Chapter 7

Precision psychiatry in bipolar disorder

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7.1 Introduction

Big data is a term used to describe large volumes of measurements, as well as the speed that data is created. There are several methods to analyze big data, including machine learning techniques. To develop a machine learning model, first, a "training" dataset is analyzed to establish a function able to distinguish individual subjects across groups. Later, this model is applied to a new dataset to test the accuracy of the method (Lance, 2020). This model can be improved at a later date by changing the algorithm or by performing additional feature reduction in the dataset (Librenza-Garcia et al., 2017). Because of this ability to evaluate a large quantity of data simultaneously, and for its flexibility to adjustments, these algorithms are ideal for assessing multifactorial disorders (Mwangi, Ebmeier, Matthews, & Douglas Steele, 2012). Another valuable aspect of this method is that machine learning models use each person's unique biological profile, unlike some traditional statistical methods focused on group-level averages. This could improve our clinical guidelines and bring precision medicine closer to psychiatry.

Since the field of big data analytics and machine learning techniques are gaining traction in psychiatric research and might provide predictive models for both clinical practice and public health systems, we provided a table with important points to be considered in machine learning-based studies (Table 7.1). Additionally, Fig. 7.1 shows how a machine learning experiment should be conducted. It is important to note that machine learning is but one of the several methods that can be used to analyze big data.

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TABLE 7.1 Important points to be considered in machine learning-based studies (Passos et al., 2019).

Methodological feature	Considerations
Representativeness of the sample	Was the study truly representative of the target population heterogeneity or included a selected group of users?
In the case of supervised machine learning studies, the subjects in different groups are comparable based on the study design or analysis	Did the study control for the most important confounding factors?
Assessment of the outcome	Independent blind assessment, medical record or self-report?
Machine learning approach	Was the machine learning algorithm used to analyze data clearly described and appropriate? Were metrics of performance presented?
Class imbalance	How did authors address the class imbalance problem?
Test dataset	Was the test dataset "unseen"?
Feature selection and hyperparameter tuning	Did the study describe both feature selection and hyperparameter tuning?
Missing data	Did the study describe how authors handled missing data, including if they were inputted or removed?

Source: Adapted from Passos, I. C., Ballester, P. L., Barros, R. C., Librenza-Garcia, D., Mwangi, B., Birmaher, B., ... Kapczinski, F. (2019). Machine learning and big data analytics in bipolar disorder: A position paper from the International Society for Bipolar Disorders Big Data Task Force. Bipolar Disorders, 21(7), 582–594. https://doi.org/10.1111/bdi.12828.

The present chapter aims to discuss how machine learning techniques and big data analytics are already being used to assess patients with bipolar disorder (BD), and how data-driven approaches can potentially aid in the diagnosis, treatment selection, prognosis, and other possible outcomes prediction in BD. Our goal was to show how these new techniques are likely to support important clinical decisions in the forthcoming years.

7.2 Diagnosis and differential diagnosis

The categorical diagnosis in psychiatry is a source of controversy for the specialty, with the clinical heterogeneity of psychiatric disorders and the overlapping of symptoms contributing to the confusion and difficulty surrounding the routine of diagnosing patients (Dwyer, Falkai, & Koutsouleris, 2018;

