The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board

Protocol

Title: Brexpiprazole for Bipolar Disorder

Principal Investigator: E. Sherwood Brown, M.D., Ph.D.

Funding Sponsor: Otsuka America Pharmaceuticals, Inc.

1. Introduction and Purpose:

Brexpiprazole is effective for both major depressive disorder and schizophrenia. However, to date no studies have examined its safety and efficacy in bipolar disorder. We hypothesize that brexpiprazole will be associated with a reduction in depressive symptom severity in outpatients with bipolar disorder, depressed mood state. The proposed open-label trial will examine brexpiprazole in a group of 20 bipolar depressed outpatients.

Primary Aim: Determine if brexpiprazole is associated with a reduction in depressive symptom severity using The Montgomery-Asberg Depression Rating Scale (MADRS) in outpatients with bipolar disorder, depressed mood state.

Secondary Aims:

1) Assess manic symptoms in patients with bipolar disorder receiving brexpiprazole.
2) Assess cognition in patients with bipolar disorder receiving brexpiprazole.
3) Assess the safety and tolerability of brexpiprazole in patients with bipolar disorder.
4) Assess quality of life in patients with bipolar disorder receiving brexpiprazole.

Additional Exploratory Analyses:

1) Assess peripheral inflammation in patients with bipolar disorder receiving brexpiprazole.
2) Assess relationships between changes in outcome measures.

2. Background:

Bipolar depression is common and challenging to treat. Brexpiprazole may be a promising treatment for Bipolar Disorder (BPD), which is a severe and persistent psychiatric illness affecting 1.6-3.5% of the population (6, 7). In addition to manic episodes, persons with BPD frequently experience depression. Depression in BPD may be particularly challenging to treat. Findings from the STEP-BD study indicate that bipolar depression may not respond well to selective serotonin reuptake inhibitors, which are a standard treatment for major depressive disorder (MDD) (8). Lamotrigine is commonly prescribed for bipolar depression, but it appears to be more effective than placebo only for severe depression (9). Only three medications (quetiapine, the combination of olanzapine and fluoxetine, and lurasidone) are FDA-approved for bipolar depression. Thus, new, safe, and effective treatments for the depressed phase of BPD are badly needed. Brexpiprazole is a partial agonist at dopamine D2 receptors that is structurally similar to aripiprazole. Data suggest that brexpiprazole is effective both as an adjunct treatment for major depressive disorder (10) and as a treatment for schizophrenia (11), and has FDA approval for both indications.

Given the promising findings in both major depressive disorder and schizophrenia, a proof-of-concept study is proposed to examine the safety and tolerability, as well as efficacy of brexpiprazole in patients with bipolar depression. Depressive symptoms will be assessed using both observer-rated and self-rated depression scales. Manic symptoms and quality of life will also be assessed. Safety and tolerability will be assessed using a side-effects scale as well as standard antipsychotic extrapyramidal symptom rating scales. Cognitive domains relevant to bipolar depression will be assessed. Because bipolar depression is associated with high sensitivity elevated C-reactive protein levels (hs-CRP, an inflammatory biomarker) (12) and data suggest that brexpiprazole decreases hs-CRP levels (13), hs-CRP levels will also be assessed at baseline and exit, and the relationships between changes in these levels and clinical outcomes explored.

3. Concise Summary of Project:

We will conduct an 8-week, non-randomized, open label study of brexpiprazole in 20 persons with bipolar disorder. Primary Aim will be to determine if brexpiprazole is associated with a reduction in depressive symptom severity using the Montgomery-Asberg Depression Rating Scale (MADRS) in outpatients with bipolar disorder, depressed mood state. Secondary Aims will be: 1) Assess manic symptoms in patients with bipolar disorder receiving brexpiprazole, 2) Assess cognition in patients with bipolar disorder receiving brexpiprazole, 3) Assess the safety and tolerability of brexpiprazole in patients with bipolar disorder, 4) Assess quality of life in patients with bipolar disorder receiving brexpiprazole.

