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Research paper

Identifying a clinical signature of suicidality among patients with mood disorders: A pilot study using a machine learning approach ☆

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ABSTRACT

Objective: A growing body of evidence has put forward clinical risk factors associated with patients with mood disorders that attempt suicide. However, what is not known is how to integrate clinical variables into a clinically useful tool in order to estimate the probability of an individual patient attempting suicide.
Method: A total of 144 patients with mood disorders were included. Clinical variables associated with suicide attempts among patients with mood disorders and demographic variables were used to 'train' a machine learning algorithm. The resulting algorithm was utilized in identifying novel or 'unseen' individual subjects as either suicide attempters or non-attempters. Three machine learning algorithms were implemented and evaluated.
Results: All algorithms distinguished individual suicide attempters from non-attempters with prediction accuracy ranging between 65% and 72% ($p < 0.05$). In particular, the relevance vector machine (RVM) algorithm correctly predicted 103 out of 144 subjects translating into 72% accuracy (72.1% sensitivity and 71.3% specificity) and an area under the curve of 0.77 ($p < 0.0001$). The most relevant predictor variables in distinguishing attempters from non-attempters included previous hospitalizations for depression, a history of psychosis, cocaine dependence and post-traumatic stress disorder (PTSD) comorbidity.
Conclusion: Risk for suicide attempt among patients with mood disorders can be estimated at an individual subject level by incorporating both demographic and clinical variables. Future studies should examine the performance of this model in other populations and its subsequent utility in facilitating selection of interventions to prevent suicide.

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1. Introduction

When a patient with a depressive episode and no known previous history of suicide attempts first presents for treatment, what is the likelihood that this individual patient will attempt suicide? This question is a major unmet challenge in mood disorder treatment and also an important question for society at large, as suicide is a tragic but highly preventable event (Mann et al., 2005).

Suicide accounted for 4.8% and 5.7% of total global deaths in female and male subjects aged 15–49 years respectively in 2010 (Lozano et al., 2012). In the same year, suicide was reported as the sixth leading cause of life years lost in North-America (Lozano et al., 2012). Furthermore, it has been reported that approximately 90% of individuals who die through suicide are diagnosed with a mental disorder prior to their death (Arsenault-Lapierre et al., 2004). However, there is little awareness in medical practice on objective stratification of suicide risk, which has led suicide to be referred to as "the quiet epidemic" (Turecki, 2014). The current situation is particularly worrisome in major depressive disorder (MDD) and bipolar disorder (BD), given the high prevalence of these disorders and the strong association between suicide and depressive symptoms.

Suicide is usually viewed as an extreme response to a catastrophic event, such as loss of a close relative (M A Oquendo et al., 2014a, 2014b). However, many individuals, including patients with mood disorders, go through these kinds of stressors and yet they do not attempt suicide (Oquendo et al., 2014a, 2014b). Consequently, a growing body of knowledge has put forward several risk factors associated with patients that attempt suicide (Brundin et al., 2015; Mann and Currier, 2010; Oquendo et al., 2014a, 2014b; Turecki, 2014). They are developmental and distal factors (as opposed to precipitating factors, such as loss of a close relative) associated to the suicidal behavior (Turecki, 2014; Turecki et al., 2012). These efforts have largely reported average *group-level* differences between suicide attempters and non-attempters. However, what is not known is how to integrate these variables to build a signature of suicide attempt and estimate the probability of an individual patient with mood disorder attempting suicide while faced with a stressful event.

In this study we set out to investigate whether a predictive clinical signature derived from easily accessible clinical and demographic variables can objectively identify *individual* patients likely to attempt suicide. Predictor variables were selected using *a priori* knowledge. Notably, the majority of clinical variables selected were related to psychiatric comorbidities (Almeida et al., 2012; Bhui et al., 2012; Blackmore et al., 2008; Blanco et al., 2012; Bostwick and Pankratz, 2000; Bottlender et al., 2000; De Araújo et al., 2015; Foley et al., 2006; Galfalvy et al., 2006; Goes et al., 2012; Goldstein et al., 2012; Gonzalez-Pinto et al., 2006; Holma et al., 2014; Isometsä et al., 2014; Johnson et al., 1991; Katz et al., 2011; Lenze et al., 2000; Morina et al., 2013; Neves et al., 2009; Oquendo et al., 2010; Schaffer et al., 2014a, 2014b; Simon et al., 2004; Soloff et al., 2000; Stein, 2006; Torres et al., 2011; Webb et al., 2014), given the recent findings that effects of mental disorders on the risk of suicide attempt were exerted almost exclusively through a general psychopathology factor representing the shared effect across all mental disorders (Hoertel et al., 2015). As a result, we implemented a set of algorithms that are able to integrate the information from multiple variables to subsequently identify an individual patient's probability or risk of being a suicide attempter.

Machine learning in psychiatric research is an emerging field with a great potential for innovation and paradigm shift as these algorithms facilitate integration of multiple measurements as well as allows objective predictions of previously 'unseen' observations. Typically, these algorithms are implemented in three key stages. First, subjects' data are separated into algorithm 'training' and 'testing' sets with the former being used to 'train' a machine learning model. Second, the predictive accuracy of the 'learnt' model is evaluated using the 'testing' set that consists of observations previously 'unseen' by the model, and algorithm accuracy, sensitivity and specificity reported. In this study, we implemented three machine learning algorithms namely; least absolute shrinkage and selection operator (LASSO) (Tibshirani, 2011), support vector machines (SVM) (Vapnik, 1998) and relevance vector machine (RVM) (Tipping, 2001). The LASSO technique was implemented using a generalized linear model (GLM) with a LASSO regularization penalty. A detailed discussion of these algorithms in the context of psychiatric research is given elsewhere (Mwangi et al., 2012).

In summary, the main objective of the current study was to establish a clinically useful predictive signature able to accurately determine individual patients' likely to commit suicide. We used easily accessible clinical variables to achieve our aim. Of note, this is a proof-of-concept study due to a small sample size.

2. Methods

The Institutional Review Board of the University of Texas Health Science Center at Houston approved the study. All subjects signed informed consent before any study-related procedures with ample time for questions. Participants included in the current study were recruited from January 2006 to June 2010.

2.1. Participants

A total of 144 subjects were recruited from the community and psychiatric clinics through flyers, radio, and newspaper advertisements. Inclusion criteria were subjects with MDD or BD types I or II (DSM-IV), and aged between 18 and 65. Exclusion criteria were head trauma with residual effects, neurological disorder, and uncontrolled major medical conditions.

2.2. Assessments

Subjects were evaluated using a socio-demographic history form to assess age, gender, years of education, and occupational status. Axis-I diagnoses and clinical characteristics were assessed with the Structured Clinical Interview for DSM-IV axis-I Disorders (SCID-I), which was administered by fully trained staff. The criterion for suicidality was one or more documented actual suicide attempts assessed by the suicide history form from the Conte Center for the Neuroscience of Mental Disorders (New York State Psychiatric Institute, Columbia University). Current dimensional mood and anxiety symptoms were assessed with the Hamilton Depression Rating Scale (HDRS), the Young Mania Rating Scale (YMRS), and Hamilton Anxiety Rating Scale (HARS). Data from all instruments were collected regardless of treatment status.