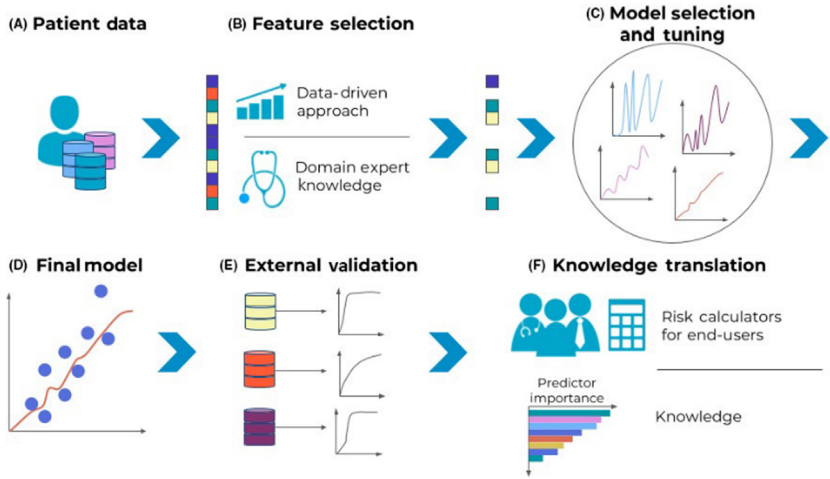

FIGURE 7.1 Essential steps to conducting machine learning models. (A) The patient data come from multiple sources and biological levels. (B) The most important features should be selected in order to reduce the dimensionality of the problem. This step is done mainly in two different forms. One way is through feature selection algorithms that automatically extract information (data driven). The other is by domain experts who identify which features should be kept through their knowledge on the subject (hypothesis driven). (C) Candidate models generated by the induction algorithm. (D) Final model chosen from the candidate pool by a performance metric, such as the area under the ROC curve or accuracy. (E) Model validation with external data, potentially from different institutions to avoid bias. (F) Translation of the knowledge to generate risk calculators (Passos et al., 2019). *Adapted from Passos, I. C., Ballester, P. L., Barros, R. C., Librenza-Garcia, D., Mwangi, B., Birmaher, B., ... Kapczinski, F. (2019). Machine learning and big data analytics in bipolar disorder: A position paper from the International Society for Bipolar Disorders Big Data Task Force.* Bipolar Disorders, 21*(7), 582–594. https://doi.org/10.1111/bdi.12828.*

Fusar-Poli, Hijazi, Stahl, & Steyerberg, 2018; Passos et al., 2019). One of the most common diagnostic mistakes, for instance, is the differential diagnosis between bipolar and unipolar depression. In some scenarios, the rates of misdiagnosis may surpass 60% of cases, and the process until receiving a correct diagnosis may take years and numerous visits to different doctors (Fajutrao, Locklear, Priaulx, & Heyes, 2009; Hirschfeld, Lewis, & Vornik, 2003).

Considering this context, a group of researchers developed a machine learning model, using an SVM algorithm, in the attempt to separate cases of bipolar depression from unipolar depression (Redlich et al., 2014). In their study, they used structural neuroimaging data obtained from a multicentric sample from two countries. The sample of the study was composed by 58 patients with bipolar depression, 58 patients with unipolar depression, and 58 healthy controls. Their best model presented a diagnostic accuracy of 69% when tested on a sample independent from the training dataset, collected in a different country.

Another study (Wollenhaupt-Aguiar et al., 2019) also applied machine learning techniques in the development of models, using support vector machine algorithms, aiming to differentiate patients with bipolar depression, unipolar depression, and healthy controls. Each one of the three groups was composed by 54 patients, and peripheral biomarkers were used as variables in the classification models. One of their models presented a performance corresponding to an area under the ROC (AUROC) curve of 0.69 in the classification between bipolar and unipolar depression. A second model presented an AUROC of 0.7 in the classification between bipolar depression and healthy controls, whereas a third model presented an AUROC of 0.74 in the classification between unipolar depression and healthy controls.

The differential diagnosis between BD, schizophrenia, and healthy controls was explored in a recently published study (Fernandes et al., 2020), which applied *linear discriminant binary classifiers* in a total of 416 participants. The researchers combined specific blood and cognitive biomarkers in their models aiming to predict diagnosis of schizophrenia and BD. Their models presented an AUROC of 0.86 for discriminating between BD patients and healthy controls, an AUROC of 0.89 in the discrimination between schizophrenia patients and healthy controls, and an AUROC of 0.80 in the discrimination between participants with BD and schizophrenia.