Subjects will be discontinued from the study if any of the following conditions occurs: change in diagnosis to other than bipolar I or II disorder, development of active suicidal or homicidal ideation with plan and intent, worsening in mood symptoms, that in the opinion of the investigators requires discontinuation, pregnancy, development of severe or life-threatening medical condition, involuntary psychiatric hospitalization or incarceration.

4. Study Procedures:

Baseline: This visit will be split into two portions: Baseline 1 and Baseline 2.

For Baseline 1 (~3 hours), the psychiatric diagnosis will be confirmed by the structured clinical interview for DSM-5 (SCID), mood assessed via the Montgomery-Asberg Depression Rating Scale (MADRS), depression via the Inventory of Depressive Symptomatology Self-Report ($IDS\text{-}SR_{30}$), mania via the Young Mania Rating Scale, and quality of life via the Quality of Life in Bipolar Disorder (QOLBD). Blood will be drawn for complete blood count (CBC), Comprehensive Metabolic Panel (CMP, includes a liver panel with AST, ALT, as well as lipids), and high-sensitivity c-reactive protein (hs-CRP). A urine sample for drug screen and pregnancy test (if applicable), psychiatrist assessment, physical exam, collection of weight and vitals will be completed.

For Baseline 2 (~2 hours), recent depressive symptoms will be assessed via the $IDS\text{-}SR_{30}$ and MADRS, mania via the YMRS, current mood via Internal State Scale (ISS), suicidal ideation will be assessed via the Columbia Suicide Severity Rating Scale (CSSRS), safety and side effects will be assessed with the SAFTEE, the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale (BAS) and Simpson-Angus Scale (SAS). Subjects will also complete the The Ray Auditory Verbal Learning Test (RAVLT) to assess word memory, the Stroop test to measure attention, speed, and accuracy of thinking, and The Trail Making Test (TMT) to measure attention, speed and accuracy. A urine sample for drug screen and pregnancy test (if applicable) will also be completed. Brexpiprazole capsules will be initiated at 0.5 mg/day.

Baseline 2 to Week 1: Subjects will be given the ISS to fill out at home. Subjects will be asked to complete the scale at home on 7 consecutive days between Baseline 2 and Week 1 visits and return the filled out scales to the researcher's office. The scale will take approximately 3-5 minutes to fill out.

Week 1, 2, 3, 6 (~1.5 hours each): Subjects will complete the MADRS, YMRS, $IDS\text{-}SR_{30}$, ISS, SAFTEE, CSSRS, AIMS, BAS, SAS, and a urine sample will be collected for a drug screen. Subjects will meet with the psychiatrist for weekly assessment and vitals will be collected.

Week 4 (~2 hours): Subjects will complete the MADRS, IDS-SR, YMRS, SAFTEE, ISS, C-SSRS, AIMS, BAS, SAS, RAVLT, Stroop, TMT, vital signs, a urine sample for a drug screen and a urine pregnancy test, and visit the doctor for a psychiatric evaluation.

Week 8 (final visit ~2.5 hours): Subjects will complete the MADRS, IDS-SR, YMRS, SAFTEE, ISS, C-SSRS, AIMS, BAS, SAS, RAVLT, Stroop, TMT, QOLBD, vital signs, a urine sample for drug screen, take a urine pregnancy test, have blood drawn for clinical testing (CBC, CMP, hs-CRP), and visit the doctor for a psychiatric evaluation and physical exam. During this visit, participants will also

be provided with aftercare referral information and will begin their medication taper. The medication taper schedule is described below under “Study Medication and Intervention Description”.

Safety Phone Call (~15 min): Participants will receive a phone call from researchers 7-10 days following their Week 8 study visit (at the end of their tapering schedule). During this phone call, the researchers will assess any withdrawal effects or adverse events and check on the status of the aftercare referrals.

Participants will be paid for their time and inconvenience per visit as follows: $60 at Baseline 1, Baseline 2, weeks 1, 2, 3, 6; $70 at week 4; $90 for week 8. Participants will also be paid for each ISS scale they bring back at the rate of $1 per scale (maximum $7). These payments will be processed during Week 1 visit. These payments will be completed via the ClinCard system. Bus or rail passes will be provided. After study completion, standard psychiatric care will be provided until referral is arranged.

