number of suicides in these studies did not appear to depend on the duration of follow-up, we used the absolute counts of subjects in the four combinations of group and outcome (high/low CSF 5-HIAA and suicide/non-suicide, DST suppressor/non-suppressor and suicide/non-suicide) in the analyses without analysing time-related factors. Median CSF 5-HIAA level is the commonest method used in the published studies included here for delineating high and low groups across the studies and, thus, was utilized as a uniform method across all studies (Table 1 gives median level for each study). DST non-suppression is defined in the majority of studies as  $>5 \mu\text{g}/\text{dl}$ , with two exceptions which use  $>6 \mu\text{g}/\text{dl}$  (see Table 2), a difference sufficiently small as to be acceptable.

We analysed the meta-data using a mixed-model approach to take into account the fact that each study has specific features that affect its results. To capture this fact mathematically, the studies included in each analysis are each considered to represent a random sample from a hypothetical population of similar studies. Thus, the specific features of each study, such as differences in study populations, are regarded as

**Table 2.** Prospective studies of completed suicide and dexamethasone suppression test response

Study	Subjects	Follow up	Suicides	Time of suicides from index	Time of plasma cortisol reading	Non-suppression	Suicides: Non-sup/Sup	Non suicides: Non-sup/Sup	OR (95% CI)
Black et al. (2002)	<i>n</i> = 432 mood disordered	2–5 yr	<i>n</i> = 11	Not given	08:00, 16:00	> 5 $\mu$ g/l/dl at either reading	6/5	172/240	1.67 (0.5–5.58)
Coryell and Schlessler (2001)	<i>n</i> = 78 affective disorder	2–15 yr	<i>n</i> = 8	Not given	08:00, 16:00	> 5 $\mu$ g/l/dl at either reading	7/1	25/45	12.6 (1.47–108.34)
Coryell and Schlessler (1981)	<i>n</i> = 243 MDD in-patients	0–3 yr	<i>n</i> = 5	Not given	08:00	> 5 $\mu$ g/l/dl*	4/1	92/146	6.34 (0.7–57.68)
Targum et al. (1983)	<i>n</i> = 49 depressed	6 mo.	<i>n</i> = 1	10 d	16:00, 23:30	> 5 $\mu$ g/l/dl at either reading	1/0	22/26	3.53 (0.14–91.09)
Boza et al. (1988)	<i>n</i> = 13 depressed alcoholics	6 yr	<i>n</i> = 2	Within 1 yr and within 2 yr	11:00, 16:00	> 6 $\mu$ g/l/dl†	2/1	1/9	31.66 (0.97–1038.9)
Roy et al. (1986)	<i>n</i> = 27 depressed	1 yr	<i>n</i> = 4	Within 1 yr	16:00, 23:00	> 5 $\mu$ g/l/dl	3/1	11/12	3.27 (0.29–36.31)
Carroll (1981)	<i>n</i> = 23 depressed and other psych. diag.	6 yr	<i>n</i> = 8	Not given	08:00, 16:00, 23:00	> 6 $\mu$ g/l/dl†	5/3	4/10	4.16 (0.66–26.29)
Population							28/11	347/488	4.65 (3.48–12.69)‡

OR, Odds ratio; CI, confidence interval.

\* As described in Schlessler et al. (1980).

† As described in Carroll et al. (1976).

‡ Computed from PQL analysis and bootstrap.

random. Our analyses were carried out using the penalized quasi-likelihood (PQL) method outlined in Platt et al. (1999). In order to make more accurate inferences, we calculated  $p$  values and confidence intervals (CIs) using parametric bootstrap (Efron and Tibshirani, 1993). In particular, for both CSF 5-HIAA and DST studies, we calculated a 95% CI for the overall odds ratio (OR) and also a 95% CI for the OR of a randomly chosen study from the appropriate hypothetical population of studies. We used funnel plots (Egger and Smith, 1995) to check for publication bias, including the test for funnel-plot asymmetry proposed by Egger et al. (1997). To assess the degree to which the results depended on just one study, we estimated the overall ORs from the data obtained by leaving out each study in turn.

### Prediction models

Given the difficulties that the low incidence of suicide presents to prediction, in order to test the predictive utility of a sequential or combinatorial approach in the largest sample possible we compiled data for 123 subjects comprised of Roy et al.'s (1986) published sample of 27 subjects and 67 subjects previously reported on by our group (Placidi et al., 2001) for which CSF 5-HIAA levels, DST results, and follow-up suicide information was available. Ascertainment details, biological test procedures, and clinical and demographic characterization for our cohort are published (Placidi et al., 2001). Roy et al.'s is the only published prospective study that provides data on both measures in the same subjects. We use Roy et al.'s designation of high ( $>75$  pmol/ml) and low ( $<75$  pmol/ml) CSF 5-HIAA.

