Outline of study submission

Date Submitted: February 12, 2020

Principal Investigator:
Jon Grant, JD, MPH, MD (CV attached)

Title: Professor of Psychiatry & Behavioral Neuroscience
Institution: University of Chicago
Address: 5841 S. Maryland Avenue, Chicago, IL 60637
Phone: 773-834-1325

Title

A Double-Blind, Placebo-Controlled Study of Brexpiprazole in the Treatment of Borderline Personality Disorder.

This project will take place at the University of Chicago. Dr. Jon E. Grant, MD, JD is the Principal Investigator and can be phoned at 773-834-1325 or reached by email at jongrant@uchicago.edu.

This clinical trial will be conducted in the spirit of Good Clinical Practice and in accordance with this IRB-approved protocol. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such a case, the deviation will be reported to the IRB as soon as possible.

Objective

The primary objective of the proposed study is to evaluate the safety and efficacy of Brexpiprazole in adults with borderline personality disorder (BPD). Eighty subjects with BPD will be randomized in a 1:1 fashion to either Brexpiprazole (starting at 1mg/day for one week and going to 2mg in a fixed dose fashion after 1 week) or matching placebo for 12 weeks of active treatment. The hypothesis to be tested is that Brexpiprazole will result in greater rates of reduction in symptoms of BPD compared to placebo (improvement in symptoms will be indicated by lower scores on established outcome measures of BPD symptoms that have been used in prior studies).

Background of BPD

Borderline personality disorder is characterized by mood instability, cognitive symptoms, impulsive behavior, and disturbed relationships (1–3). A variety of psychotherapies have been developed (4–6) and, while research on the use of medication is ongoing, no drug has been approved in the United States or elsewhere for its treatment (7). Second generation antipsychotics have been the most intensively studied (8–11). Current treatments for BPD are often inadequate. Dialectical behavioral therapy has been shown to reduce BPD but finding trained psychologists is difficult.

Choice of Medication

One illness that is difficult to treat is borderline personality disorder (12–17), which is characterized by a pervasive pattern of severe psychopathological symptoms with instability of

affect regulation, impulse control, and aggression (18-24). Dysfunctions in the serotoninergic and dopaminergic systems have been demonstrated in—and considered as possible causes for—symptoms associated with the disorder (25-28). Several studies on the use of traditional (29) and atypical antipsychotic agents in patients with borderline personality disorder (30–31) have shown a positive effect on individual symptoms (29, 32–36). However, we are not aware of any study evaluating Brexpiprazole in the treatment of patients with borderline personality disorder. In the proposed double-blind, placebo-controlled study, the influence of Brexpiprazole on the multifaceted psychopathological symptoms and aggression of patients with borderline personality disorder will be investigated.

Brexpiprazole therefore has distinctive properties that make it a promising option for patients with BPD. Brexpiprazole is a novel D2 partial agonist, has affinity for 5-HT1A, acts as an antagonist of the noradrenergic α1/2 receptor, partial agonist for D3, and antagonist for 5-HT2A (37-39). In addition, because of low rates of side effects, Brexpiprazole should be a well-tolerated and in fact desired medication approach to BPD.

The aim of the present study is to examine the efficacy and safety of Brexpiprazole vs. placebo in adults with BPD, as indicated by a score of at least 9 on the Zanarini Rating Scale for Borderline Personality Disorder ("Zanarini scale"), a scale of illness severity, at the baseline visit.

Study Design/Methodology

Eighty individuals with a prior diagnosis of BPD will be recruited for a double-blind, placebo-controlled pilot study in which Brexpiprazole or placebo is administered in a 1:1 fashion. All 80 subjects will have current BPD per DSM-5 criteria. Following baseline measures, subjects will receive Brexpiprazole (1mg/day for one week and then 2mg/day thereafter) or inactive placebo. Participants will be seen every week for the first 2 weeks and then every 2 weeks after that. At week 12, subjects will start a 1-week taper off the medication. Efficacy and safety measures will be performed at each visit.

Study Population/Sample Size

80 male and female outpatients aged 18-65 with a current primary diagnosis of BPD.