Study Medication and Intervention Description:

Participants will be initiated on a 0.5 mg/day brexpiprazole dose (week 0/baseline); after one week the dose will be increased to 1 mg/day (week 1), after another week to 2 mg/day (week 2). If any dose appears to be poorly tolerated, the dose titration can be slowed or stopped based on clinician judgment. If response in weeks 3-6, defined as a 50% reduction in the MADRS, has not been achieved, and the current dose is well tolerated, then additional dose increases to 3 mg/day and 4 mg/day (maximum allowed dose in protocol) will occur with at least a one week interval between dose increases.

Following the last study visit (Week 8), participants will be gradually tapered off the medication every 2 days until they stop taking the medication completely. For example, if a participants takes 4 mg of brexpiparzole at Week 8, then he/she will take 3 mg for 2 days, then 2 mg for 2 days, then 1 mg for 2 days, and then 0.5 mg for 2 days. At the end of the tapering period (7-10 days depending on the highest brexpiprazole dose at the end of the study), participants will receive a safety phone call from a research staff member to assess any withdrawal symptoms and check on the status of the aftercare referrals.

5. Sub-Study Procedures:

No sub-study procedures are anticipated at this time.

6. Criteria for Inclusion of Subjects:

- Outpatient men and women ages 18-65
- Bipolar I or II disorders, currently depressed mood state based on a SCID for DSM-5; Mixed features in DSM-5 are allowed, but those with a Young Mania Rating Scale score ≥ 15 will be excluded
- MADRS score ≥ 25 at baseline 2 visit.

7. Criteria for Exclusion of Subjects:

- Mood disorders other than bipolar I or II disorders (e.g., bipolar NOS, or cyclothymic disorders, schizophrenia, schizoaffective disorder, or unipolar depression based on the SCID), other disorders, e.g. anxiety disorders, will be allowed
- Current (last 14 days) treatment with an antipsychotic or antidepressant. If a participant has been treated with any antipsychotic or antidepressant in the last 14 days, then they will not be enrolled in the study. No washout of antipsychotic or antidepressant will be done
- History of neuroleptic malignant syndrome or tardive dyskinesia
- Prior history of brexpiprazole use
- Vulnerable populations (e.g., pregnant, nursing, cognitively impaired, incarcerated)

- High risk for suicide defined as > 1 attempt in past 12 months that required medical attention, any attempt in the past 3 months or current suicidal ideation with plan and intent such that outpatient care is precluded
- Severe or life-threatening medical condition, or laboratory or physical examination findings consistent with serious medical illness (e.g., dangerously abnormal electrolytes)
- Moderate or severe hepatic or renal impairment based on medical history and laboratory analyses
- Taking moderate or strong inducers or inhibitors of CYP2D6 or CYP3A4

8. Sources of Research Material:

Clinical information will be obtained via the Structured Clinical Interview for DSM (SCID), Montgomery-Asberg Depression Rating Scale (MADRS), Inventory of Depressive Symptomatology–Self-Report 30-item version (IDS-SR_{30}), Young Mania Rating Scale (YMRS), Columbia Suicide Severity Rating Scale (C-SSRS), Systematic Assessment for Treatment Emergent Effects (SAFTEE), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale (BAS), Simpson-Angus Scale (SAS), Ray Auditory Verbal Learning Test (RAVLT), The Stroop and Trail Making Test (TMT).

Biological information will be obtained via blood drawn (2 tbsp ~ 29mLs) for laboratory analyses including a complete blood count (CBC) and Comprehensive Metabolic Panel (CMP, includes a liver panel with AST, ALT, as well as lipids), high-sensitivity c-reactive protein (hs-CRP). A redraw may be requested if the first sample cannot be processed. A physical examination will be performed, weight obtained, and a urine sample collected for a drug screen and pregnancy testing.

