Lower CSF MHPG predicts short-term risk for suicide attempt

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Abstract
Post-mortem studies document alterations in the central noradrenergic system in suicide. However, studies of non-fatal suicide attempts have, thus far, found no consistent relationship to the noradrenaline metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in cerebrospinal fluid (CSF). We therefore conducted a prospective study of CSF MHPG and suicidal acts in major depression and bipolar depression. CSF MHPG was assayed in 184 drug-free patients with DSM-IV major depressive disorder or bipolar disorder, presenting for treatment of a current depressive episode, who were then followed-up for up to 12 months. Survival analysis was conducted using Cox proportional hazards modelling to test association of CSF MHPG and future suicidal behaviour, and potential clinical mediators. Twenty-seven individuals made a suicide attempt (two fatal) in the follow-up period. Lower CSF MHPG predicted future suicide attempt or suicide (22% increase in hazard for each 10 pmol/ml lower MHPG, \( p = 0.045 \)). Lower CSF MHPG also correlated with higher medical lethality of future suicidal act (mean MHPG: 49±18 vs. 32±12 pmol/ml for low- vs. high-lethality, \( t = 2.8, d.f. = 25, p = 0.009 \)). Smoking and self-rated depression severity were also associated with lower CSF MHPG and with future suicide attempt, but were not statistically significant mediators in multivariate models. In conclusion, lower CSF MHPG is associated with short-term risk for future suicidal behaviour in the 12 months following a major depressive episode. Psychopathology that mediates the relationship between lower CSF MHPG and future suicidal behaviour needs to be identified.

Introduction
Post-mortem studies document alterations in the central noradrenergic system in suicide. However, studies of non-fatal suicide attempts have, thus far, found no consistent relationship to the noradrenaline metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in cerebrospinal fluid (CSF). We therefore conducted a prospective study of CSF MHPG and suicidal acts in major depression and bipolar depression. CSF MHPG was assayed in 184 drug-free patients with DSM-IV major depressive disorder or bipolar disorder, presenting for treatment of a current depressive episode, who were then followed-up for up to 12 months. Survival analysis was conducted using Cox proportional hazards modelling to test association of CSF MHPG and future suicidal behaviour, and potential clinical mediators. Twenty-seven individuals made a suicide attempt (two fatal) in the follow-up period. Lower CSF MHPG predicted future suicide attempt or suicide (22% increase in hazard for each 10 pmol/ml lower MHPG, \( p = 0.045 \)). Lower CSF MHPG also correlated with higher medical lethality of future suicidal act (mean MHPG: 49±18 vs. 32±12 pmol/ml for low- vs. high-lethality, \( t = 2.8, d.f. = 25, p = 0.009 \)). Smoking and self-rated depression severity were also associated with lower CSF MHPG and with future suicide attempt, but were not statistically significant mediators in multivariate models. In conclusion, lower CSF MHPG is associated with short-term risk for future suicidal behaviour in the 12 months following a major depressive episode. Psychopathology that mediates the relationship between lower CSF MHPG and future suicidal behaviour needs to be identified.

Key words: CSF MHPG, depression, mediation model, smoking, suicide attempt.
Given that the noradrenergic system is stress-responsive, these generally negative findings may reflect the inability of cross-sectional and retrospective study design to adequately assess associations between state-dependent biological alterations and past suicidal behaviour. State-dependent biological abnormalities are best detected in closer time proximity to the behaviour of interest and a short-term, prospective study may therefore be better able to detect these effects. Prospective studies of CSF MHPG and suicide and suicide attempt have been few. A study of hospitalized suicide attempters found that those who made a further suicide attempt or died by suicide in the year following their index attempt were more likely to have CSF MHPG levels above the median (Traskman-Bendz et al. 1992). Other studies using death records 1–12 yr after index admission for a suicide attempt report no differences in baseline CSF MHPG between those who did or did not eventually die by suicide during follow-up (Engstrom et al. 1999; Nordström et al. 1994; Sunnqvist et al. 2008). No difference in CSF MHPG levels was observed in suicide attempters in an 11-year follow-up in schizophrenia (Cooper et al. 1992), or in a 2-yr follow-up of bipolar disorder (Sher et al. 2006). In the latter study CSF MHPG level was negatively correlated with maximum lethality of follow-up attempt, raising the possibility that the relationship of low CSF MHPG to future suicide attempts might be stronger in those making more lethal suicide attempts. With the exception of Nordström et al. who examined only suicide and not non-fatality in follow-up (Nordström et al. 1994), none of the prospective studies cited above examined time to event which may be important if the relationship between CSF MHPG and suicidality is state-dependent. Survival analyses techniques are able to assess the salience of putative risk factors over time in increasing the likelihood of a suicide attempt (Leon et al. 1990). Therefore, in the present study we use survival analysis to examine the association of CSF MHPG with short-term risk of future suicide attempt in a cohort of individuals in a major depressive episode at time of entry into the study. We also examine clinical correlates of CSF MHPG for potential mediation effects.