Subjects

Inclusion criteria:

1) Men and women age 18-65;
2) Primary diagnosis of BPD
3) Zanarini scale score of at least 9 at baseline
4) Ability to understand and sign the consent form.

Exclusion criteria:

1) Unstable medical illness based on history or clinically significant abnormalities on baseline physical examination
2) Subjects with schizophrenia or bipolar I disorder
3) Subjects with an active substance use disorder
4) Current pregnancy or lactation, or inadequate contraception in women of childbearing potential
5) Subjects considered an immediate suicide risk based on the Columbia Suicide Severity rating Scale (C-SSRS) (www.cssrs.columbia.edu/docs)

6) Illegal substance use based on urine toxicology screening (excluding marijuana given the high rates of marijuana use in BPD and the lack of interaction with brexpiprazole).
7) Initiation of psychological interventions within 3 months of screening
8) Use of any new psychotropic medication started within the last 3 months prior to study initiation
9) Previous treatment with Brexpiprazole
10) Cognitive impairment that interferes with the capacity to understand and self-administer medication or provide written informed consent

Advertisements will target this study population. Interested individuals will be asked to contact a study coordinator or complete an online survey expressing interest. Individuals will then undergo a phone screen before being scheduled for a first appointment. After being screened, potential subjects will be scheduled for a first appointment in which we will confirm medical and psychiatric history, laboratory tests, and inclusion/exclusion criteria.

Drugs, Dosages, and Regimens

All subjects who are randomized to Brexpiprazole will receive 1mg/day during the first week of the study, and then 2mg/day for the remainder of the study. Dosage changes and reductions will not be permitted. After study conclusion, the dose will be tapered off during a 1-week follow-up period.

Randomization

Participants are randomized (1:1) to receive placebo or brexpiprazole by the investigational pharmacy at the University of Chicago. The study blind will be maintained by over-encapsulation, making placebo and active treatments appear identical in size, weight, shape, and color. Dosage changes and reductions will not be permitted during the study and participants will be discontinued if they experienced intolerance.

Blinding

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that patient may be broken by the treating physician.

Treatment Duration, Visit Frequency, and Procedures

This is a 13-week study (12 weeks of acute treatment followed by a 1-week tapering phase). Subjects will be seen at baseline and then every week for the first 2-4 weeks and then every two weeks after that.

Assessments at each visit

Those subjects who appear appropriate for the study, based on telephone screening, will be invited for a baseline assessment. The duration of the baseline assessment will be approximately 90 minutes and will include the following: Informed consent, Demographic data, Concomitant medications (no psychotropic medications will be allowed), Family history data, Medical evaluation including physical examination, EKG, weight, and vital signs, Urine pregnancy test (for women of childbearing years) and urine drug screen, and a psychiatric evaluation (using the following measures: MINI International Neuropsychiatric Interview (40); Depressive symptoms will be rated with the 24-item Hamilton Depression Rating Scale (HAM-D) (41); Anxiety

symptoms will be assessed using the Hamilton Anxiety Rating Scale (HAM-A) (42); Psychosocial functioning will be evaluated using the patient-rated version of the Sheehan Disability Scale (SDS) (43); Quality of Life Inventory (QOLI) (44); The Cambridge-Chicago Compulsivity Trait Scale (CHI-T); and the Columbia Suicide Severity Rating Scale (C-SSRS)). During the consent process, individuals will be given time to review the consent form and given the opportunity to ask any questions that may arise before signing the informed consent form. Throughout the study, subjects will be asked questions about the study to ensure that they continue understanding study procedures. Blood samples will be collected at both baseline and last visits to measure blood sugar, glutathione, and cholesterol levels. All follow-up visits will include safety measures (adverse events, vital signs, C-SSRS), weight, BPD measures, and other psychiatric measures.

Due to the pandemic of COVID19, study participants can perform their baseline and follow-up visits online using encrypted Zoom instead of in person visits. All inventories will be assessed. Blood samples and urine toxicology, however, will be at the discretion of the study PI. In cases where they are considered medically necessary, the participant can have them drawn locally and submitted to the study team.