2.3. Selection of predictor variables and machine learning

Selection of predictor variables to be utilized in 'training' an algorithm is a challenge in machine learning. However, a recommended method of selecting relevant predictor variables is the use of expert domain knowledge – largely from previously published literature (Mwangi et al., 2013; Perlis, 2013). We performed a structured search on Pubmed to find relevant studies that report association of clinical and demographic variables included in this study with suicide attempts (Table 1). Of note, we chose patients with mood disorders because (a) the developmental variables associated with suicide in both BD and MDD are somewhat similar (see Table 1); and (b) our goal was to create a tool that could be used with the large number of patients with mood disorders treated in primary care settings (Table 1).

Three machine learning algorithms (LASSO, SVM, and RVM) were implemented in MATLAB (The Mathworks, Inc., Natick, Massachusetts, United States). Specifically, predictor variables (see Table 1) were normalized by z-scoring and together with corresponding categorical labels (1 – suicide attempt, 0 – non-attempt) input into the machine learning algorithm. Here, we briefly describe these machine learning algorithms but detailed and technical discussions are given elsewhere (Tibshirani, 2011; Tipping, 2001; Vapnik, 1998). SVM and RVM are 'kernel-learning' algorithms which transform a set of input variables (feature vectors) into a 'kernel' or similarity matrix through a 'kernel function' and subsequently used in the algorithm 'learning' process. These algorithms can utilize multiple types of kernel functions (e.g. linear, polynomial, Gaussian) but in the current study a linear function was utilized in training both SVM and RVM algorithms as described elsewhere (Mwangi et al., 2012). In contrast, the LASSO utilizes a typical linear regression formulation but introduces a 'penalization' procedure by assigning some predictor variables

Table 1
Clinical and demographic variables selected to develop to 'train' the model.

Variable	Type	Study	Results
Age	Continuous variable	Gonzalez-Pinto et al. (2006)	Suicidal risk was higher in young patients with BD.
		Galfalvy et al. (2006)	Younger age predicted suicide attempts among patients with BD.
		Perlis et al. (2007)	Younger age was associated with suicide risk in patients with MDD.
Gender	Categorical variable: 0 – male; 1 – female.	Schaffer et al. (2015)	Female gender was associated with suicide attempts among patients with BD.
		Schaffer et al. (2014)	Female gender was associated with suicide attempts among patients with BD.
		Perlis et al. (2007)	Female gender was associated with suicide risk among patients with MDD.
Race	Categorical variable: 0 – Caucasian 1 – Non-Caucasian	Bhui et al. (2012)	Black African men have the highest rates of suicide compared to the white group.
Years of education	Continuous variable	De Araújo et al. (2015)	Elementary school as highest education level completed was associated with suicide attempt.
Current employed	Categorical variable: 0 – no; 1 – yes.	Blackmore et al. (2008)	Being unemployed was significantly associated with a suicidal act.
Mood diagnosis	Categorical variable: 0 – BD; 1 – MDD.	Holma et al. (2014)	Patients with BD had higher cumulative incidence of suicide attempts compared to those with MDD.
		Bottlender et al. (2000)	Patients with BD had higher past suicide attempts compared to those with MDD.
Social phobia	Categorical variable: 0 – no; 1 – yes.	Simon et al. (2004)	Comorbid social phobia was associated with greater likelihood of suicide attempts in patients with BD.
		Stein (2006)	Social anxiety disorder is associated with an increased risk for MDD and a more malignant course, characterized by increased likelihood of suicide attempts
Specific phobia	Categorical variable: 0 – no; 1 – yes.	Goes et al. (2012)	Subject with specific phobia was associated with increased suicide attempts among patients with BD.
Panic disorder	Categorical variable: 0 – no; 1 – yes.	Simon et al. (2004)	Comorbid panic disorder was associated with greater likelihood of suicide attempts in patients with BD.
		Katz et al. (2011)	Comorbid panic disorder was associated with greater likelihood of suicide attempts in patients with MDD.
Generalized anxiety disorder	Categorical variable: 0 – no; 1 – yes.	Simon et al., 2004	Comorbid generalized anxiety disorder was associated with greater likelihood of suicide attempts in patients with BD.
		Foley et al. (2006)	Comorbid generalized anxiety disorder was associated with greater likelihood of suicide attempts in patients with MDD.
		Lenze et al. (2000)	Comorbid generalized anxiety disorder was associated with greater likelihood of suicide attempts in depressed elderly patients.
Obsessive compulsive disorder	Categorical variable: 0 – no; 1 – yes.	Simon et al., 2004	Current obsessive compulsive disorder was associated with greater likelihood of suicide attempts in patients with BD.
		Torres et al. (2011)	MDD was associated with suicide attempts in patients with obsessive compulsive disorder.
Posttraumatic stress disorder	Categorical variable: 0 – no; 1 – yes.	Simon et al., 2004	Comorbid posttraumatic stress disorder was associated with greater likelihood of suicide attempts in patients with BD.
		Morina et al. (2013)	Comorbid posttraumatic stress disorder was associated with greater likelihood of suicide attempts in patients with MDD.
Alcohol/cocaine dependence	Categorical variables: 0 – no; 1 – yes.	Oquendo et al. (2010)	Comorbid alcohol use disorders were associated with suicide risk among individuals with BD.
		Blanco et al. (2012)	Substance use disorder was associated with higher rates of suicide attempts in patients with MDD.
		Webb et al. (2014)	Comorbid alcohol or drug use disorders predicted suicide attempts among patients with BD.
Number of depressive episodes and prior hospitalization by depressive episodes	Continuous variable.	Goldstein et al. (2012)	Severity and number of depressive symptoms was associated with suicide attempts among patients with BD
		Isometsa et al. (2014)	Patients with BD and prior hospitalization by depressive episode had increased suicide risk.
		Gonzalez-Pinto et al. (2006)	Number of depressive episodes and hospitalization was associated with suicidal risk in patients with BD.
Psychotic symptoms	Categorical variable: 0 – no; 1 – yes.	Johnson et al. (1991)	Comorbid psychotic symptoms were associated with suicide attempts among patients with MDD.
		Bottlender et al. (2000)	Psychotic symptoms were associated with suicidality among patients with BD.