Another study (Rabelo-da-Ponte et al., 2020) used an *elastic net* algorithm in order to develop a model which could predict the diagnosis of BD in a Brazilian community cohort, followed from birth up to 22 years ($n = 3778$ subjects), using clinical and demographic variables. Their best model achieved an AUC of 0.82, using variables such as suicide risk, financial problems, parental physical abuse, and generalized anxiety disorder evaluated at age 18, to predict a diagnosis of BD at age 22.

7.3 Prognosis prediction

Prognosis is a venerable component of clinical medicine and an essential component of scientific psychiatry. By focusing on the individual rather than on the disease, the prognosis becomes the cornerstone for shared decision-making approaches and personalized medicine (Fusar-Poli et al., 2018). During recent years, advanced prognostic methods such as machine learning approaches have been used in mental health with the aim of improving clinical risk prediction, in particular with high-dimensional data that characterizes psychiatric disorders (Dwyer et al., 2018; Hahn, Nierenberg, & Whitfield-Gabrieli, 2017; Passos et al., 2019). Some of these studies used machine learning techniques to predict clinical outcomes in patients with BD.

A study (Acosta et al., 2019) built a supervised machine learning model with clinical and demographic data to predict psychosis among 64 youth (children and adolescents) outpatients with BD. The study reported an accuracy of 75% and an AUC of 0.86 in predicting psychosis. The most relevant

predictive variables in differentiating participants with psychosis were bullying, the severity of the disease (the Clinical Global Impression-Severity scale), and suicidal behavior. Another study (Salvini, Da Silva Dias, Lafer, & Dutra, 2015) also used demographic and clinical features, including follow-up variables, to assess depression relapse in 108 patients with BD and achieved an accuracy of 85% and a sensitivity of 92%. Furthermore, a study (Faurholt-Jepsen et al., 2016) using voice features collected in phone calls to classify patients' affective states, achieved an AUC of 0.78 (depressed vs euthymic) and 0.89 (manic/mixed vs euthymic).

These proof-of-concept and experimental protocols illustrate machine learning's potential to aid in the clinical assessment of BD patients, yielding models with sufficient accuracy to monitor mood states in real-time, which may help assess disease activity and advance early interventions (Passos et al., 2019).

7.4 Suicidality prediction

Suicide is a global health concern with approximately 800,000 deaths by suicide worldwide every year, which is one person every 40 seconds (WHO| Suicide data, 2017). In the United States, suicide rates have risen to a 30-year high, tragically making suicide one of the top 10 causes of death among those aged 10−64 (Curtin, Warner, & Hedegaard, 2016). While universal screening for suicide is a goal, it is not yet the standard, as implementation serves as the chief barrier. Patients and healthcare providers alike need a simple yet effective means of quickly identifying risk factors for potential suicidal patients during preliminary evaluations. The grave disparity among research advances and current suicide rates has opened the door for machine learning and big data (Cavalcante Passos, Mwangi, & Kapczinski, 2019).

Some studies have used machine learning techniques to predict suicidality. A study (Passos et al., 2016) tested a set of machine learning algorithms coupled with clinical and demographic variables to develop a clinical signature of suicidality in 144 patients with mood disorders, including BD. The study reported a balanced accuracy of 72% and an AUC of 0.77 in predicting suicide attempts. Prior hospitalizations for depression, comorbid posttraumatic stress disorder, cocaine dependence, and history of psychotic symptoms were the most robust variables in the model.

Other studies also predicted suicidality by using machine learning coupled with a combined genomic and clinical risk assessment approach and built models with an AUC of 0.98 (Niculescu et al., 2015) and 0.82 (Levey et al., 2016) in patients with BD. It is also worth mentioning that a recent text classification study used letters and diaries of Virginia Woolf to identify written patterns associated with suicide (De Ávila Berni et al., 2018). The authors found an AUC of 0.80 and a balanced accuracy of 80.45% by using Naïve Bayes machine learning algorithm.