Efficacy evaluation:
The primary outcome measure will be the change from baseline using the Zanarini Rating Scale for Borderline Personality Disorder ("Zanarini scale") (45). This semistructured interview has anchored ratings (0=no symptoms, 4=severe symptoms) on nine items that correspond to the DSM-5 BPD criteria. Its subscales will be considered secondary efficacy measures.

Secondary efficacy measures include Modified Overt Aggression Scale (46), the Young Mania Rating Scale (47), and the self-report version of the Zanarini scale (48), the Borderline Evaluation of Severity Over Time (49), the Barratt Impulsiveness Scale (50) the Minnesota Impulsive Disorders Interview (51), the Symptom Checklist–90–Revised (SCL-90-R) (52), and the scales listed above (41-44).

Cognitive Measures
Cognitive assessments consist of two previously validated tests taken from CANTABeclipse software. The choice of cognitive challenges was based on the clinical features of BPD. The order of the tasks will be fixed and participants will complete the tasks at first visit (baseline), midway through 13-week timeline, and endpoint.

Cognitive flexibility, i.e., set-shifting, will be measured using the Intra-dimensional/Extra-dimensional Shift Task (ID/ED task). Participants are presented with two stimuli on-screen for each trial and attempted to learn an underlying 'rule' about which stimulus was correct. Key outcome measures will be number of errors made at the intra-dimensional shift and at the extra-dimensional shift stage.

The Tower of London task will be used to examine executive planning. On each trial of the task, subjects observe two sets of pockets each containing three colored balls on-screen. On 'move' trials, subjects have to attempt to work out 'in mind' the minimum number of moves required to move the balls in one set of pockets to match a goal arrangement also shown in the other set of pockets.

The probabilistic beliefs task will allow us to examine the subject's self-other distinction. Participants observe a sequence of neutral images on the screen and are occasionally asked to

make responses on a keyboard. Participants will be asked to keep track of the images they see and make predictions about what will happen next. They will also be asked to keep track of another theoretical person's beliefs about what will happen next. The task will allow us to submit self-other distinctions, a potentially important dimension of BPD, to quantitative assessment and computational modelling.

Subject Withdrawal
If a subject withdraws from the study, all instruments administered at the screening visit will be completed at the final visit. These will be conducted when the subject is able to come in for an early termination visit. Withdrawn subjects will be given the phone number of the principal investigator as well as the phone numbers of local resources for depression treatment.

Safety Assessments
Safety and tolerability will be assessed using spontaneously reported adverse events data, C-SSRS, vital signs, and by evaluating premature termination. Safety assessments (sitting blood pressure, heart rate, adverse effects, and concomitant medications) will be documented at each visit. Subjects who are an immediate suicide risk will be removed from the study and appropriate clinical intervention (e.g. hospitalization) will be arranged. Study team members are mandated reporters and as such, will arrange for the subject to be taken to the emergency room if any intent to harm themselves is expressed. Urine pregnancy tests will be performed at the initial visit. Subjects who have a positive urine pregnancy test will be excluded from the study. Assessment of side effects will be done at each visit.

Adverse Event Reporting
Unanticipated (unexpected) problems/events, those that are not already described as potential risks in the consent form, or not part of an underlying disease, will be reported to the IRB as soon as possible. The same will be done for serious problems/events and, in the opinion of the investigator, are possibly, probably or definitely related to the research procedures. A follow-up report will also be submitted to the IRB with any documentation related to a previously submitted adverse event.

Risks
Participants may experience side effects while taking the drugs used in this study. Side effects are usually reversible when the drug is stopped but occasionally continue and may cause serious complications, if subjects experience any side effects, they will be asked to contact the study doctor immediately.

There may be other risks that could arise which are not reasonably foreseeable. If new information becomes available which could influence their willingness to continue, this new information will be discussed with the participant.

While taking the study drug, the subject's condition may remain the same or worsen due to no effect of the study drug.