Methods

Subjects

A total of 184 subjects consented to undergo lumbar puncture. Subjects were part of a larger cohort who had presented for treatment at university hospitals in New York and Pittsburgh and enrolled in a clinical study of mood disorders under the same protocol after giving written informed consent as required by the relevant Institutional Review Boards. About half (55%) were female, the average age was 37 ± 12 yr, and 149 subjects (81%) self-identified as Caucasians. A small number of the bipolar patients (n = 27) were the basis of a previous report by our group (Sher et al. 2006).

Patients were assessed by psychiatrists or clinical psychologists and diagnosed according to DSM-IV criteria for Axis I and Axis II diagnoses using the SCID-I, SCID-II or SCID-NP (First et al. 1996, 2002). Seventy-eight percent (n = 144) of subjects had a lifetime diagnosis of major depressive disorder (MDD), and 22% (n = 40) bipolar disorder. All subjects met criteria for a major depressive episode at the time of assessment. Rating of current depression severity, hopelessness, perceived reasons for living, and suicidal ideation, and lifetime impulsivity, aggression and hostility were conducted using the 17-item Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI), Beck Hopelessness Scale (BHS), Reasons For Living Inventory (RFIL), Barratt Impulsivity Scale (BIS), Brown–Goodwin Lifetime History of Lifetime Aggression scale (BGLHA), Buss–Durkee Hostility Inventory (BDHI) and the Scale for Suicidal Ideation (SSI) as previously described (Oquendo et al. 2004). Clinical assessment was carried out within 2 wk of lumbar puncture.

The number, method, and medical damage of past suicide attempts were recorded on the Columbia Suicide History Form (Oquendo et al. 2003). Attempt lethality was assessed using the Lethality Rating Scale which rates attempts based on objective medical sequelae of the attempt: from 0 for minimal medical damage to 8 for suicide death. Attempts rating ≥4 were considered high-lethality, as this score indicates that medical in-patient treatment for the sequelae of the attempt was required. In total, 101 subjects (55%) subjects reported a history of past suicide attempt, with 1–9 attempts (median 2, interquartile range 1–3).

While 159 subjects returned for follow-up interviews 3 months and 1 yr after their baseline interview, 25 of the subjects were lost to follow-up and no further information is available for them. Those lost to follow-up did not differ from the rest of subjects in terms of average MHPG levels (t = 0.5, d.f. = 182, p = 0.588), or percentage of subjects with past attempt (χ² = 1.5, d.f = 1, p = 0.216). For a detailed description of the follow-up study see Oquendo et al. (2004). Time in study was not related to CSF MHPG level (correlation coefficient −0.02, p = 0.847).
Twenty-seven subjects (17%) made 42 suicide attempts during the 1-yr follow-up period (one subject made four attempts, four made three attempts, four made two attempts and 18 made one attempt), two of which were fatal.

Subjects were negative for illicit drugs on toxicology screen and free from psychotropic drugs known to affect monoamine turnover for at least 2 wk prior to lumbar puncture (longer for longer half-life medications, such as 6 wk for fluoxetine).