9. Recruitment Methods and Consenting Process:

Participants will be recruited from the community through advertisements (flyers, newspaper ads, etc.), by previous contact with the Psychoneuroendocrinology Research Program (PNE), and by referrals. Dr. Brown has been successful in recruiting this patient population (bipolar depression) in the past, as evidenced by completion of recruitment (80 participants) for STU122009-069 (bipolar depression clinical trial), as well as ongoing clinical trials in bipolar disorder and substance use (STU112013-075, STU072014-005, STU102015-062). We will look to aforementioned studies for possible participants who expressed interest in future research.

Our success in recruiting participants for our previous and ongoing large scale studies demonstrates that we have the resources and contacts necessary to recruit participants for this project, and that we already have established measures in place to accomplish our recruitment goals (20 participants).

Potential participants who are referred to us or who respond via the various recruitment strategies will be contacted by telephone. Participants who remain interested and eligible for participation based on the telephone prescreen may be asked to come into our clinic for a diagnostic screening visit. Once noted as eligible, the staff member will discuss the procedures they will undergo if they choose to participate in the study. After reading the informed consent, study staff will discuss these issues with the potential participant and will answer any questions he or she may have about the study and participation. If the individual chooses to sign the informed consent document, he or she may begin testing for the study. All research procedures, risks and potential benefits, as well as incentives for participation are clearly and accurately explained in the consent.

10. Potential Risks:

Study Procedure/Intervention

As per exclusion criteria, participants with any prior history of brexpiprazole use will be excluded from the study. However, to avoid unforeseen events, we will still inform participants that brexpiprazole is contraindicated in patients with a known hypersensitivity to brexpiprazole or any of its components. Adverse reactions have included rash, facial swelling, urticaria (hives), and anaphylaxis (a severe, potentially life-threatening allergic reaction). Components of brexpiprazole include brexpiprazole, lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, lowsubstituted hydroxypropyl cellulose, magnesium stearate, hypromellose, and talc.

Brexpiprazole may cause some, all or none of the side-effects listed below.

Most common (>10%)	**Less Common (1-10%)**
- Akathisia (agitation, restlessness) - Weight gain	- Headache, drowsiness, fatigue, dizziness, anxiety, movement disorders, sedation, abnormal dreams, insomnia, excessive sweating, decreased cortisol, indigestion, increased appetite, constipation, diarrhea, abdominal pain, flatulence, nausea, excess drooling, dry mouth/throat, urinary tract infection, tremor, muscle pain, increased creatine, blurred vision, upper respiratory infection
Serious but Rare - Dystonia (involuntary muscle contractions) - Hyperglycemia (high blood sugar) - Increased fat levels (cholesterol and triglycerides) in the blood. - Low white blood cell count. - Decreased blood pressure (orthostatic hypotension). - Seizures (convulsions). - Body temperature dysregulation. - Difficulty swallowing.	

Black Box Warning
WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS - **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. REXULTI (BREXPIPRAZOLE) is not approved for the treatment of patients with dementia-related psychosis.** - **Antidepressants increase the risk of suicidal thoughts and behaviors in patients aged 24 years and younger in short-term studies. Monitor closely for clinical worsening and for emergence of suicidal thoughts and behaviors.**

There are also certain medications that may have clinically significant interactions with brexpiprazole. These medications are moderate or strong inducers or inhibitors of CYP3A4 or CYP2D6. Examples of these medications include, but are not limited to, paroxetine, fluoxetine, quinidine, many HIV medications, etc. A full list of these medications will be made available to participants. This list will also be attached in the IRB application. Participants who currently take moderate or strong inducers or inhibitors of CYP3A4 or CYP2D6 will be excluded from the study. If participants start taking moderate or strong inducers or inhibitors of CYP3A4 or CYP2D6 during their study participation, they will be discontinued from the study and appropriate aftercare referral information will be provided.

Participants will be instructed to let the researchers know of any prescription medications, over-the-counter medications, vitamins and herbal supplements they are currently taking or of ANY new medications they may start taking during their study participation.

Participants will also be informed of potential interaction brexpiprazole may have with alcohol.

<u>Psychological Stress</u>

Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions, take a break or stop your participation in this study at any time.