We first assessed how CSF 5-HIAA (+Low, -High) and DST (+non-suppressor, -suppressor), taken as binary screening tests for the outcome of completed suicide, perform individually in terms of sensitivity, specificity, PPV, and likelihood ratio (LR). The LR can be understood, by a version of Bayes' theorem, as the ratio between post-test odds and pre-test odds, and thus, is a measure of how much prediction has improved after the administration of the test.

We then tested the sensitivity, specificity, PPV and LR of two combinatory models. The first combines the two binary screening tests with 'AND', whereby subjects are labelled positive only if they are positive on both tests. We extended this model a further step to include the clinical variable of prior suicide attempt. The second model combines the two binary screening tests with 'OR', whereby subjects were required to test positive on either of the binary screening tests to be deemed a positive.

While identifying those at risk for any suicidal act is

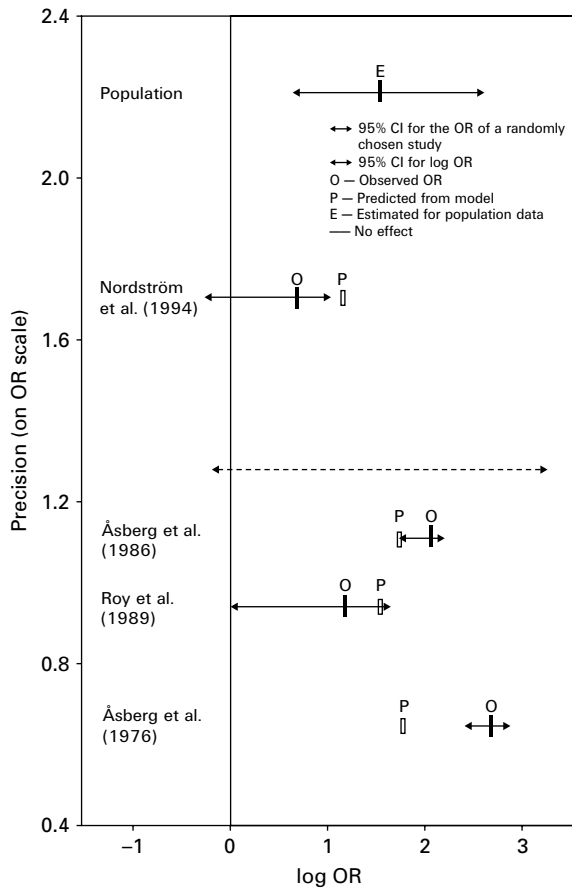
important, because of the variability in the lethality of suicidal behaviour and in biological indicators across different types of suicide attempts (Mann, 2003), we restricted our demonstration to the question of predicting completed suicide.

## Results

### Meta-analyses

In the CSF 5-HIAA meta-analysis a funnel plot gives minimal indication of publication bias and the  $p$  value of Egger et al.'s (1997) funnel plot asymmetry test is 0.16 (d.f. = 2,  $t = 2.19$ ) with the estimated overall log OR 1.50 and bootstrap 95% CI 0.611–2.61,  $p = 0.03$ . This translates into an estimated OR of 4.48 (95% CI 1.84–13.6). Thus, the odds of suicide completion are estimated to be 4.5-fold greater for the low CSF 5-HIAA group compared with the high CSF 5-HIAA group. When meta-data were analysed omitting each study in turn, all the estimated overall log ORs fell within the CI, indicating that the results of the meta-analysis of the four CSF 5-HIAA studies do not depend unduly on any one study. A 95% CI for log OR for a single study chosen at random from a hypothetical population of studies of this type is  $-0.227$  to 3.22. Figure 1 shows the raw ORs for each CSF 5-HIAA study (arranged to form a 'funnel' plot), the estimated overall OR, and CIs.