**Monoamine metabolite assay**

Lumbar puncture and assay of CSF levels of MHPG were carried out as previously described (Mann et al. 1996).

**Statistical analysis**

CSF MHPG levels had an approximately normal distribution with one outlier (120 pmol/ml), which was censored at 95 pmol/ml. Values were dichotomized by median split only for plotting purposes. Association between CSF MHPG levels and baseline clinical and demographic variables, and history of past suicide attempt were tested using Pearson’s correlation coefficient and t-tests as appropriate. Self-report state-dependent clinical variables, BDI, BHS, SSI, were adjusted for clinician-rated severity of depression (HAMD<sub>17</sub>) before computing the correlation coefficients. As CSF MHPG level was not associated with age or sex, subsequent analyses were not controlled for these variables.

Association between baseline CSF MHPG level and suicide attempt or suicide during follow-up was examined using survival analysis by Cox proportional hazards regression. MHPG level was treated as a quantitative variable in this analysis. To facilitate comparison with other published studies, the incidence of suicide attempt in below vs. above median CSF MHPG level groups was compared using the log-rank test. For individuals who made more than one attempt in follow-up, only the first attempt was used. Potential clinical mediators of CSF MHPG and suicide attempt or death in follow-up were examined in the same manner.

**Multivariate prediction**

Clinical and demographic variables associated with CSF MHPG may explain away the effect on the risk of suicide attempt. Since there were four such factors, and 8–10 events per predictor variable are needed to have adequate power in the Cox model with multiple predictors to determine whether MHPG remained significant after adjustment for the other risk factors, the full model could not be fit. Instead, two mediation models (Baron & Kenny, 1986) were constructed using those of the factors that were also predictors of future suicidal act. Model 1 examined potential pathway whereby lower CSF MHPG was a mediator between smoking and risk of future suicide attempt or death, and model 2 tested self-rated depression severity BDI (adjusted for clinician-related depression severity HAMD<sub>17</sub> by taking the residuals from a linear regression model with BDI as outcome and HAMD<sub>17</sub> as predictor to obtain a measure of subjective depression that is independent from the clinician-related measure) as a potential clinical mediator for suicide risk conferred by low CSF MHPG levels. For both mediation models, direct and indirect effects were calculated and a bootstrap test of mediation was performed (Shrout & Bolger, 2002).

**Results**

**Baseline clinical correlates of CSF monoamine metabolites**

Table 1 contains measures of association CSF MHPG and clinical and demographic data. Significance levels were not corrected for multiple testing. CSF MHPG was lower in those with a history of drug or alcohol substance-use disorder (p = 0.029), current smokers (p = 0.033), and Caucasians (p = 0.048). Main diagnosis (MDD vs. bipolar disorder) did not affect MHPG levels, although the presence of comorbid cluster B disorders was associated with lower MHPG values on the trend level. There was no correlation of CSF MHPG with clinician-rated depression severity (HAMD<sub>17</sub>). The self-report measures of depression (adjusted for HAMD<sub>17</sub>) BDI was modestly inversely correlated with CSF MHPG (Pearson r = −0.18, p = 0.018), and the adjusted hopelessness BHS showed a trend towards inverse correlation (Pearson r = −0.13, p = 0.084). Unadjusted BDI and BHS were not associated with MHPG (BDI: r = −0.11, p = 0.151; BHS: r = −0.12, p = 0.116). Presence of suicidal ideation in the 2 wk preceding lumbar puncture was also associated on a strong trend level with lower CSF MHPG (t = 2.0, d.f. = 24.9, p = 0.056), although severity of ideation was not (r = −0.09, p = 0.227). There was no correlation of CSF MHPG with severity of lifetime aggression, impulsivity and hostility, or with reported reasons for living or reported history of childhood abuse.
Table 1 shows CSF MHPG levels in relation to past suicidal behaviour. There was no difference between individuals with and without a history of suicide attempt, and no difference in CSF MHPG levels between high- and low-lethality past attempts.