Risks of Brexpiprazole
The most common side effects associated with Brexpiprazole include:

- Weight gain
- Inner sense of restlessness (feeling like one needs to move)

Brexpiprazole may cause more serious side effects including:

- Stroke in elderly people
- Neuroleptic Malignant Syndrome (high fever, stiff muscles, sweating, changes in pulse, heart rate and blood pressure)
- Tardive dyskinesia (uncontrollable body movements)
- High blood sugar
- Low white blood cell count
- Decreased blood pressure
- Seizures
- Problems controlling your body temperature so that the individual feel too warm
- Difficulty swallowing that can cause food or liquid to get into the lungs

Risks of Electrocardiagram
If subjects are asked to get an ECG, they may have some discomfort when the electrodes (soft patches attached using adhesive tape) are removed from their chest and limbs. There is a possibility they could develop a minor rash when the electrodes were placed. This rash should go away without treatment.

Risks of blood draws
Needle sticks can cause discomfort, pain, burning sensation or bruising.

Data and Safety Monitoring Plan

1. Responsibility for Data and Safety Monitoring
   The PI will have overall responsibility for monitoring the integrity of study data and participant safety.
2. Procedures for Monitoring Participant Safety
   The PI will implement the following procedures to ensure data integrity and the safety of participants during the study.
   - A number of elements of the research plan are intended to minimize the risks of study participation. If subjects become actively suicidal with intent and plan to kill themselves, the PI will evaluate them and refer them for immediate non-study treatment. Any participant endorsing suicidal thoughts with intent and plan will be immediately evaluated by the PI and referred to a higher level of care if clinically indicated.
   - The PI will evaluate patient safety and resolve any safety issues if necessary, as such issues arise. The PI will also be responsible for preparing written summary reports of adverse events and will prepare a written report summarizing any decisions that are made pertaining to participant disposition.
   - Data integrity and confidentiality will be safeguarded as discussed above in the Data Management and Statistical Analysis section under Research Methods.

Monitoring Committee

We will establish a monitoring committee and define in detail its role, its composition, and its operating procedures for reviewing patient safety and data from this study. The monitoring committee, comprised of two individuals independent of personnel involved in the study, including a psychiatrist and a statistician, will come together via conference call yearly. The committee will use a standardized approach employing contemporary bio statistical, psychiatric/psychological, and ethical principles to review study design and interim data every year. The committee will audit the records from the study and will ensure the data are being collected, managed and protected. The committee will have the ability to ask for more frequent

reviews at any time if they deem it necessary. In addition, the PI will inform the committee of any serious adverse event.
The PI will prepare a specific report for the committee in advance of each meeting. Attention will be given to data quality and timeliness, recruitment, risk versus benefit, adverse events and other factors that could affect study outcome.

3. **Reporting Adverse Events**
    - Any serious adverse event will be reported to the Institutional Review Board (IRB) at the University of Chicago in a full written report within 10 working days of the event. For fatal/life-threatening serious adverse events, the PI will notify the IRB Chair by phone immediately.
    - Any moderate adverse event which appears definitely, probably, or possibly related to study participation will be reported to the University of Chicago IRB in writing within 20 working days.
    - Any mild adverse event will be summarized in the IRB annual progress reports.

Data Analysis

Data analysis will involve all visits during the 12-week double-blind treatment phase (up until week 12). Data from the tapering phase (weeks 12-13), although collected, will not be included for purposes of the primary goal of this study.

All enrolled subjects will be included in the analyses of baseline demographics and safety according to an intent-to-treat (ITT) principle. For statistical analysis, the full-analysis set will be defined as all participants who took at least 1 dose of the study drug and had at least 1 post-baseline primary efficacy assessment. The safety-analysis set will be defined as all randomized participants who took at least 1 dose of the study drug and completed at least 1 follow-up safety assessment.

The statistical model will be a linear mixed-effects regression model (LME) that includes terms for treatment group, time, and treatment-by-time interaction. The analyses will run using the nlme package on R for Windows (R Foundation, Vienna, Austria; http://www.r-project.org). Literature suggests LME without imputation may provide more accurate and stable results than LME models using fixed and multiple imputation methods for handling missing data, so no imputation will be undertaken for missing data. All tests of hypotheses will be performed using a two-sided significance level of 0.05.