BD, bipolar disorder; MDD, major depressive disorder.

zero coefficients or weighting factors – a process also referred to as regularization. The penalization or regularization process reportedly improves the linear regression algorithm prediction accuracy and generalization ability but entails identifying an *optimal* regularization parameter (Tibshirani, 2011). In the current study, the regularization parameter was identified through a 10-
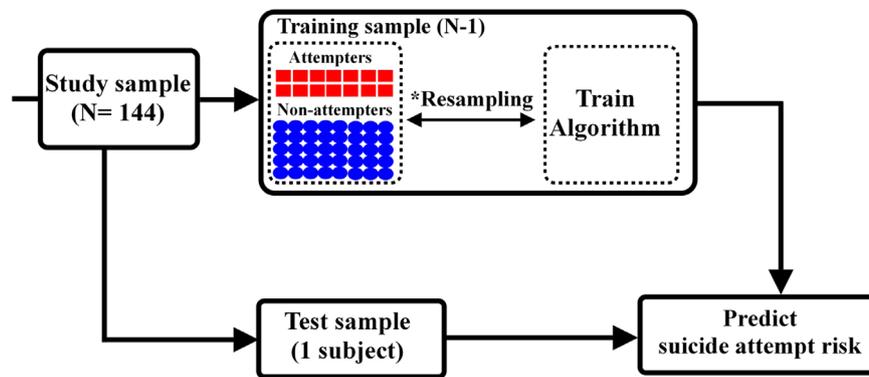
Fig. 1. Flow diagram showing algorithm training and testing process. *The class imbalance problem was addressed through a resampling step, which entailed under-sampling the majority class (suicide non-attempters) followed by algorithm training. This process was repeated 1000 iterations and algorithm predicted probabilities averaged over the resampling iterations. Class imbalance is a recurrent challenge in machine learning as recently highlighted by Libbrecht et al., (2015). A leave-one-out cross-validation approach was used to separate algorithm training and testing data.

fold cross-validation process using training data only.

2.4. Class imbalance problem

Class imbalance is a common problem in machine learning where observations (subjects) in one class (e.g. suicide non-attempters) exceed observations in the other class (e.g. suicide attempters). A typical machine learning algorithm trained using an imbalanced data set assigns new observations to the majority class (e.g. suicide non-attempters) (Dubey et al., 2014). In this study, the class imbalance problem was circumvented by 'under-sampling' the majority class (suicide non-attempters) followed by training an algorithm with a balanced sample – a process which was repeated until all observations in the majority class were selected at least once and predictions aggregated as shown in Fig. 1.

2.5. Model testing and validation

A unique characteristic of machine learning algorithms is the ability to utilize a *cross-validation* approach to separate data into model 'training' and 'testing' sets. In this study, a *leave-one-out* cross-validation (LOOCV) approach was used. LOOCV involves training a machine learning algorithm with all subjects except one while the 'left out' subject is used for algorithm testing. This iterative process is repeated until all subjects are left out for algorithm testing at least once as shown in Fig. 1 and described elsewhere (Johnston et al., 2014). Cross-validation is used in machine learning to establish the generalization ability of an algorithm to new or previously 'unseen' subjects. The validity of the algorithms in predicting individual suicide attempters from non-attempters was evaluated using *prediction accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)*. In this study, sensitivity and specificity represented correctly predicted suicide attempters (true positives) and correctly predicted non-attempters (true negatives) respectively. A 'classical' prediction accuracy was calculated as the sum of true positives, true negatives and divided by the total sample. In contrast, to account for the class imbalance problem, a 'balanced' accuracy was calculated as the average of predicted sensitivity (true positives) and specificity (true negatives) as reported elsewhere (Feis et al., 2013). In addition, PPV was calculated as the proportion of subjects predicted as suicide attempters that were actual positives (attempters) and NPV as the proportion of subjects predicted as non-attempters but were actual non-attempters (true negatives). Receiver operating characteristic curves and the corresponding area under curve were computed and reported. Lastly, chi-square statistical test between actual and machine learning

predicted labels were calculated and the results reported. The outcome of a chi-square test was considered significant at $p < 0.05$.

3. Results

A total of 144 subjects with BD or MDD were included in the study. Table 2 summarizes subjects' clinical and demographic characteristics. All algorithms (RVM, SVM and LASSO) distinguished individual suicide attempters from non-attempters with prediction accuracy ranging (64.7–72%) and all models were significant (chi-square $p < 0.05$) as detailed in Table 3. In

Table 2
Demographic and clinical characteristics.

	Attempters ($n=43$)	Non-attempters ($n=101$)	*p*-Value
Age (years)	35.26 ± 11.14	37.53 ± 12.96	0.317
Years of education	13.22 ± 3.56	14.55 ± 3.098	**0.026**
Gender			
Male	14 (32.5%)	39 (38.6%)	0.616
Female	29 (67.5%)	62 (61.4%)	
Currently employed	13 (30.2%)	50 (49.5%)	0.051
Race			**0.037**
Caucasian	22 (51.2%)	72 (71.3%)	
African American	7 (16.2%)	6 (5.9%)	
Hispanic or Latino	14 (32.6%)	23 (22.8%)	
Number of hospitalization	1.58 ± 1.8	0.29 ± 0.82	**< 0.001**
Mood disorder diagnosis			**0.014**
BD	40 (93%)	74 (73.2%)	
MDD	3 (7%)	27 (26.7%)	
Comorbid anxiety disorders			
GAD	6 (13.9%)	14 (13.9%)	1.000
OCD	4 (9.3%)	11 (10.9%)	1.000
Social Phobia	7 (16.3%)	14 (13.9%)	0.905
Panic Disorder	13 (30.2%)	18 (17.8%)	0.150
PTSD	13 (30.2%)	16 (15.8%)	0.081
Specific Phobia	5 (11.6%)	6 (5.9%)	0.404
Comorbid substance use disorder			
Cocaine	10 (23.3%)	9 (8.9%)	**0.039**
Alcohol	23 (53.5%)	31 (30.7%)	**0.016**
Lifetime psychotic symptoms	18 (41.9%)	19 (18.8%)	**0.007**

Independent *t*-test was performed to numeric variables, while chi-square test with Yates correction was performed to categorical variables. BD, bipolar disorder; GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder.

Table 3

Algorithm performance in identifying individual suicide attempters from non-attempters among patients with mood disorders. The balanced accuracy (sensitivity+specificity/2) was used to identify the best performing algorithm due to the class imbalance problem.

Algorithm	RVM	SVM	LASSO
Area under curve	0.77	0.65	0.73
Balanced accuracy (%) (Specificity+sensitivity/2)	72	64.7	68
Classical accuracy (%)	71.5	67.4	72.9
Specificity (%)	71.3	71.3	80.2
Sensitivity (%)	72.1	58.1	55.8
PPV (%)	51.7	46.3	54.6
NPV (%)	85.7	80.0	81.0

LASSO, least absolute selection shrinkage and selection operator; NPV, negative predictive value; PPV, positive predictive value; RVM, relevance vector machine; SVM, support vector machines.

particular, the RVM algorithm correctly identified 103 out of 144 as either attempters or non-attempters. This translated into 72% accuracy (72.1% sensitivity and 71.3% specificity) and significant at χ^2 $p < 0.0001$. The RVM receiver operating characteristic (ROC) curve and the 'confusion matrix', which were used in calculating the sensitivity, specificity and area under ROC curve values, are shown in Fig. 2. To calculate 'concentration of risk' – RVM predicted subjects' probabilities were divided into 20 groups of equal sizes (ventiles) and number of subjects correctly predicted within the top two ventiles calculated. In both top two ventiles, 5 out of 7 subjects were correctly predicted – translating into 71.4 % accuracy in both ventiles. Individual subjects' predicted probabilities are shown in Table S1 of Supplementary materials.