Loss of Confidentiality

Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Risks to Sperm, Embryo, Fetus or Breast-fed Infant

Males: Being in this research may damage sperm, which could cause harm to a child that a participant may father while on this study. Subjects who participate in this study and are sexually active, must agree to use a medically-acceptable form of birth control. Medically-acceptable forms of birth control include:

(1) surgical sterilization (vasectomy), or
(2) a condom used with a spermicide (a substance that kills sperm).

Females: Subjects participating in this study while pregnant or breast-feeding an infant may expose the unborn child or infant to risks. For that reason, pregnant and breast-feeding females cannot participate in the study. If a participant becomes pregnant, a blood pregnancy test will be done (using 1 teaspoon of blood drawn from a vein by needle-stick), and it must be negative before the subject participates in this study. Subjects who participate in this study and are sexually active, they and any person that they have sex with must use medically-acceptable birth control (contraceptives) during the study. Medically-acceptable birth control (contraceptives) includes:

(1) surgical sterilization (such as hysterectomy or “tubes tied”),

(2) approved hormonal contraceptives (such as birth control pills, patch or ring; Depo-Provera, Implanon),

(3) barrier methods (such as condom or diaphragm) used with a spermicide (a substance that kills sperm), or

(4) an intrauterine device (IUD).

If a subject does become pregnant during this study, they are informed that they must tell the researchers immediately.

Risks of Blood Drawing

Risks associated with drawing blood from the arm include minimal discomfort and/or bruising. Infection, excess bleeding, clotting, and/or fainting also are possible, although unlikely.

11. Subject Safety and Data Monitoring:

The likely risks from the study are primarily medication side effects and the risk of untreated bipolar disorder and depressive symptoms. Brexpiprazole is reasonably well tolerated and may have metabolic side effects than most other atypical antipsychotics. All participants will receive active medication (brexpiprazole) during the study, as well as frequent monitoring and follow-up appointments with a psychiatrist and research coordinator. Thus, all participants will receive care for mood symptoms. At the end of study, patients will be given follow-up appointments at treatment facilities we have worked with in the past, and, if needed, we will provide a longer period of aftercare until treatment can be transitioned to another provider. These are our standard procedures for research studies and have been in place for over 17 years. Another potential risk is worsening of mood symptoms. If participants have a worsening of mood symptoms, such as active suicidal ideation, study participation will be discontinued, and we will provide them with referrals for appropriate care. Some level of suicidal ideation is common in the participants we research. However, we want to take steps to prevent risk of suicidal acts. Thus, the emergence of intense suicidal thoughts with a clear plan (e.g. overdose) and the intent to act on the plan would require discontinuation from the study. However, recurrent suicidal thoughts accompanied by a clear

understanding that the participant does not plan to act on these thoughts would not require discontinuation.

Potential pharmacokinetic or pharmacodynamic drug-drug interactions will be managed using inclusion, exclusion, and discontinuation criteria and dose adjustments. Clinical assessments are collected by trained and experienced staff members who will be able to reassure participants if they are distressed during study visits. If participants become fatigued or stressed during the testing, rest periods will be provided. Standard, appropriate measures will be used to minimize risk of infection during venipuncture.

All investigators and research staff will be available 24 hours a day. The consent form will have both daytime and nighttime numbers for reaching study personnel. Business cards for the research coordinator and psychiatrists will also be provided. In the event an investigator or research coordinator is on vacation or out-of-town, coverage will be provided, and both the research coordinator and UT Southwestern answering service are informed of the name and pager number of the physician-on-call. In the event of a medical or psychiatric emergency, appropriate medical advice will be provided including recommendations for emergency room evaluation if necessary. The PI and other physicians involved with the study have staff privileges at the Parkland and William P. Clements University Hospital Emergency Rooms, which are likely to be the most commonly used hospitals by the participants. The physicians and other staff have extensive experience working with patients with bipolar disorder and substance use disorders.

All women of childbearing potential (premenopausal and without a clearly documented hysterectomy, ovariectomy or bilateral tubal ligation) must have a urine pregnancy test with negative results prior to receiving study medication. These participants will also be asked to use effective forms of contraception during the study. Pregnancy or failure to use contraceptives will result in discontinuation from the study.