Probability of future suicide attempt or suicide was significantly different for above and below median baseline CSF MHPG groups (log rank test $\chi^2 = 5.6$, d.f. = 1, $p = 0.0018$) (Fig. 1). Lower CSF MHPG predicted future suicide attempt or suicide (22% increase in hazard for each 10 pmol/ml lower MHPG, $p = 0.045$). Lower CSF MHPG correlated with higher medical lethality of future suicidal act, as shown in Fig. 2 (mean MHPG: $49 \pm 18$ vs. $32 \pm 12$ pmol/ml for low- vs. high-lethality, $t = 2.8$, df = 25, $p = 0.009$). Baseline CSF MHPG levels were lowest in subjects with a suicide attempt in the 3 months following baseline assessment, compared to all other subjects.

<table>
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<tr>
<th>Test statistic</th>
<th>p</th>
<th>d.f.</th>
<th>CSF MHPG pmol/ml (mean ± S.D.)</th>
<th>Male</th>
<th>46 ± 18</th>
<th>−0.11</th>
<th>182</th>
<th>0.909</th>
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<tr>
<td></td>
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<td>Causalisan</td>
<td>Female</td>
<td>46 ± 18</td>
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<td>48 ± 19</td>
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<td>42 ± 17</td>
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<td>Non-smoker</td>
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<td>48 ± 18</td>
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<td>No substance use disorder</td>
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<td>48 ± 18</td>
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<td>Past suicide attempt</td>
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<td>Suicidal ideation in past 2 wk</td>
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<td>Low-lethality past attemptb</td>
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<td>Pearson's r Pearson's r</td>
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<td>Clinician-rated depression (HAMD17)</td>
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<td>182</td>
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<td>Self-rated depression (BDI)c</td>
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<td>−2.38</td>
<td>168</td>
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<td>Hopelessness (BHS)c</td>
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<td>Reasons for Living (RFLI)c</td>
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<td>Aggression (BGLHA)</td>
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<td>0.06</td>
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<td>Hostility (BDHI)</td>
<td>0.06</td>
<td>0.75</td>
<td>159</td>
<td>0.452</td>
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</table>

MDD, Major depressive disorder; HAMD17, Hamilton Depression Rating Scale – 17 item; BDI, Beck Depression Inventory; BHS, Beck Hopelessness Scale; SSI, Scale for Suicidal Ideation; RFLI, Reasons For Living Inventory; BGLHA, Brown–Goodwin Lifetime History of Aggression; BIS, Barratt Impulsivity Scale; BDHI, Buss–Durkee Hostility Index.

a t test, unequal variance.
b In suicide attempters only.
c Adjusted for clinician-rated depression (HAMD17).

CSF MHPG and past and future suicide attempt

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Probability of future suicide attempt or suicide was significantly different for above and below median baseline CSF MHPG groups (log rank test $\chi^2 = 5.6$, d.f. = 1, $p = 0.0018$) (Fig. 1). Lower CSF MHPG predicted future suicide attempt or suicide (22% increase in hazard for each 10 pmol/ml lower MHPG, $p = 0.045$). Lower CSF MHPG correlated with higher medical lethality of future suicidal act, as shown in Fig. 2 (mean MHPG: $49 \pm 18$ vs. $32 \pm 12$ pmol/ml for low- vs. high-lethality, $t = 2.8$, df = 25, $p = 0.009$). Baseline CSF MHPG levels were lowest in subjects with a suicide attempt in the 3 months following baseline assessment, compared to all other subjects.
with follow-up data (mean MHPG: 35 ± 17 vs. 47 ± 18 pmol/ml, t = 2.0, d.f. = 157, p = 0.043). Bipolar vs. MDD diagnosis was not a significant moderator of the association between MHPG and future suicide attempts as tested in a linear Cox regression model with interaction between MHPG and main diagnosis [hazard ratio (HR) 0.965, z = −1.31, p = 0.19], and did not affect the medical lethality of the attempts during follow-up (average lethality 3.4 for those with comorbid cluster B disorder, vs. 4.7 for those without, t = 1.3, d.f. = 25, p = 0.194).