7.5 Treatment selection

People with BD spend up to a third of their lives depressed, often suffering from long-term disability and early mortality (Saunders & Goodwin, 2010). These patients are submitted to multiple therapeutic regimens to control depressive and manic symptoms through life and, even though there are guidelines to guide treatments (Yatham et al., 2018), around 60% of them relapse into a mood episode within 2 years of treatment initiation (Gitlin, Swendsen, Heller, & Hammen, 1995). To construct these therapeutic guidelines, researchers use randomized clinical trials and meta-analyses that provide average group-level results based on measures of central tendency and variance. Machine learning techniques can be used to develop a novel way to make treatment decisions, using big data to propose more accurate treatments.

Artificial intelligence can be used to create user-friendly tools to direct personalized treatments, aid hospital workflows, and optimize clinical records (Chekroud et al., 2017). A calculator could predict, for example, the probability of a patient responding to certain medication. This use of machine learning techniques was already implemented in a sample of BD patients. The system LITHIA was able to predict symptom reduction with lithium use at 8 weeks posttreatment with at least 80% accuracy (Fleck et al., 2017). Another example of this use of algorithms to find which patients would have treatment response was the study developed by Nunes et al. (2020). Using a random forest model, they analyzed a large sample of clinical data from lithium-treated patients ($n = 1266$, 34.7% responders), collected across seven sites, internationally. Their model was able to predict lithium response, with an AUROC curve of 0.80 (95% CI 0.78−0.82). It is also important to point out that this model, which featured variables related to clinical course and the absence of rapid cycling, demonstrated a particularly low false-positive rate (specificity 0.91 [0.88−0.92]).

Machine learning techniques can also be used to predict medication side effects. A study utilizing 1445 bipolar patients' electronic health records was able to determine, with an AUROC curve of 0.81, about 74% of renal insufficiency cases (Castro et al., 2016). To build this model, the authors considered the following variables to be of greater risk: use of lithium more than once daily, lithium levels greater than 0.6 mEq/L, and concomitant use of first-generation antipsychotics. These results propose an optimistic view of how in the near future, physicians could stratify risk for renal failure among lithium-treated patients.

In the future, machine learning techniques can also help guide the medical staff to propose other interventions to bipolar patients. Wade et al. used neuroimaging to predict which patients would respond to electro-electroconvulsive therapy with up to 89% accuracy (Wade et al., 2016). Treatment response and side effects prediction may potentially reduce the

duration of mood episodes and help to tailor the maintenance treatment. This could change how doctors prescribe medication and other interventions, avoiding options with a low success probability and testing multiple medications (Librenza-Garcia et al., 2017). These studies demonstrate the big data analytics' potential to change how we prescribe bipolar patients.

7.6 Supervised and unsupervised learning

The process of learning for a machine learning algorithm can be divided into different types, supervised and unsupervised, depending on the characteristics of the process of learning.

Supervised learning refers to the process in which a human programmer ("the supervisor") gives the machine specific information, also known as training labels, such as the predictors and/or the expected outcomes, for the training process. In this type of learning, which is the most commonly used in medicine, the machine learns in a fixed direction, from the predictor toward the outcome. Moreover, the supervisor being someone who knows the correct answer to the problem the machine is trying to solve, is able to point out and address eventual mistakes in the learning process. Tasks such as *regression* and *classification* use supervised learning methods (Dwyer et al., 2018; Kueper, Terry, Zwarenstein, & Lizotte, 2020; Passos et al., 2019). Most part of the studies above mentioned used supervised learning.

Unsupervised learning, however, is a process of learning that does not require to be given specific training labels, such as outcomes or predictors, before learning from data. One example of unsupervised learning task is *clustering*, which refers to the grouping of data according to specific characteristics that they share among them, such as exploring symptoms or biomarkers and grouping them autonomously. This type of learning is useful, because it may find correlations among variables that were not visible to researchers before the analysis (Dwyer et al., 2018; Passos et al., 2019; Roohi, Faust, Djuric, & Diamandis, 2020).