Sample Size

The sample size was calculated for the primary endpoint of change from baseline. Assuming a similar magnitude of effect seen in other studies of medications for BPD, it was determined that 40 participants would be needed in each treatment group to detect a difference with an overall 5% type-I error risk. Given the particularly low rates of adverse events reported with Brexpiprazole, as well as its more positive side effect profile in terms of sexual side effects, we expect few drop-outs from the study and therefore a smaller sample is needed.

Ethical Considerations

This study will be conducted according to US and international standards of Good Clinical Practice (FDA regulations 21 CFR 312 for IND studies and FDA guidance E6) for all studies. Applicable government regulations and University of Chicago research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the University of Chicago Institutional Review Board (IRB) for formal approval to conduct the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

Data Handling and Record Keeping

All subject data will be maintained by the study personnel under the supervision of the principal investigator. Subjects will be seen at the University of Chicago. Patient binders will be kept in a locked room only accessible to research staff.

Estimated Total Costs/Budget

$400,000.

Publication/Presentation Schedule

These data will be presented at the American College of Neuropsychopharmacology (ACNP), the American Psychiatric Association annual meeting, or the NCDEU annual meeting. The resulting article will be submitted to a peer-reviewed publication (e.g., American Journal of Psychiatry, Biological Psychiatry) within 3 months of study completion.

References

1. Gunderson J: Borderline Personality Disorder, 2nd ed. Washington, DC, American Psychiatric Press, 2000
2. Nakao K, Gunderson JG, Phillips KA, Tanaka N: Functional impairment in personality disorders. J Pers Disord 1992; 6:24–31
3. Black DW, Blum N, Pfohl B, Hale N: Suicidal behavior in borderline personality disorder: prevalence, risk factors, prediction, and prevention. J Pers Disord 2004; 18:226–239
4. Linehan MM, Comtois KA, Murray AM, Brown MZ, Gallop RJ, Heard HL, Korslund KE, Tutek DA, Reynolds SK, Lindenboim N: Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. Arch Gen Psychiatry 2006; 63:757–766
5. Blum N, St John D, Pfohl B, Stuart S, McCormick B, Allen J, Arndt S, Black DW: Systems training for emotional predictability and problem solving (STEPPS) for outpatients with borderline personality disorder: a randomized controlled trial and 1-year follow-up. Am J Psychiatry 2008; 165:468–478
6. McMain SF, Guimond T, Streiner DL, Cardish RJ, Links PS: Dialectical behavior therapy compared with general psychiatric management for borderline personality disorder: clinical outcomes and functioning over a 2-year follow-up. Am J Psychiatry 2012; 169:650–661
7. Lieb K, Völlm B, Rücker G, Timmer A, Stoffers JM: Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. Br J Psychiatry 2010; 196:4–12
8. Nickel MK, Muehlbacher M, Nickel C, Kettler C, Pedrosa Gil F, Bachler E, Buschmann W, Rother N, Fartacek R, Egger C, Anvar J, Rother WK, Loew TH, Kaplan P: Aripiprazole in the