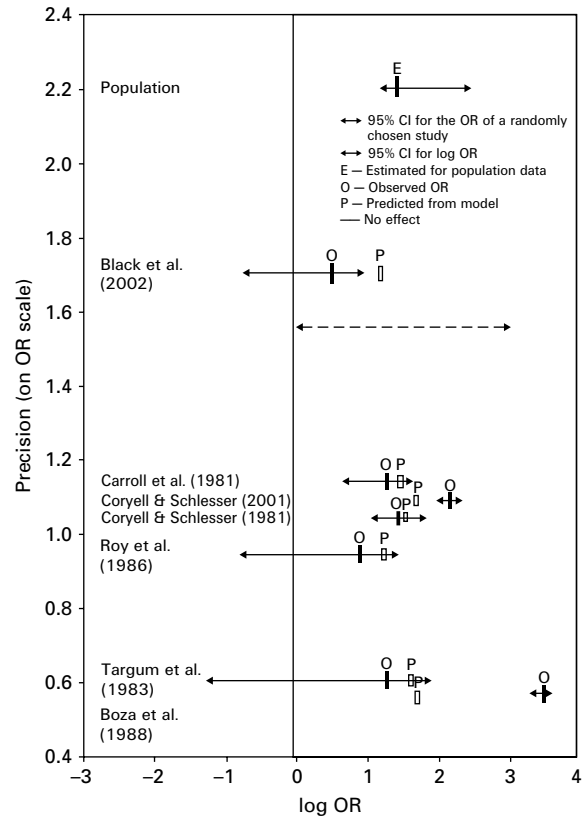
In the DST meta-analysis the funnel plot suggests publication bias and the  $p$  value derived from Egger et al.'s (1997) funnel plot asymmetry test is 0.10 (d.f. = 5,  $t = 2.01$ ). Egger et al. (1997) propose  $p = 0.10$  as the cut-off for testing for publication bias so this dataset is a borderline case. This outcome appears to depend heavily on one study, Boza et al. (1988), with a large OR. When that study is excluded the  $p$  value is 0.44 (d.f. = 4,  $t = 0.86$ ), so it is difficult to judge whether any publication bias is present in the DST meta-data. Nevertheless the estimated overall log OR is 1.54 and bootstrap 95% CI is 1.25–2.54,  $p = 0.002$ . This translates to an estimated OR of 4.65 and 95% CI of 3.48–12.69. Thus, the odds of suicide completion are estimated to be 4.5-fold greater among non-suppressors compared with suppressors. When the meta-data were analysed leaving out each study in turn, all the estimated overall log ORs fell within the CI, indicating that the DST meta-analysis results do not depend unduly on just one study. A 95% CI for log OR for a single study chosen at random from a hypothetical population of studies of this type is 0.0375–3.04. Figure 2 shows the raw ORs for each DST study (arranged to form a 'funnel plot'), the estimated overall OR, and CIs intervals.



**Figure 1.** Log odds ratios (OR) (95% CI) for CSF 5-HIAA studies predicting suicide. Estimate of overall population OR, marked by 'E', is arbitrarily placed at top. 'O' is placed over estimated OR for corresponding individual study. These estimates involve adding 1/2 to each cell (Agresti, 1990). 'P' is placed over predicted OR for each study from PQL mixed model. It estimates what the true OR for that study should be taking all the data into account. Horizontal solid lines show 95% CIs for log ORs. Intervals for 'O's are based on the individual studies. Interval for 'E' is a bootstrap interval based on the PQL analysis. Solid vertical line at 0 corresponds to no effect. Horizontal dotted line indicates 95% CI for OR of a randomly chosen study from the hypothetical population of studies modelled in PQL analysis.

**Combinatory prediction models**

Table 3 gives details of sample re-analysis, for CSF 5-HIAA alone, DST alone, both tests combined in an 'AND' model, and both tests combined 'AND' a history of a previous suicide attempt (one of the strongest clinical predictors of suicide). Combining the two tests with 'AND' resulted in a loss of sensitivity from 75% to 37.5% and an increase in specificity and PPV, from



**Figure 2.** Log odds ratios (OR) (95% CI) for Dexamethasone Suppression Test studies predicting suicide. Estimate of overall population OR, marked by 'E', is arbitrarily placed at the top. 'O' is placed over estimated OR for corresponding individual study. These estimates involve adding 1/2 to each cell (Agresti, 1990). 'O's by themselves, form a 'funnel plot'. 'P' is placed over predicted OR for each study from PQL mixed model. It estimates what the true OR for that study should be taking all the data into account. Horizontal solid lines show 95% CIs for log ORs. Intervals for 'O's are based on the individual studies. Interval for 'E' is a bootstrap interval based on the PQL analysis. Solid vertical line at 0 corresponds to no effect. Horizontal dotted line indicates 95% CI for OR of a randomly chosen study from the hypothetical population of studies modelled in PQL analysis.