These are general guidelines. In all cases, physician judgment will be used to determine whether or not a participant can safely remain in the study.

12. Procedures to Maintain Confidentiality:

Blood specimens will be provided to Quest Diagnostics for analysis, removing identifying information (e.g., name) that could be linked to the patient's identity prior to sending for analysis. The blood provided to Quest will have the participant's date of birth to correctly link the results to the participant. The results of this test will be de-identified and added to the rest of the de-identified data. Once de-identified, only the identified investigators can learn/discover the names of participant.

Data Management Plan

All data related to the participant's participation in this study will be given a study ID which cannot be traced back to the patient except by study staff. All personal information which can identify the patient's identity will be kept separately from study documents and assessments. All clinical assessments will be collected in paper form and scores transferred to a computer database maintained on a password protected computer, on a secure server behind a firewall. The paper forms will be kept in binders marked only with the patient's study ID and will be kept in a locked room for the required time period following the completion of this study.

A Certificate of Confidentiality will be obtained for this study.

13. Potential Benefits:

This is a non-randomized open-label clinical trial, thus all participants will receive study medication. All participants may personally benefit from the study by experiencing a significant reduction in symptoms of depression associated with bipolar disorder. The researchers hope the information learned from this study will benefit others with bipolar depression in the future. Information gained from this research could lead to better treatment of patients with bipolar depression.

14. Biostatistics:

Primary Aim: Determine if brexpiprazole is associated with a reduction in depressive symptom severity in outpatients with bipolar disorder, depressed mood state.

1) The MADRS will be the primary outcome measure with the IDS-SR as a secondary outcome measure. Weekly scores on the MADRS and IDS-SR will be assessed using one-way repeated measures. Analysis of Covariance (rm-ANCOVA), controlling for age and sex as potential confounding variables, with time as the main effect. Participants will be included if they complete one post-baseline assessment (intent-to-treat sample). In addition, rates of depression response (≥ 50% reduction from baseline) and remission (≤10 on the MADRS and ≤12 on the IDS-SR) will be assessed. A significance level of 0.05 will be set for all analyses, with all tests being two-tailed.

Secondary Aims:

2) Assess manic symptoms in patients with bipolar disorder receiving brexpiprazole. YMRS scores will be assessed as with the primary aim above.
3) Assess cognition in patients with bipolar disorder receiving brexpiprazole. Scores on the RAVLT, Stroop and TMT will be assessed at baseline compared to weeks 4 and 8 separately using paired t-tests or paired-sample Wilcoxon Signed Rank test.
4) Assess the safety and tolerability of brexpiprazole in patients with bipolar disorder. Scores on the SAFTEE, C-SSRS, AIMS, BAS and SAS will be assessed as with the primary aim.
5) Assess quality of life in patients with bipolar disorder receiving brexpiprazole. The QOLBD will be assessed as above for cognition.
6) Assess peripheral inflammation in patients with bipolar disorder receiving brexpiprazole. Values on hs-CRP will be compared between baseline and exit as with cognition above.
7) Assess relationships between changes in outcomes measures. Correlations between outcome measures (e.g. depressive symptoms and cognition, depressive symptoms and inflammation) will be assessed using Pearson's or Spearman's correlation coefficients.

References:

1. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. The American journal of psychiatry. 2011;168(12):1266-77. doi: 10.1176/appi.ajp.2011.10111704. PubMed PMID: 22193671; PubMed Central PMCID: PMC3893686.
2. Levine J, Schooler NR. SAFTEE: a technique for the systematic assessment of side effects in clinical trials. Psychopharmacology bulletin. 1986;22(2):343-81. Epub 1986/01/01. PubMed PMID: 3774930.
3. Guy W. Early Clinical Drug Evaluation Unit (ECDEU) Assessment Manual for Psychopharmacology, Revised. In: Health NIoM, editor. Bethesda MD: NIMH Publication; 1976. p. 217-22.
4. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta psychiatrica Scandinavica Supplementum. 1970;212:11-9. Epub 1970/01/01. PubMed PMID: 4917967.
5. Barnes TR. A rating scale for drug-induced akathisia. The British journal of psychiatry : the journal of mental science. 1989;154:672-6. Epub 1989/05/01. PubMed PMID: 2574607.
6. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Archives of general psychiatry. 1994;51(1):8-19. Epub 1994/01/01. PubMed PMID: 8279933.
7.Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Archives of general psychiatry. 2007;64(5):543-52. doi: 10.1001/archpsyc.64.5.543. PubMed PMID: 17485606; PubMed Central PMCID: PMC1931566.

8. Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med. 2007;356(17):1711-22. Epub 2007/03/30. doi: NEJMoa064135 [pii] 10.1056/NEJMoa064135. PubMed PMID: 17392295.
9. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. The British journal of psychiatry : the journal of mental science. 2009;194(1):4-9. Epub 2009/01/02. doi: 194/1/4 [pii] 10.1192/bjp.bp.107.048504. PubMed PMID: 19118318.
10. Thase ME, Youakim JM, Skuban A, Hobart M, Augustine C, Zhang P, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. The Journal of clinical psychiatry. 2015;76(9):1224-31. Epub 2015/08/25. doi: 10.4088/JCP.14m09688. PubMed PMID: 26301701.
11. Correll CU, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, et al. Efficacy and Safety of Brexpiprazole for the Treatment of Acute Schizophrenia: A 6-Week Randomized, Double-Blind, Placebo-Controlled Trial. The American journal of psychiatry. 2015;172(9):870-80. Epub 2015/04/18. doi: 10.1176/appi.ajp.2015.14101275. PubMed PMID: 25882325.
12. De Berardis D, Conti CM, Campanella D, Carano A, Scali M, Valchera A, et al. Evaluation of C-reactive protein and total serum cholesterol in adult patients with bipolar disorder. International journal of immunopathology and pharmacology. 2008;21(2):319-24. PubMed PMID: 18547475.
13. Henderson DC, Fan X, Copeland PM, Sharma B, Borba CP, Boxill R, et al. Aripiprazole added to overweight and obese olanzapine-treated schizophrenia patients. Journal of clinical psychopharmacology. 2009;29(2):165-9. doi: 10.1097/JCP.0b013e31819a8dbe. PubMed PMID: 19512978.
14. First M SR, Gibbon M, JBW W Structured Clinical Interview for DSM-IV Axis I Disorders. New York: Biometrics Research Department, NY State Psychiatric Institute1995.
15. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. The British journal of psychiatry : the journal of mental science. 1979;134:382-9. Epub 1979/04/01. PubMed PMID: 444788.
16. Rush AJ, Carmody T, Reimitz PE. The Inventory of Depressive Symptomatology (IDS): Clinician (IDS-C) and self-report (IDS-SR) ratings of depressive symptoms. International journal of methods in psychiatric research. 2000;9:45-59.
17. Rush AJ, Giles DE, Schlesser MA, Fulton CL, Weissenburger J, Burns C. The Inventory for Depressive Symptomatology (IDS): preliminary findings. Psychiatry research. 1986;18(1):65-87. Epub 1986/05/01. PubMed PMID: 3737788.
18. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychological medicine. 1996;26(3):477-86. Epub 1996/05/01. PubMed PMID: 8733206.
19. Trivedi MH, Rush AJ, Ibrahim HM, Carmody TJ, Biggs MM, Suppes T, et al. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychological medicine. 2004;34(1):73-82. PubMed PMID: 14971628.
20. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. The British journal of psychiatry : the journal of mental science. 1978;133:429-35. PubMed PMID: 728692.
21. Michalak EE, Murray G, Collaborative RTtSPIiBD. Development of the QoL.BD: a disorder-specific scale to assess quality of life in bipolar disorder. Bipolar disorders. 2010;12(7):727-40. doi: 10.1111/j.1399-5618.2010.00865.x. PubMed PMID: 21040290.
22. Schmidt M. Rey Auditory Verbal Learning Test: A Handbook. Los Angeles: Western Psychological Services; 1996.
23. Spreen O. A compendium of neuropsychological tests: Administration, norms, and commentary: Oxford University Press; 1998.