The most relevant predictor variables in distinguishing suicide attempters from non-attempters that were assigned positive coefficients or weighting factors by RVM – indicating an increase in suicide attempters included; 1) a high number of previous hospitalizations for depression, 2) a history of psychosis, 3) cocaine dependence, and 4) PTSD. In contrast, patients' age and mood diagnosis (0 – bipolar disorder or 1 – unipolar depression) were assigned negative weighting factors indicating a reduction of these variables was relevant in identifying suicide attempters. Fig. 3 shows predictor variables with corresponding weighting factors.

An additional RVM algorithm was evaluated by removing previous number of hospitalizations in the analysis and the algorithm was able to identify individual subjects with accuracy=68.9%, sensitivity=74%, specificity=63%, $p < 0.05$ and area under ROC curve=0.71. This is an indication that past hospitalization variable was not the only contributor to the algorithm performance.
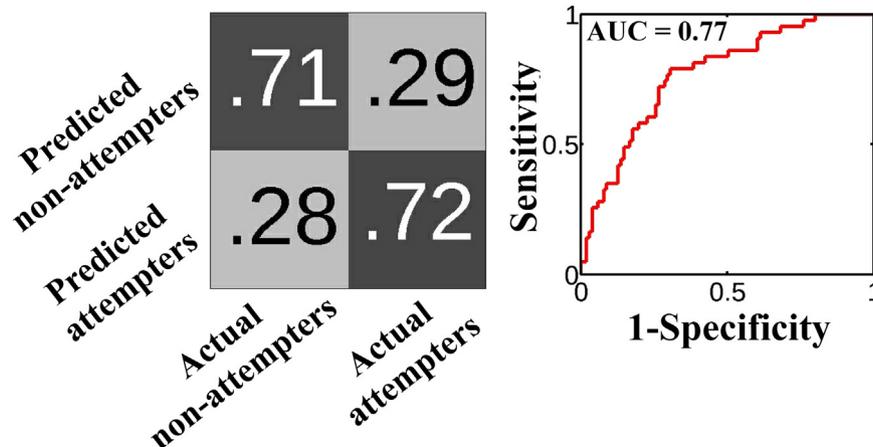
4. Discussion

Although risk factors for suicide are widely known, synthesizing easily accessible clinical information to optimize suicide risk identification in subjects with mood disorders has been an elusive goal up to now. This is the first study to evaluate the feasibility of using a clinical tool developed with advanced machine learning algorithms to identifying an individual's risk of being a suicide attempter among patients with mood disorders. All algorithms achieved greater than chance ($> 50\%$) accuracy in distinguishing attempters from non-attempters. Most notably, the RVM algorithm achieved the best prediction accuracy 72% and an area under receiver operating characteristic curve of 0.77. Notably, the prediction accuracy, sensitivity and specificity of the machine learning algorithm in identifying previously 'unseen' suicide attempters was determined through a robust cross-validation approach. The main outcome of the machine learning algorithm was a probability score able to quantify the risk of a subject being a suicide attempter.

Most relevant predictor variables distinguishing suicide attempters from non-attempters by RVM included number of prior hospitalizations for depression, lifetime psychotic symptoms, and comorbidity with cocaine dependence or PTSD. Previous average group level studies showed that these variables are associated with suicide attempts in patients with BD. In this sense, a prospective study with 72 bipolar I disorder patients showed that suicidal risk was higher with more hospitalization (Gonzalez-Pinto et al., 2006), while two studies showed that psychotic symptoms were associated with suicidality in patients with MDD and BD (Bottlender et al., 2000; Johnson et al., 1991). In addition, a cross-sectional study with 500 patients with BD reported that patients with BD and comorbid PTSD presented more suicide attempts compared against patients with BD and without PTSD (Simon et al., 2004). Finally, a review suggested that there is cross-sensitization between cocaine use and number of mood episodes in patients with bipolar disorder leading to faster illness progression, which may potentially increase the number of suicide attempts (Post and Kalivas, 2013).

In contrast with other branches of medicine (e.g. cardiology, oncology) – the lack of risk stratification approaches in psychiatric clinical practice is notable (Kapczinski and Passos, 2015). Noteworthy risk stratification applications include, prediction of cardiac arrest risk, cancer screening, and prediction of mortality risk in intensive care units (Anothaisintawee et al., 2012; Lee et al., 1999). Indeed, in personalized medicine, risk stratification plays an important role in treatment planning from the time of diagnosis.
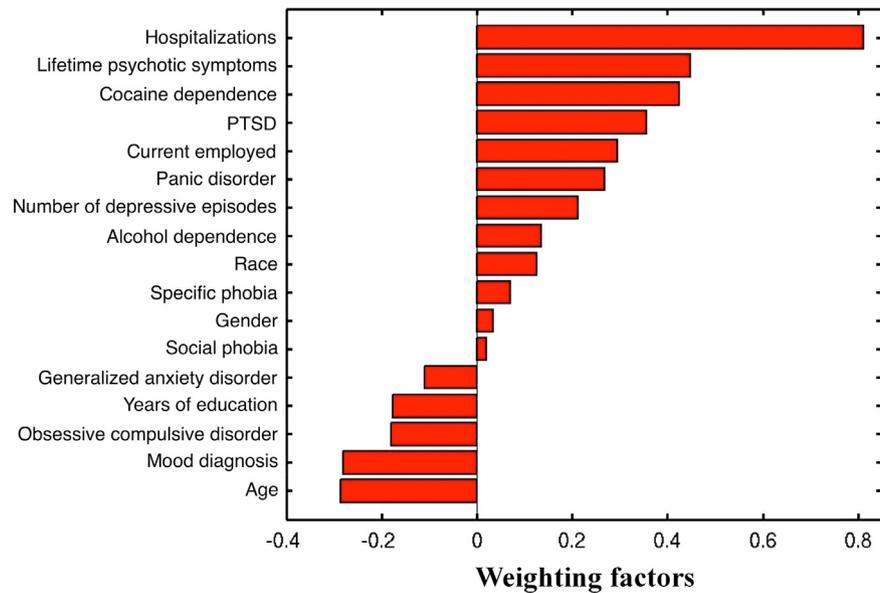

Fig. 2. 'Confusion matrix' and receiver operating characteristic (ROC) curve. 'Confusion matrix' and receiver operating characteristic (ROC) curve were used in computing the algorithm accuracy, sensitivity, specificity and area under the ROC curve. The RVM algorithm performed best as compared to SVM and LASSO.