**Mediation models**

Clinical and demographic factors that were significantly associated with CSF MHPG were smoking, past substance-use disorder, adjusted BDI and race. Of these four, smoking status and adjusted BDI were significant risk factors for future suicide attempt or suicide in univariate Cox models [smoking: HR 2.6, z = 2.4, p = 0.014; adjusted BDI: HR (for each 10-point increase) 1.6, z = 2.1, p = 0.033]. In mediation model 1, an estimated 91% of the risk associated with smoking was a direct risk, and only 9% was the estimated indirect effect through lower MHPG scores, not significant (indirect effect bootstrap 95% CI −0.03 to 0.32), indicating no mediation. In model 2, an estimated 81% of the risk associated with lower MHPG levels was a direct effect, the 19% estimated indirect effect through higher subjective depression scores did not quite reach significance level (indirect effect 95% CI −0.01 to 0.001).

**Discussion**

We found that lower baseline CSF MHPG was associated with increased risk of making a fatal or non-fatal suicide attempt in a 1-yr follow-up period following presentation with a major depressive episode: each 10 pmol/ml lower CSF MHPG level increased the risk of a suicidal act by 22%. Moreover, baseline CSF MHPG levels were particularly low in subjects who made a suicide attempt within 3 months of index assessment (Fig. 1). We found no association between past suicide attempt and baseline CSF MHPG level, including past attempts that had occurred in the 3 months prior to index assessment (data not shown). This suggests that CSF MHPG may be primarily a state-related correlate of future suicidal behaviour, most useful in terms of assessing future short-term risk. This would be consistent with the generally negative findings of other studies of CSF MHPG, most obviously those using retrospective methods or extended prospective follow-up periods. One study of
suicide attempters with a mixture of diagnoses found higher median baseline CSF MHPG associated with a future suicide attempt in a 1-yr follow-up period and the difference in results may be explained by diagnostic and other study population effects (Traskman-Bendz et al. 1992). The only other prospective study that used survival analysis to examine time to event and baseline CSF MHPG levels was also conducted in a hospitalized suicide attempter cohort but reported only on suicide in follow-up and found no difference in survival curves for above and below median baseline CSF MHPG-level groups in the 11-yr follow-up, or in the first year following baseline assessment (Nordström et al. 1994).

However, there are several findings in post-mortem tissue that corroborate the findings of the present study. We have already mentioned in the Introduction post-mortem findings that demonstrate an association of suicide with low noradrenergic neurons in the locus coeruleus and elevated locus coeruleus tyrosine hydroxylase and α2 receptors. Low number of noradrenergic neurons in suicide victims can be related to low norepinephrine or MHPG. The same conclusion may not be drawn from the findings of elevated locus coeruleus tyrosine hydroxylase and α2 receptors in suicide, these findings have been interpreted as evidence of low norepinephrine because experimental depletion of norepinephrine in animals up-regulates tyrosine hydroxylase and α2 receptors in the locus coeruleus, just as is observed in the locus coeruleus in human suicide victims (Ordway & Klimek, 2001).

We found no differences between average MHPG values or in the rate of follow-up attempts by main diagnosis (MDD or bipolar disorder). Main diagnosis was not a significant moderator of the association between MHPG and future suicide attempt, although the estimates pointed to possibly higher risk in the bipolar patients. Due to the small number of bipolar subjects in the pooled sample, we did not separate MDD and bipolar subjects, future studies of larger sample size are needed to verify the findings in the two diagnostic groups separately. There was a trend-level difference between average MHPG values between those with and without a comorbid cluster B disorder. Cluster B disorder was a risk factor for future suicide attempt. MHPG was not a significant risk factor in the subjects with comorbid cluster B disorder, who had somewhat lower MHPG levels on average, raising the question of mediation or confounding in the association between MHPG, cluster B disorder and suicide attempt risk. However, in a joint Cox regression model, cluster B disorders explained away only about 9% of the risk effect due to MHPG (data not shown), which can be interpreted as a lack of support for the mediation hypothesis, or it may be a sign of the presence of some patients with many risk factors in a sample of limited size. At a minimum, this finding raises some questions about the validity of MHPG as a biomarker of future risk of suicide attempt in depressed patients with comorbid cluster B disorders.