In addition to supervised and unsupervised learning, there is another type called semisupervised learning, which combines aspects of both methods of learning to create a model to solve a specific problem. In this method, some observations are labeled while others are not (Dwyer et al., 2018).

7.7 Conclusion

The field of artificial intelligence in BD is rapidly expanding. These technologies are helping us to improve our understanding of the pathophysiology of this disorder, and in the near future, they could change our overall understanding of this mental illness. Machine learning techniques may also help differentiate BD from healthy controls and other psychiatric diagnoses and may aid in predicting severe outcomes such as suicide attempts.

Furthermore, a focus on individuals, not group-level averages, by using machine learning models to leverage each person's unique biological profile, could improve treatment selections, and bring precision medicine closer to psychiatry.

It is important to note, however, that although we have a plethora of studies using machine learning and big data approaches to tackle complex questions in BD, knowledge translation to clinical practice is still underdeveloped. Obstacles, including computational power, multimodality, assessment of rare events, cost and nonstationary distribution of the data, heterogeneity both phenotypically and etiologically, lack of a uniform pipeline for machine learning studies, lack of interpretability, and ethical issues need to be addressed.

References

Acosta, J. R., Librenza-Garcia, D., Watts, D., Francisco, A. P., Zórtea, F., Raffa, B., … Passos, I. C. (2019). Bullying and psychotic symptoms in youth with bipolar disorder. *Journal of Affective Disorders*, *265*, 603−610. Available from https://doi.org/10.1016/j.jad.2019.11.101.

Castro, V. M., Roberson, A. M., McCoy, T. H., Wiste, A., Cagan, A., Smoller, J. W., … Perlis, R. H. (2016). Stratifying risk for renal insufficiency among lithium-treated patients: An electronic health record study. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *41*(4), 1138−1143. Available from https://doi.org/10.1038/npp.2015.254.

Cavalcante Passos, I., Mwangi, B., & Kapczinski, F. (2019). *Personalized psychiatry: Big data analytics in mental health*. Available from https://doi.org/10.1007/978-3-030-03553-2.

Chekroud, A. M., Gueorguieva, R., Krumholz, H. M., Trivedi, M. H., Krystal, J. H., & McCarthy, G. (2017). Reevaluating the efficacy and predictability of antidepressant treatments: A symptom clustering approach. *JAMA Psychiatry*, *74*(4), 370−378. Available from https://doi.org/10.1001/jamapsychiatry.2017.0025.

Curtin, S. C., Warner, M., & Hedegaard, H. (2016). Increase in suicide in the United States, 1999−2014. *NCHS Data Brief*.

De Ávila Berni, G., Rabelo-Da-Ponte, F. D., Librenza-Garcia, D., Boeira, M. V., Kauer-Sant'Anna, M., Passos, I. C., & Kapczinski, F. (2018). Potential use of text classification tools as signatures of suicidal behavior: A proof-of-concept study using Virginia woolf's personal writings. *PLOS ONE*, *13*(10), e0204820. Available from https://doi.org/10.1371/journal.pone.0204820.

Dwyer, D. B., Falkai, P., & Koutsouleris, N. (2018). Machine learning approaches for clinical psychology and psychiatry. *Annual Review of Clinical Psychology*, *14*, 91−118. Available from https://doi.org/10.1146/annurev-clinpsy-032816-045037.

Fajutrao, L., Locklear, J., Priaulx, J., & Heyes, A. (2009). A systematic review of the evidence of the burden of bipolar disorder in Europe. *Clinical Practice and Epidemiology in Mental Health*, *5*, 3. Available from https://doi.org/10.1186/1745-0179-5-3.