55% to 88% and from 9.5% to 23% respectively over either single test. Table 4 gives results of sample reanalysis when CSF 5-HIAA and DST tests are combined using an 'OR' model. Combining the tests with 'OR' resulted in higher sensitivity but lower specificity and PPV than the 'AND' model.

**Discussion**

An optimal prediction model for suicide requires high sensitivity to minimize false negatives, that is,

**Table 3.** Combinatory model for suicide prediction using 'AND'

Test		Suicide +	Suicide –	Sensitivity	Specificity	Positive predictive value	Likelihood ratio																												
DST alone	Test +	4	38	50% (4/8)	55.8% (48/86)	9.5% (4/42)	1.1 (50/0.45)																												
	Test –	4	48					CSF 5-HIAA alone	Test +	6	33	75% (6/8)	61% (53/86)	15% (6/39)	1.9 (75/0.39)	Test –	2	53	CSF 5-HIAA and DST	Test +	3	10	37.5% (3/8)	88% (76/86)	23% (3/13)	2.6 (37.5/0.18)	Test –	5	76	CSF 5-HIAA and DST and suicide attempt	Test +	3	6	37.5% (3/8)	93% (80/86)
CSF 5-HIAA alone	Test +	6	33	75% (6/8)	61% (53/86)	15% (6/39)	1.9 (75/0.39)																												
	Test –	2	53					CSF 5-HIAA and DST	Test +	3	10	37.5% (3/8)	88% (76/86)	23% (3/13)	2.6 (37.5/0.18)	Test –	5	76	CSF 5-HIAA and DST and suicide attempt	Test +	3	6	37.5% (3/8)	93% (80/86)	33% (3/9)	5.3 (37.5/0.07)	Test –	5	80						
CSF 5-HIAA and DST	Test +	3	10	37.5% (3/8)	88% (76/86)	23% (3/13)	2.6 (37.5/0.18)																												
	Test –	5	76					CSF 5-HIAA and DST and suicide attempt	Test +	3	6	37.5% (3/8)	93% (80/86)	33% (3/9)	5.3 (37.5/0.07)	Test –	5	80																	
CSF 5-HIAA and DST and suicide attempt	Test +	3	6	37.5% (3/8)	93% (80/86)	33% (3/9)	5.3 (37.5/0.07)																												
	Test –	5	80																																

CSF 5-HIAA test + = <75 pmol/ml; DST test + = non-suppression.

**Table 4.** Combinatory model for suicide prediction using 'OR'

Test		Suicide +	Suicide –	Sensitivity	Specificity	Positive predictive value	Likelihood ratio
CSF or DST	Test +	7	62	87.5% (7/8)	27.9% (24/86)	10% (7/69)	1.1 (87.5/0.73)
	Test –	1	24				

CSF 5-HIAA test + = <75 pmol/ml; DST test + = non-suppression.

undetected suicides, and preferably but less critically, high specificity to reduce the number of false positives, which may overburden limited resources. Given the multi-determined nature of suicidal behaviour, a model that incorporates multiple, largely independent, predictors will have greater predictive power. Our meta-analyses of all published prospective studies of both CSF 5-HIAA and DST have shown they have potential as predictors of suicide. Taken as indicators of the diathesis for suicide and stress response respectively, these predictors are the best currently studied predictors for inclusion in combinatory models. This paper offers an evaluation of these available biological predictors, however, the results are modest and further efforts to identify and refine biological tests are awaited.

#### Choosing a predictive model

To maximize sensitivity we combined the two biological tests with an 'OR' condition, such that a positive test on either DST or CSF 5-HIAA constituted an overall positive response. This resulted in relatively high sensitivity of 87.5%. However, a large number of false positives were produced resulting in low specificity of 28%. In the test sample, this combination

model had greater sensitivity than CSF 5-HIAA or DST alone. As expected, this model resulted in much lower specificity than either of the single tests, and that is why it had a lower PPV than the CSF 5-HIAA test alone. Nevertheless a sensitivity of ~88%, means that, for example, in a sample of 1000 persons with a true base rate of suicide of 5%, we would detect about 18/20 suicides, a very good result. The 'cost' of this success would be that with a specificity of 28%, we would incorrectly identify 705 individuals as potential suicides and they would receive intensive preventive treatment unnecessarily.