Fig. 3. Clinical signature. Bar graph showing weighting factors assigned to each clinical variable by RVM based on their relevance in distinguishing suicide attempters from non-attempters. Clinical variables which increase the probability of an individual patient being a suicide attempter were assigned positive weighting factors whilst those that decrease the probability of a patient being a suicide attempt were assigned negative weighting factors. Variables related to anxiety and substance use disorder are lifetime comorbidities. PD, panic disorder; PTSD, posttraumatic stress disorder. Predictor variables weighting factors should be interpreted with caution as they are selected to collective maximize prediction accuracy as opposed to representing individual coefficient accuracy.

For instance, in acute care of myocardial infarction efforts to develop treatment algorithms on the basis of clinical presentation are increasingly integrated in clinical practice (5).

One important question is how this suicide risk stratification tool can be applied in a clinical practice to optimize individual patient treatment? For example, it is possible that individual patients with a high risk of attempting suicide as identified by the algorithm would benefit from preventive strategies or antisuicidal drugs. For instance, a randomized clinical trial of suicidal patients reported that a selective serotonin-reuptake inhibitor led to a greater acute improvement in suicidal ideation compared to a noradrenergic-dopaminergic drug. Notably, this therapeutic advantage was greater in patients with the most severe suicidal ideation (Grunebaum et al., 2012). Furthermore, evidence from meta-analysis reported that lithium reduces suicide attempts (Cipriani et al., 2013). In addition, clozapine recently emerged as one option for treatment-resistant patients with BD and also showed a protective effect against suicidal behavior compared with olanzapine (Meltzer et al., 2003). These studies further highlight the need to develop novel suicide stratification algorithms as presented in this study and allow individualized treatments and care for patients predicted with a high risk of attempting suicide.

The current study has some potential limitations. The study sample is small and from the Texas region which may not fully represent the entire United States population. This may explain the reason why comorbid generalized anxiety disorder (GAD) and obsessive-compulsive disorder (OCD) findings were not fully in agreement with previous studies. However, multivariate machine learning techniques may have found unexpected interactions among predictive variables and therefore unexpected results on GAD and OCD. Therefore, future studies should confirm or reject these results. In this sense, the current study serves as a proof-of-concept and future longitudinal studies should collect larger samples from multiple centers to replicate current findings. In line with our hypothesis, our findings are related to patients with mood disorder and may not be generalized to patient with other mental disorders. However, future studies may utilize a similar approach to accommodate other mental disorders. Of note, borderline personality disorder that is also shown to be associated with suicide attempts in patients with mood disorders (Schaffer et al., 2014a) was not included in the algorithm due to missing data in our database. Notwithstanding these limitations, this study is the first to describe and implement a risk stratification tool using machine learning algorithms to identify an individual's probability of attempting suicide among patients with mood disorders. This algorithm could be used in a primary care setting by general practitioners to identify the risk of a mood disorder patient attempting suicide. Future work will focus on validating the algorithm using a larger sample as well as developing a web-based suicide risk calculator. Importantly, the strengths of our study include the application and testing of a multivariate machine learning algorithm in suicide stratification leading to a high area under the ROC curve of 0.77. Notably, a recent study reported that most breast cancer prediction algorithms, including the widely-studied 'Gail score' report area under ROC curves below .70 (Anothaisintawee et al., 2012). Indeed, machine learning is a fascinating field that may change the traditional doctor-patient relationship in psychiatry. We hypothesize that highly accurate predictive models will support important clinical decisions such as selection of treatment options, preventive strategies, and prognosis orientations. For instance, several studies recently utilized machine learning techniques to predict treatment response using functional brain scans and neurocognitive data (Hahn et al., 2015; Johnston et al., 2015; Van Waarde et al., 2015). Moreover, a recent study reported a prediction model able to estimate the risk of renal failure in patients with BD treated with lithium (Castro et al., 2015). Therefore, future studies should develop web-based calculators and medical devices based on validated models to allow translation of these predictive models into clinical practice.

In summary, we report a highly accurate algorithm able to identify suicide attempts in patients with mood disorders using clinical and demographic data. These results suggest that it is possible to utilize clinical measures in identifying individual patients at greater risk of attempting suicide. Lastly, we hypothesize that the combination of genetics, blood markers, neuroimaging, and the clinical signature together with a machine learning algorithm could generate an even more accurate multi-modal signature.

Contributors

Dr. Passos participated in the study design, data collection, data analysis, interpretation of findings, literature search, writing, implementation and approval of final manuscript. Dr. Mwangi participated in the study design, writing, figures, tables, and approval of final manuscript. Dr. Cao participated in the study design, literature search, figures, tables, and approval of final manuscript. Dr. Hamilton participated in the literature search, writing, and approval of final manuscript. Dr. Wu participated in literature search, figures, tables, and approval of final manuscript. Dr. Zhang participated in the literature search, writing and approval of final manuscript. Dr. Zunta-Soares participated in literature search, writing, and approval of final manuscript. Dr. Quevedo participated in the study design, interpretation of findings, writing, and approval of final manuscript. Dr. Kauer-Sant'Anna participated in the study design, interpretation of findings, writing, and approval of final manuscript. Dr. Kapczinski participated in the study design, data analysis, interpretation of findings, literature search, writing, and approval of final manuscript. Dr Soares participated in the study design, data analysis, interpretation of findings, literature search, writing, and approval of final manuscript.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2015.12.066.

References

Almeida, O.P., Draper, B., Snowdon, J., Lautenschlager, N.T., Pirkis, J., Byrne, G., Sim, M., Stocks, N., Flicker, L., Pfaff, J.J., 2012. Factors associated with suicidal thoughts in a large community study of older adults. Br. J. Psychiatry 201, 466–472. http://dx.doi.org/10.1192/bjp.bp.112.110130.

Anothaisintawee, T., Teerawattananon, Y., Wiratkapun, C., Kasamesup, V., Thakkinstian, A., 2012. Risk prediction models of breast cancer: a systematic review of model performances. Breast Cancer Res. Treat. 133, 1–10. http://dx.doi.org/10.1007/s10549-011-1853-z.

Arsenault-Lapierre, G., Kim, C., Turecki, G., 2004. Psychiatric diagnoses in 3275 suicides: a meta-analysis. BMC Psychiatry 4, 37. http://dx.doi.org/10.1186/1471-244X-4-37.

Bhui, K.S., Dinos, S., McKenzie, K., 2012. Ethnicity and its influence on suicide rates and risk. Ethn. Health 17, 141–148. http://dx.doi.org/10.1080/13557858.2011.645151.

Blackmore, E.R., Munce, S., Weller, I., Zagorski, B., Stansfeld, S.A., Stewart, D.E., Caine, E.D., Conwell, Y., 2008. Psychosocial and clinical correlates of suicidal acts: results from a national population survey. Br. J. Psychiatry 192, 279–284. http://dx.doi.org/10.1192/bjp.bp.107.037382.