Faurholt-Jepsen, M., Busk, J., Frost, M., Vinberg, M., Christensen, E. M., Winther, O., … Kessing, L. V. (2016). Voice analysis as an objective state marker in bipolar disorder. *Translational Psychiatry*, *6*(7), e856. Available from https://doi.org/10.1038/tp.2016.123.

Fernandes, B. S., Karmakar, C., Tamouza, R., Tran, T., Yearwood, J., Hamdani, N., ... Leboyer, M. (2020). Precision psychiatry with immunological and cognitive biomarkers: A multi-domain prediction for the diagnosis of bipolar disorder or schizophrenia using machine learning. *Translational Psychiatry*, *10*(1), 162. Available from https://doi.org/10.1038/s41398-020-0836-4.

Fleck, D. E., Ernest, N., Adler, C. M., Cohen, K., Eliassen, J. C., Norris, M., ... Strakowski, S. M. (2017). Prediction of lithium response in first-episode mania using the LITHium Intelligent Agent (LITHIA): Pilot data and proof-of-concept. *Bipolar Disorders*, *19*(4), 259−272. Available from https://doi.org/10.1111/bdi.12507.

Fusar-Poli, P., Hijazi, Z., Stahl, D., & Steyerberg, E. W. (2018). The science of prognosis in psychiatry: A review. *JAMA Psychiatry*, *75*(12), 1289−1297. Available from https://doi.org/10.1001/jamapsychiatry.2018.2530.

Gitlin, M. J., Swendsen, J., Heller, T. L., & Hammen, C. (1995). Relapse and impairment in bipolar disorder. *American Journal of Psychiatry*, *152*(11), 1635−1640. Available from https://doi.org/10.1176/ajp.152.11.1635.

Hahn, T., Nierenberg, A. A., & Whitfield-Gabrieli, S. (2017). Predictive analytics in mental health: Applications, guidelines, challenges and perspectives. *Molecular Psychiatry*, *22*(1), 37−43. Available from https://doi.org/10.1038/mp.2016.201.

Hirschfeld, R. M. A., Lewis, L., & Vornik, L. A. (2003). Perceptions and impact of bipolar disorder: How far have we really come? Results of the National Depressive and Manic-Depressive Association 2000 Survey of individuals with bipolar disorder. *Journal of Clinical Psychiatry*, *64*(2), 161−174. Available from https://doi.org/10.4088/JCP.v64n0209.

Kueper, J. K., Terry, A. L., Zwarenstein, M., & Lizotte, D. J. (2020). Artificial intelligence and primary care research: A scoping review. *Annals of Family Medicine*, *18*(3), 250−258. Available from https://doi.org/10.1370/afm.2518.

Lance, B. (2020). Machine learning with R: Expert techniques for predictive modeling, 3rd edition. *Journal of Strength and Conditioning Research*.

Levey, D. F., Niculescu, E. M., Le-Niculescu, H., Dainton, H. L., Phalen, P. L., Ladd, T. B., ... Niculescu, A. B. (2016). Towards understanding and predicting suicidality in women: Biomarkers and clinical risk assessment. *Molecular Psychiatry*, *21*(6), 768−785. Available from https://doi.org/10.1038/mp.2016.31.

Librenza-Garcia, D., Kotzian, B. J., Yang, J., Mwangi, B., Cao, B., Pereira Lima, L. N., ... Passos, I. C. (2017). The impact of machine learning techniques in the study of bipolar disorder: A systematic review. *Neuroscience and Biobehavioral Reviews*, *80*, 538−554. Available from https://doi.org/10.1016/j.neubiorev.2017.07.004.

Mwangi, B., Ebmeier, K. P., Matthews, K., & Douglas Steele, J. (2012). Multi-centre diagnostic classification of individual structural neuroimaging scans from patients with major depressive disorder. *Brain*, *135*(Pt 5), 1508−1521. Available from https://doi.org/10.1093/brain/aws084.