Large numbers of false positives present a problem in suicide prevention insofar as many intervention measures, such as hospitalization, are impractical for large misidentified groups of individuals (Pokorny, 1983). The predictive model using 'AND' to combine tests increases the specificity of prediction. As the biological tests are applied in combination, or sequentially, specificity rises from 55% (DST alone) to 88% (combination of DST and CSF 5-HIAA) (Table 3). However, this model, while it achieved greater specificity and thus reduced the number of false positives (from 38 to 10), did so at an unacceptable cost of sensitivity, which declined to 37.5%. It would fail to identify 5/8 suicides.

In other attempts to develop a predictive model, clinical predictors have shown specificity and sensitivity in the order of 55–79% and 72–75% respectively (Modestin and Kopp, 1988; Pokorny, 1983) and our, albeit imperfect, models improve those results to 88% sensitivity but only 28% specificity.

The challenge for prediction models, then, is to sustain the kind of sensitivity in our 'OR' model while improving specificity. Further improvement in the sensitivity of the individual predictors included in the model will, in part, address this difficulty.

### *Improving biological predictors of suicide*

Our meta-analyses of prospective CSF 5-HIAA and DST studies confirm that low CSF 5-HIAA and DST non-suppression have some predictive power with respect to completed suicide in mood disorders. Individuals in the low CSF 5-HIAA group were 4.5-fold more likely to commit suicide compared with the high CSF 5-HIAA group, and DST non-suppressors also had a more than 4-fold increased risk of suicide than non-suppressors. However, further research is required to refine such 'tests' and improve their sensitivity; for example, optimizing the threshold for defining low CSF 5-HIAA, and taking into account time dependency for state-dependent markers such as DST non-suppression. Moreover, any biological assessment needs to account for medication effects, as well as effects of substance and alcohol use, age, sex and so on. It is also likely that future biological predictors will involve brain receptor scans and genotype results for a panel of candidate genes.

### *Clinical implications*

The development of both reliable biological tests and more accurate models for suicide prediction will have implications for clinical assessment, intervention, and treatment practices. Biological measures have a potentially important place in the prediction of suicidal behaviour, as an adjunct to, rather than a substitute for, current clinical practice. The prediction models demonstrated in this study can combine both biological and clinical predictors, as demonstrated by the inclusion of prior suicide history (Table 3). An expanded model may include other clinical predictors such as a previous suicide attempt, family history of suicidal acts, and greater aggression/impulsivity and pessimism. However, close attention to the causal relationship between biological and clinical factors is necessary, as the model requires relatively orthogonal variables. Other avenues of assessing serotonergic

function are being developed and refined, such as use of positron emission tomography to quantify serotonin transporter or receptor binding (van Heeringen et al., 2003), or genotyping for variants in susceptibility genes, that may, in a clinical setting, allow assessment of serotonergic and other biological functions to be included in evaluations of suicide risk. Additionally, neurophysiological tests of domains of prefrontal cortical function such as Wisconsin Card Sorting Test and the Buschke Selective Reminding Test total recall have been shown to be abnormal in high lethality suicide attempters (Keilp et al., 2001), and may have some utility in identifying high-risk individuals. If clinical and neuropsychological assessments are used as an initial screen, biological testing might then be restricted to a smaller higher-risk group. Such pre-screening allows more resources to be directed towards fewer, but higher risk, individuals.

Ultimately the choice of model is contingent on the purpose and context for which a model is required. Given that the concern is greater over missing a potential suicide rather than conserving treatment resources, one would seek to maximize sensitivity and thus identify the most potential suicides. Therefore, one would choose the 'OR' model. We have compared the models as proof of principle, to show that by combining predictors it is possible to increase the sensitivity and specificity above that of any individual predictor.

### **Conclusion**

Predicting risk for completed suicide requires a multidimensional approach that includes biological, clinical, and neuropsychological indices. Given the multi-determined nature of suicidal behaviour, a combinatory or sequential screening method using largely orthogonal variables that addresses both long-term traits and short-term state-dependent risk, is optimal for predicting risk (Amsel and Mann, 2001). Prospective biological studies, while producing at times divergent results, have reached some consensus in terms of some key neurobiological systems involved in suicidal behaviour in mood disorders, including the serotonergic system and the HPA axis. While the specific functions and interrelation of these systems remains to be determined, prospective biological studies have demonstrated that anomalies in both are indicative of elevated risk of future suicidal behaviour. Integrating more refined measures of such markers into clinical assessment may enhance detection of higher risk patients and thereby improve suicide prevention.



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## Statement of Interest

None.

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