Blanco, C., Alegría, A.A., Liu, S.-M., Secades-Villa, R., Sugaya, L., Davies, C., Nunes, E.V., 2012. Differences among major depressive disorder with and without co-occurring substance use disorders and substance-induced depressive disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J. Clin. Psychiatry 73, 865–873. http://dx.doi.org/10.4088/JCP.10m06673.

Bostwick, J.M., Pankratz, V.S., 2000. Affective disorders and suicide risk: a reexamination. Am. J. Psychiatry 157, 1925–1932.

Bottlender, R., Jäger, M., Strauss, A., Möller, H.J., 2000. Suicidality in bipolar compared to unipolar depressed inpatients. Eur. Arch. Psychiatry Clin. Neurosci. 250, 257–261.

Brundin, L., Erhardt, S., Bryleva, E.Y., Achtyes, E.D., Postolache, T.T., 2015. The role of inflammation in suicidal behaviour. Acta Psychiatr. Scand. 132, 192–203. http://dx.doi.org/10.1111/acps.12458.

Castro, V.M., Roberson, A.M., McCoy, T.H., Wiste, A., Cagan, A., Smoller, J.W., Rosenbaum, J.F., Ostacher, M., Perlis, R.H., 2015. Stratifying risk for renal insufficiency among lithium-treated patients: an electronic health record study. Neuropsychopharmacology . http://dx.doi.org/10.1038/npp.2015.254.

Cipriani, A., Hawton, K., Stockton, S., Geddes, J.R., 2013. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ 346, f3646.

De Araújo, R.M.F., Mazzochi, L., Lara, D.R., Ottoni, G.L., 2015. Thinking about dying and trying and intending to die: results on suicidal behavior from a large Web-based sample. J. Clin. Psychiatry 76, e359–e365. http://dx.doi.org/10.4088/JCP.13m08864.

Dubey, R., Zhou, J., Wang, Y., Thompson, P.M., Ye, J., 2014. Analysis of sampling techniques for imbalanced data: An $n=648$ ADNI study. Neuroimage 87, 220–241. http://dx.doi.org/10.1016/j.neuroimage.2013.10.005.

Feis, D.-L., Schoene-Bake, J.-C., Elger, C., Wagner, J., Tittgemeyer, M., Weber, B., 2013. Prediction of post-surgical seizure outcome in left mesial temporal lobe epilepsy. NeuroImage Clin. 2, 903–911. http://dx.doi.org/10.1016/j.nicl.2013.06.010.

Foley, D.L., Goldston, D.B., Costello, E.J., Angold, A., 2006. Proximal psychiatric risk factors for suicidality in youth: the Great Smoky Mountains Study. Arch. Gen. Psychiatry 63, 1017–1024. http://dx.doi.org/10.1001/archpsyc.63.9.1017.

Galfalvy, H., Oquendo, M.A., Carballo, J.J., Sher, L., Grunebaum, M.F., Burke, A., Mann, J.J., 2006. Clinical predictors of suicidal acts after major depression in bipolar disorder: a prospective study. Bipolar Disord. 8, 586–595. http://dx.doi.org/10.1111/j.1399-5618.2006.00340.x.

Goes, F.S., McCusker, M.G., Bienvenu, O.J., Mackinnon, D.F., Mondimore, F.M., Schweizer, B., Depaulo, J.R., Potash, J.B., 2012. Co-morbid anxiety disorders in bipolar disorder and major depression: familial aggregation and clinical characteristics of co-morbid panic disorder, social phobia, specific phobia and obsessive-compulsive disorder. Psychol. Med. 42, 1449–1459. http://dx.doi.org/10.1017/S0033291711002637.

Goldstein, T.R., Ha, W., Axelson, D.A., Goldstein, B.I., Liao, F., Gill, M.K., Ryan, N.D., Yen, S., Hunt, J., Hower, H., Keller, M., Strober, M., Birmaher, B., 2012. Predictors of prospectively examined suicide attempts among youth with bipolar disorder. Arch. Gen. Psychiatry 69, 1113–1122. http://dx.doi.org/10.1001/archgenpsychiatry.2012.650.

Gonzalez-Pinto, A., Mosquera, F., Alonso, M., López, P., Ramírez, F., Vieta, E., Baldessarini, R.J., 2006. Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. Bipolar Disord. 8, 618–624. http://dx.doi.org/10.1111/j.1399-5618.2006.00368.x.

Grunebaum, M.F., Ellis, S.P., Duan, N., Burke, A.K., Oquendo, M.A., John Mann, J., 2012. Pilot randomized clinical trial of an SSRI vs bupropion: effects on suicidal behavior, ideation, and mood in major depression. Neuropsychopharmacology 37, 697–706. http://dx.doi.org/10.1038/npp.2011.247.

Hahn, T., Kircher, T., Straube, B., Wittchen, H.-U., Konrad, C., Ströhle, A., Wittmann, A., Pfleiderer, B., Reif, A., Arolt, V., Lueken, U., 2015. Predicting treatment response to cognitive behavioral therapy in panic disorder with agoraphobia by integrating local neural information. JAMA Psychiatry 72, 68. http://dx.doi.org/10.1001/jamapsychiatry.2014.1741.

Hoertel, N., Franco, S., Wall, M.M., Oquendo, M.A., Kerridge, B.T., Limosin, F., Blanco, C., 2015. Mental disorders and risk of suicide attempt: a national prospective study. Mol. Psychiatry 20, 718–726. http://dx.doi.org/10.1038/mp.2015.19.

Holma, K.M., Haukka, J., Suominen, K., Valtonen, H.M., Mantere, O., Melartin, T.K., Sokero, T.P., Oquendo, M.A., Isometsä, E.T., 2014. Differences in incidence of suicide attempts between bipolar I and II disorders and major depressive disorder. Bipolar Disord. 16, 652–661. http://dx.doi.org/10.1111/bdi.12195.

Isometsä, E., Sund, R., Pirkola, S., 2014. Post-discharge suicides of inpatients with bipolar disorder in Finland. Bipolar Disord. 16, 867–874. http://dx.doi.org/10.1111/bdi.12237.

Johnson, J., Horwath, E., Weissman, M.M., 1991. The validity of major depression with psychotic features based on a community study. Arch. Gen. Psychiatry 48, 1075–1081.

Johnston, B.A., Coghill, D., Matthews, K., Steele, J.D., 2015. Predicting methylphenidate response in attention deficit hyperactivity disorder: a preliminary study. J. Psychopharmacol. 29, 24–30. http://dx.doi.org/10.1177/0269881114548438.

Johnston, B.A., Mwangi, B., Matthews, K., Coghill, D., Konrad, K., Steele, J.D., 2014. Brainstem abnormalities in attention deficit hyperactivity disorder support high accuracy individual diagnostic classification. Hum. Brain Mapp. 35, 5179–5189. http://dx.doi.org/10.1002/hbm.22542.