Niculescu, A. B., Levey, D. F., Phalen, P. L., Le-Niculescu, H., Dainton, H. D., Jain, N., ... Salomon, D. R. (2015). Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach. *Molecular Psychiatry*, *20*(11), 1266−1285. Available from https://doi.org/10.1038/mp.2015.112.

Nunes, A., Ardau, R., Berghöfer, A., Bocchetta, A., Chillotti, C., Deiana, V., ... Alda, M. (2020). Prediction of lithium response using clinical data. *Acta Psychiatrica Scandinavica*, *141*(2), 131−141. Available from https://doi.org/10.1111/acps.13122.

Passos, I. C., Mwangi, B., Cao, B., Hamilton, J. E., Wu, M. J., Zhang, X. Y., ... Soares, J. C. (2016). Identifying a clinical signature of suicidality among patients with mood disorders: A

pilot study using a machine learning approach. *Journal of Affective Disorders*, *193*, 109−116. Available from https://doi.org/10.1016/j.jad.2015.12.066.

Passos, I. C., Ballester, P. L., Barros, R. C., Librenza-Garcia, D., Mwangi, B., Birmaher, B., … Kapczinski, F. (2019). Machine learning and big data analytics in bipolar disorder: A position paper from the International Society for Bipolar Disorders Big Data Task Force. *Bipolar Disorders*, *21*(7), 582−594. Available from https://doi.org/10.1111/bdi.12828.

Rabelo-da-Ponte, F. D., Feiten, J. G., Mwangi, B., Barros, F. C., Wehrmeister, F. C., Menezes, A. M., … Kunz, M. (2020). Early identification of bipolar disorder among young adults − a 22-year community birth cohort. *Acta Psychiatrica Scandinavica*, *142*(6), 476−485. Available from https://doi.org/10.1111/acps.13233.

Redlich, R., Almeida, J. R., Grotegerd, D., Opel, N., Kugel, H., Heindel, W., … Dannlowski, U. (2014). Brain morphometric biomarkers distinguishing unipolar and bipolar depression: A voxel-based morphometry-pattern classification approach. *JAMA Psychiatry*, *71*(11), 1222−1230. Available from https://doi.org/10.1001/jamapsychiatry.2014.1100.

Roohi, A., Faust, K., Djuric, U., & Diamandis, P. (2020). Unsupervised machine learning in pathology: The next frontier. *Surgical Pathology Clinics*, *13*(2), 349−358. Available from https://doi.org/10.1016/j.path.2020.01.002.

Salvini, R., Da Silva Dias, R., Lafer, B., & Dutra, I. (2015). A multi-relational model for depression relapse in patients with bipolar disorder. *Studies in Health Technology and Informatics*, *216*, 741−745. Available from https://doi.org/10.3233/978-1-61499-564-7-741.

Saunders, K. E. A., & Goodwin, G. M. (2010). The course of bipolar disorder. *Advances in Psychiatric Treatment*, *16*, 318−328. Available from https://doi.org/10.1192/apt.bp.107.004903.

Wade, B. S. C., Joshi, S. H., Njau, S., Leaver, A. M., Vasavada, M., Woods, R. P., … Narr, K. L. (2016). Effect of electroconvulsive therapy on striatal morphometry in major depressive disorder. *Neuropsychopharmacology*, *41*(10), 2481−2491. Available from https://doi.org/10.1038/npp.2016.48.

WHO Suicide Data. (2017). *WHO*. Retrieved from http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/

Wollenhaupt-Aguiar, B., Librenza-Garcia, D., Bristot, G., Przybylski, L., Stertz, L., Kubiachi Burque, R., … Kapczinski, F. (2019). Differential biomarker signatures in unipolar and bipolar depression: A machine learning approach. *Australian and New Zealand Journal of Psychiatry*, *54*(4), 393−401. Available from https://doi.org/10.1177/0004867419888027.

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Bond, D. J., Frey, B. N., … Berk, M. (2018). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disorders*, *20*(2), 97−170. Available from https://doi.org/10.1111/bdi.12609.