treatment of patients with borderline personality disorder: a double blind, placebo-controlled study. Am J Psychiatry 2006; 163: 833–838
9. Schulz SC, ZanariniMC, Bateman A, Bohus M, Detke HC, Trzaskoma Q, Tanaka Y, Lin D, Deberdt W, Corya S: Olanzapine for the treatment of borderline personality disorder: variable dose 12-week randomised double-blind placebo-controlled study. Br J Psychiatry 2008; 193:485–492
10. Zanarini MC, Schulz SC, Detke HC, Tanaka Y, Zhao F, Lin D, Deberdt W, Kryzhanovskaya L, Corya S: A dose comparison of olanzapine for the treatment of borderline personality disorder: a 12-week randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2011; 72:1353–1362
11. Pascual JC, Soler J, Puigdemont D, Pérez-Egea R, Tiana T, Alvarez E, Pérez V: Ziprasidone in the treatment of borderline personality disorder: a double-blind, placebo-controlled, randomized study. J Clin Psychiatry 2008; 69:603–608
12. Rinne T, de Kloet ER, Wouters L, Goekoop JG, de Rijk RH, van den Brink W: Fluvoxamine reduces responsiveness of HPA axis in adult female BPD patients with a history of sustained childhood abuse. Neuropsychopharmacology 2003; 28:126–132
13. Flewett T, Bradley P, Redvers A: Management of borderline personality disorder. Br J Psychiatry 2003; 183:78–79
14. Verheul R, Van Den Bosch LM, Koeter MW, De Ridder MA, Stijnen T, Van Den Brink W: Dialectical behaviour therapy for women with borderline personality disorder: 12-month, randomized clinical trial in the Netherlands. Br J Psychiatry 2003;182:135–140
15. Nickel M, Nickel C, Leiberich P, Mitterlehner F, Tritt K, Forthuber P, Rother W, Loew T: Psychosocial characteristics in people who often change their psychotherapists. Wien Med Wochenschr 2004; 154:163–169
16. Nickel M, Nickel C, Mitterlehner F, Tritt K, Lahmann C, Leiberich P, Rother W, Loew T: Topiramate treatment of aggression in female borderline personality disorder patients: a double-blind, placebo-controlled study. J Clin Psychiatry 2004; 65:1515–1519
17. Nickel M, Nickel C, Kaplan P, Lahmann C, Mühlbacher M, Tritt K, Krawczyk J, Leiberich PK, Rother W, Loew T: Treatment of aggression with topiramate in male borderline patients: a double-blind, placebo-controlled study. Biol Psychiatry 2005; 57:495–499
18. MacKinnon DF, Zandi PP, Gershon E, Nurnberger JI, Reich T, De Paulo JR: Rapid switching of mood in families with multiple cases of bipolar disorder. Arch Gen Psychiatry 2003; 60:921–928
19. Crandell LE, Patrick MP, Hobson RP: “Still-face” interactions between mothers with borderline personality disorder and their 2-month-old infants. Br J Psychiatry 2003; 183:239–247
20. Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M: Borderline personality disorder. Lancet 2004; 364:453–461
21. Frankenburg FR, Zanarini MC: The association between borderline personality disorder and chronic medical illnesses,poor health-related lifestyle choices, and costly forms of health care utilization. J Clin Psychiatry 2004; 65:1660–1665
22. Sher L, Oquendo MA, Li S, Huang YY, Grunebaum MF, Burke AK, Malone KM, Mann JJ: Lower CSF homovanillic acid levels in depressed patients with a history of alcoholism. Neuropsychopharmacology 2003; 28:1712–1719
23. Yen S, Shea MT, Sanislow CA, Grilo CM, Skodol AE, Gunderson JG, McGlashan TH, Zanarini MC, Morey LC: Borderline personality disorder criteria associated with prospectively observed suicidal behavior. Am J Psychiatry 2004; 161:1296–1298
24. Zanarini MC, Frankenburg FR, Hennen J, Silk KR: The longitudinal course of borderline psychopathology: 6-year prospective follow-up of the phenomenology of borderline personality disorder. Am J Psychiatry 2003; 160:274–283