Kapczinski, F., Passos, I.C., 2015. Wet minds, dry minds, and the future of psychiatry as a science. Acta Psychiatr. Scand. 131, 7–8. http://dx.doi.org/10.1111/acps.12357.

Katz, C., Yaseen, Z.S., Mojtabai, R., Cohen, L.J., Galynker, I.I., 2011. Panic as an independent risk factor for suicide attempt in depressive illness: findings from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). J. Clin. Psychiatry 72, 1628–1635. http://dx.doi.org/10.4088/JCP.10m06186blu.

Lee, T.H., Marcantonio, E.R., Mangione, C.M., Thomas, E.J., Polanczyk, C.A., Cook, E.F., Sugarbaker, D.J., Donaldson, M.C., Poss, R., Ho, K.K., Ludwig, L.E., Pedan, A., Goldman, L., 1999. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 100, 1043–1049.

Lenze, E.J., Mulsant, B.H., Shear, M.K., Schulberg, H.C., Dew, M.A., Begley, A.E., Pollock, B.G., Reynolds, C.F., 2000. Comorbid anxiety disorders in depressed elderly

patients. Am. J. Psychiatry 157, 722–728.

Libbrecht, et al., 2015. Machine learning applications in genetics and genomics. Nature Reviews Genetics 16, 321–332. http://dx.doi.org/10.1038/nrg3920.

Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., Abraham, J., Adair, T., Aggarwal, R., Ahn, S.Y., Alvarado, M., Anderson, H.R., Anderson, L.M., Andrews, K.G., Atkinson, C., Baddour, L.M., Barker-Collo, S., Bartels, D.H., Bell, M. L., Benjamin, E.J., Bennett, D., Bhalla, K., Bikbov, B., Bin Abdulhak, A., Birbeck, G., Blyth, F., Bolliger, I., Boufous, S., Bucello, C., Burch, M., Burney, P., Carapetis, J., Chen, H., Chou, D., Chugh, S.S., Coffeng, L.E., Colan, S.D., Colquhoun, S., Colson, K. E., Condon, J., Connor, M.D., Cooper, L.T., Corriere, M., Cortinovis, M., de Vaccaro, K.C., Couser, W., Cowie, B.C., Criqui, M.H., Cross, M., Dabhadkar, K.C., Da-hodwala, N., De Leo, D., Degenhardt, L., Delossantos, A., Denenberg, J., Des Jarlais, D.C., Dharmaratne, S.D., Dorsey, E.R., Driscoll, T., Duber, H., Ebel, B., Er-win, P.J., Espindola, P., Ezzati, M., Feigin, V., Flaxman, A.D., Forouzanfar, M.H., Fowkes, F.G.R., Franklin, R., Fransen, M., Freeman, M.K., Gabriel, S.E., Gakidou, E., Gaspari, F., Gillum, R.F., Gonzalez-Medina, D., Halasa, Y.A., Haring, D., Harrison, J. E., Havmoeller, R., Hay, R.J., Hoen, B., Hotez, P.J., Hoy, D., Jacobsen, K.H., James, S. L., Jasrasaria, R., Jayaraman, S., Johns, N., Karthikeyan, G., Kassebaum, N., Keren, A., Khoo, J.-P., Knowlton, L.M., Kobusingye, O., Koranteng, A., Krishnamurthi, R., Lipnick, M., Lipshultz, S.E., Ohno, S.L., Mabweijano, J., MacIntyre, M.F., Mallinger, L., March, L., Marks, G.B., Marks, R., Matsumori, A., Matzopoulos, R., Mayosi, B. M., McAnulty, J.H., McDermott, M.M., McGrath, J., Mensah, G.A., Merriman, T.R., Michaud, C., Miller, M., Miller, T.R., Mock, C., Mocumbi, A.O., Mokdad, A.A., Moran, A., Mulholland, K., Nair, M.N., Naldi, L., Narayan, K.M.V., Nasseri, K., Norman, P., O'Donnell, M., Omer, S.B., Ortblad, K., Osborne, R., Ozgediz, D., Pa-hari, B., Pandian, J.D., Rivero, A.P., Padilla, R.P., Perez-Ruiz, F., Perico, N., Phillips, D., Pierce, K., Pope, C.A., Porrini, E., Pourmalek, F., Raju, M., Ranganathan, D., Rehm, J.T., Rein, D.B., Remuzzi, G., Rivara, F.P., Roberts, T., De León, F.R., Ro-senfeld, L.C., Rushton, L., Sacco, R.L., Salomon, J.A., Sampson, U., Sanman, E., Schwebel, D.C., Segui-Gomez, M., Shepard, D.S., Singh, D., Singleton, J., Sliwa, K., Smith, E., Steer, A., Taylor, J.A., Thomas, B., Tleyjeh, I.M., Towbin, J.A., Truelsen, T., Undurraga, E.A., Venketasubramanian, N., Vijayakumar, L., Vos, T., Wagner, G. R., Wang, M., Wang, W., Watt, K., Weinstock, M.A., Weintraub, R., Wilkinson, J. D., Woolf, S., Wulf, S., Yeh, P.-H., Yip, P., Zabetian, A., Zheng, Z.-J., Lopez, A.D., Murray, C.J.L., AlMazroa, M.A., Memish, Z.A., 2012. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380, 2095–2128. http://dx.doi.org/10.1016/S0140-6736(12)61728-0.

Mann, J.J., Apter, A., Bertolote, J., Beautrais, A., Currier, D., Haas, A., Hegerl, U., Lonnqvist, J., Malone, K., Marusic, A., Mehlum, L., Patton, G., Phillips, M., Rutz, W., Rihmer, Z., Schmidtke, A., Shaffer, D., Silverman, M., Takahashi, Y., Varnik, A., Wasserman, D., Yip, P., Hendin, H., 2005. Suicide prevention strategies: a sys-tematic review. JAMA 294, 2064–2074. http://dx.doi.org/10.1001/jama.294.16.2064.

Mann, J.J., Currier, D.M., 2010. Stress, genetics and epigenetic effects on the neu-robiology of suicidal behavior and depression. Eur. Psychiatry 25, 268–271. http://dx.doi.org/10.1016/j.eurpsy.2010.01.009.

Meltzer, H.Y., Alps, L., Green, A.I., Altamura, A.C., Anand, R., Bertoldi, A., Bourgeois, M., Chouinard, G., Islam, M.Z., Kane, J., Krishnan, R., Lindenmayer, J.P., Potkin, S., 2003. Clozapine treatment for suicidality in schizophrenia: International Sui-cide Prevention Trial (InterSePT). Arch. Gen. Psychiatry 60, 82–91.