We also observed that greater lethality of future suicidal act was related to lower CSF MHPG, and was not significantly associated with either Axis I or Axis II diagnosis. It has been suggested that compared to those who make low-lethality attempts, high-lethality suicide attempters more closely resemble, biologically and behaviourally, those who die by suicide (Placidi et al. 2001). Given that post-mortem studies provide the most robust evidence to date of noradrenergic system alterations in suicidal behaviour, we might expect to see differences associated with higher lethality suicidal acts, which here include two suicide deaths. Other prospective studies of CSF MHPG and suicidal behaviour examining method of non-fatal attempt (violent or non-violent) and/or lethality of attempt (Roy et al. 1985; Träskman et al. 1981) found no association, with the exception of Sher et al. (2006) who report on a subsample of this cohort.

CSF MHPG, pessimism, and suicidal behaviour
Clinical correlates of norepinephrine function have largely been assessed in depletion paradigms, and a recent meta-analysis of depletion studies found that acute depletion of norepinephrine was only indirectly related to mood state (Ruhe et al. 2007), and surmised that deficient norepinephrine function may represent a vulnerability trait for depression, rather than a direct cause. This may also be the case with respect to suicidal behaviour, and one potential pathway whereby deficits in noradrenergic system function contribute to suicidal behaviour may be via trait pessimism. Selective norepinephrine reuptake inhibitors have been shown to increase the relative processing of positive to negative affect information in healthy volunteers, indicating norepinephrine involvement in the kind of negative processing biases that are thought to underlie pessimism (Harmer et al. 2004).

We have assessed pessimism in mood disorder individuals as an excess of subjective, or self-rated, severity of depression (BDI) and hopelessness (BHS) with respect to clinician-rated severity of depression (HAMD17) (Mann et al. 1999; Oquendo et al. 2004) and have shown that pessimism, operationalized in this way is predictive of suicide attempt in a follow-up study (Oquendo et al. 2004). In that study lower CSF
reactivity and lower indices including lower tyrosine hydroxylase immunobinding in the locus coeruleus (2) has been linked to alterations in brain noradrenergic system function. Consistent with that observation, we found that smoking was associated with lower levels of CSF MHPG and with future suicidal act; however, CSF MHPG did not mediate the effect of smoking on risk for future suicidal acts. A lifetime diagnosis of substance-use disorder was also associated with lower CSF MHPG levels, but was not correlated with future suicide attempt, and when entered into a multivariate model was cancelled out by smoking (data not shown). Thus, although smoking is a strong predictor of suicidal behaviour, there does not appear to be a direct casual relation between smoking, altered noradrenergic system function, and suicidal behaviour.

**Limitations**

We had no follow-up data on 25 individuals, and 32 individuals had follow-up data only at the 3-month time-point. However, time in study was not correlated to CSF MHPG level, and the Cox proportional hazard model takes length of time in follow-up into account.

Using prospective data establishes clear time delineation between baseline patient characteristics and suicide attempts or suicides that follow, but establishing the temporal precedence of multiple baseline risk factors can present difficulties. Thus, in this study we built mediation models based on hypothesized direction of mediation, e.g. that greater subjective depression is a mediator of the risk associated with lower MHPG level, and not vice versa.

We did not correct for multiple testing when looking at the correlates of CSF MHPG. Any test other than our main one (baseline MHPG level predicts future suicide attempts) should be viewed as exploratory analysis requiring further confirmation from independent studies.

**Conclusion**

In mood disorders, alterations in noradrenergic system indices may have potential as biomarkers for identifying individuals at short-term risk for suicide attempt.
attempt, particularly high-lethality attempts which are more likely to result in death. Larger prospective clinical studies are needed to more fully elucidate the clinical and behavioural factors that mediate between the effect of deficits in noradrenergic system function on suicidal behaviour.

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Statement of Interest

None.

References