25. Friedel RO: Dopamine dysfunction in borderline personality disorder: a hypothesis. Neuropsychopharmacology 2004; 29: 1029–1039
26. Hansenne M, Pitchot W, Pinto E, Reggers J, Scantamburlo G, Fuchs S, Pirard S, Ansseau M: 5-HT1A dysfunction in borderline personality disorder. Psychol Med 2002; 32:935–941
27. Oquendo MA, Mann JJ: The biology of impulsivity and suicidality. Psychiatr Clin North Am 2000; 23:11–25
28. Nickel M, Leiberich P, Mitterlehner F: Atypical neuroleptics in personality disorders. Psychodynamic Psychotherapy 2003; 2:25–32
29. Soloff PH, George A, Nathan S, Schulz PM, Cornelius JR, Herring J, Perel JM: Amitriptyline versus haloperidol in borderlines: final outcomes and predictors of response. J Clin Psychopharmacol 1989; 9:238–246
30. Leucht S, Wahlbeck K, Hamann J, Kissling W: New-generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. Lancet 2003; 361: 1581–1589
31. Pascual JC, Oller S, Soler J, Barrachina J, Alvarez E, Perez V: Ziprasidone in the acute treatment of borderline personality disorder in psychiatric emergency services. J Clin Psychiatry 2004; 65:1281–1282
32. Zanarini MC, Frankenburg FR, Panachini EA: A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. J Clin Psychiatry 2004; 65:903–907
33. Ferrerri MM, Loze JY, Rouillon F, Limosin F: Clozapine treatment of a borderline personality disorder with severe self-mutilating behaviours. Eur Psychiatry 2004; 19:177–178
34. Bogenschutz MP, George NH: Olanzapine versus placebo in the treatment of borderline personality disorder. J Clin Psychiatry 2004; 65:104–109
35. Zanarini MC, Frankenburg FR: Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. J Clin Psychiatry 2001; 62:849–854
36. Zanarini MC: Update on pharmacotherapy of borderline personality disorder. Curr Psychiatry Rep 2004; 6:66–70
37. Maeda K, Sugino H, Akazawa H, Amada N, Shimada J, Futamura T, Yamashita H, Ito N, McQuade RD, Mørk A, Pehrson AL, Hentzer M, Nielsen V, Bundgaard C, Arnt J, Stensbøl TB, Kikuchi T. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther. 2014 Sep;350(3):589-604.
38. Maeda K, Lerdrup L, Sugino H, Akazawa H, Amada N, McQuade RD, Stensbøl TB, Bundgaard C, Arnt J, Kikuchi T. Brexpiprazole II: antipsychotic-like and procognitive effects of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther. 2014 Sep;350(3):605-14
39. Yoon S, Jeon SW, Ko YH, Patkar AA, Masand PS, Pae CU, Han C (2017). Adjunctive Brexipiprazole as a Novel Effective Strategy for Treating Major Depressive Disorder: A Systematic Review and Meta-Analysis. J Clin Psychopharmacol. 37(1):46-53.
40. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, hergueta T, baker R, Dunbar GC (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 59 Suppl 20:22-33.
41. Hamilton M (1960). A rating scale for depression. J Neurol Neurosurg Psychiatry. 23:56-62.
42. Hamilton M (1959) The assessment of anxiety states by rating. Br J Med Psychol. 32:50-55
43. Sheehan DV (1983). The Anxiety Disease. New York: Scribner's.
44. Frisch MB, Cornell J, Villaneuva M (1993). Clinical validation of the Quality of Life Inventory: a measure of life satisfaction for use in treatment planning and outcome assessment. Psychol Assess. 4:92-101.

45. Zanarini MC, Vujanovic AA, Parachini EA, Boulanger JL, Frankenburg FR, Hennen J: Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): a continuous measure of DSM-IV borderline psychopathology. J Pers Disord 2003; 17:233–242
46. Kay SR, Wolkenfeld F, Murrill LM: Profiles of aggression among psychiatric patients, I: nature and prevalence. J Nerv Ment Dis 1988; 176:539–546
47. Young RC, Biggs JT, Ziegler VE, Meyer DA: A rating scale for mania: reliability, validity, and sensitivity. Br J Psychiatry 1978; 133:429–435
48. Zanarini MC, Frankenburg FR: Self-Report Version of the Zanarini Rating Scale for Borderline Personality Disorder. Belmont, Mass, Mclean Hospital, 2008
49. Pfohl B, Blum N, McCormick B, St John D, Allen J, Black DW: Reliability and validity of the Borderline Evaluation of Severity Over Time (BEST): a self-rated scale to measure severity and change in persons with borderline personality disorder. J Pers Disord 2009; 23:281–293
50. Barratt E: Anxiety and impulsiveness related to psychomotor efficiency. Percept Mot Skills 1959; 9:191–198
51. Chamberlain SR, Grant JE: Minnesota Impulse Disorders Interview (MIDI): Validation of a structured diagnostic clinical interview for impulse control disorders in an enriched community sample. Psychiatry Res 2018; 265:279-283
52. Derogatis LR: SCL-90-R Administration, Scoring, and Procedures Manual II. Towson, Md, Clinical Psychometric Research, 1983