Morina, N., Ajdukovic, D., Bogic, M., Franciskovic, T., Kucukalic, A., Lecic-Tosevski, D., Morina, L., Popovski, M., Priebe, S., 2013. Co-occurrence of major depressive episode and posttraumatic stress disorder among survivors of war: how is it different from either condition alone? J. Clin. Psychiatry 74, e212–e218. http://dx.doi.org/10.4088/JCP.12m07844.

Mwangi, B., Ebmeier, K.P., Matthews, K., Steele, J.D., 2012. Multi-centre diagnostic classification of individual structural neuroimaging scans from patients with major depressive disorder. Brain 135, 1508–1521. http://dx.doi.org/10.1093/brain/aws084.

Mwangi, B., Tian, T.S., Soares, J.C., 2013. A review of feature reduction techniques in neuroimaging. Neuroinformatics 12, 229–244. http://dx.doi.org/10.1007/s12021-013-9204-3.

Neves, F.S., Malloy-Diniz, L.F., Corrêa, H., 2009. Suicidal behavior in bipolar disorder: what is the influence of psychiatric comorbidities? J. Clin. Psychiatry 70, 13–18.

Oquendo, M.A., Currier, D., Liu, S.-M., Hasin, D.S., Grant, B.F., Blanco, C., 2010. In-creased risk for suicidal behavior in comorbid bipolar disorder and alcohol use disorders: results from the National Epidemiologic Survey on Alcohol and Re-lated Conditions (NESARC). J. Clin. Psychiatry 71, 902–909. http://dx.doi.org/10.4088/JCP.09m05198gry.

Oquendo, M.A., Perez-Rodriguez, M.M., Poh, E., Sullivan, G., Burke, A.K., Sublette, M. E., Mann, J.J., Galfalvy, H., 2014a. Life events: a complex role in the timing of suicidal behavior among depressed patients. Mol. Psychiatry 19, 902–909. http://dx.doi.org/10.1038/mp.2013.128.

Oquendo, M.A., Sullivan, G.M., Sudol, K., Baca-Garcia, E., Stanley, B.H., Sublette, M.E., Mann, J.J., 2014b. Toward a biosignature for suicide. Am. J. Psychiatry 171, 1259–1277. http://dx.doi.org/10.1176/appi.ajp.2014.14020194.

Perlis, R.H., 2013. A clinical risk stratification tool for predicting treatment re-sistance in major depressive disorder. Biol. Psychiatry 74, 7–14. http://dx.doi.org/10.1016/j.biopsych.2012.12.007.

Perlis, et al., 2007. Treatment-Associated Suicidal Ideation and Adverse Effects in an Open, Multicenter Trial of Fluoxetine for Major Depressive Episodes. Psychother Psychosom 76, 40–46. http://dx.doi.org/10.1159/000096363.

Post, R.M., Kalivas, P., 2013. Bipolar disorder and substance misuse: pathological and therapeutic implications of their comorbidity and cross-sensitisation. Br. J. Psychiatry 202, 172–176. http://dx.doi.org/10.1192/bjp.bp.112.116855.

Tibshirani, Robert, 2011. Regression shrinkage and selection via the lasso: a retro-spective. J. R. Stat. Soc. 73, 273–282.

Schaffer, A., Isometsä, E.T., Tondo, L., Moreno, H., Turecki, D., Reis, G., Cassidy, C., Sinyor, F., Azorin, M., Kessing, J.-M., Ha, L.V., Goldstein, K., Weizman, T., Beau-trais, A., Chou, A., Diazgranados, Y.-H., Levitt, N., Zarate, A.J., Rihmer, C.A., Ya-tham, L.N., Z., 2014a. International Society for Bipolar Disorders Task Force on Suicide: meta-analyses and meta-regression of correlates of suicide attempts and suicide deaths in bipolar disorder. Bipolar Disord. . http://dx.doi.org/10.1111/bdi.12271

Schaffer, A., Sinyor, M., Reis, C., Goldstein, B.I., Levitt, A.J., 2014b. Suicide in bipolar disorder: characteristics and subgroups. Bipolar Disord. 16, 732–740. http://dx.doi.org/10.1111/bdi.12219.

Shaffer, et al., 2015. International Society for Bipolar Disorders Task Force on Sui-cide: meta-analyses and meta-regression of correlates of suicide attempts and suicide deaths in bipolar disorder. Bipolar disorders 17 (1), 1–16. http://dx.doi.org/10.1111/bdi.12271.

Simon, N.M., Otto, M.W., Wisniewski, S.R., Fossey, M., Sagduyu, K., Frank, E., Sachs, G.S., Nierenberg, A.A., Thase, M.E., Pollack, M.H., 2004. Anxiety disorder co-morbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am. J. Psychiatry 161, 2222–2229. http://dx.doi.org/10.1176/appi.ajp.161.12.2222.

Soloff, P.H., Lynch, K.G., Kelly, T.M., Malone, K.M., Mann, J.J., 2000. Characteristics of suicide attempts of patients with major depressive episode and borderline personality disorder: a comparative study. Am. J. Psychiatry 157, 601–608.

Stein, M.B., 2006. An epidemiologic perspective on social anxiety disorder. J. Clin. Psychiatry 67 (Suppl 1), 3–8.

Tipping, M.E., 2001. Sparse bayesian learning and the relevance vector machine. J. Mach. Learn. Res., 211–244.

Torres, A.R., Ramos-Cerqueira, A.T.A., Ferrão, Y.A., Fontenelle, L.F., do Rosário, M.C., Miguel, E.C., 2011. Suicidality in obsessive-compulsive disorder: prevalence and relation to symptom dimensions and comorbid conditions. J. Clin. Psychiatry 72, 17–26. http://dx.doi.org/10.4088/JCP.09m05651blu.

Turecki, G., 2014. The molecular bases of the suicidal brain. Nat. Rev. Neurosci. 15, 802–816. http://dx.doi.org/10.1038/nrn3839.

Turecki, G., Ernst, C., Jollant, F., Labonté, B., Mechawar, N., 2012. The neurodeve-lopmental origins of suicidal behavior. Trends Neurosci. 35, 14–23. http://dx.doi.org/10.1016/j.tins.2011.11.008.

Van Waarde, J.A., Scholte, H.S., van Oudheusden, L.J.B., Verwey, B., Denys, D., van Wingen, G.A., 2015. A functional MRI marker may predict the outcome of electroconvulsive therapy in severe and treatment-resistant depression. Mol. Psychiatry 20, 609–614. http://dx.doi.org/10.1038/mp.2014.78.

Vapnik, V.N., 1998. Wiley: Statistical Learning Theory. Wiley, New York, p. 768.

Webb, R.T., Lichtenstein, P., Larsson, H., Geddes, J.R., Fazel, S., 2014. Suicide, hospital-presenting suicide attempts, and criminality in bipolar disorder: examination of risk for multiple adverse outcomes. J. Clin. Psychiatry 75, e809–e816. http://dx.doi.org/10.4088/JCP.13m08899.