# Depression Distribution Study Descriptions

## Contents

# Study 7 – Genetics of Recurrent Early-Onset Depression (GenRED)

## Summary

- **Grant Numbers:** R01MH060912
- **PI:** J. Raymond Depaulo, William A. Scheftner, Raymond R. Crowe, Myrna Weissman, George Zubenko, and Douglas F. Levinson.
- **Study Design & Aims:** The data and biomaterials of this family case study (Study 7) were from Genetics of Recurrent Early-Onset Depression (GenRED) project which were collected at six sites. This project is a part of the second NIMH Human Genetics Initiative. The goals of the GenRED project are (1) to collect a sample of sibling pairs affected with recurrent, early-onset major depressive disorder plus additional affected relatives by first-degree extension, to carry out an initial genome scan in collaboration with the Center for Inherited Disease Research, and (3) to make cell lines and DNA specimens from this sample available to other scientists through the NIMH-sponsored cell repository program (the Center for Genetic Studies) (Levinson et al. 2003).

  A study of Depression (GenRED I). This is a second revision of a collaborative R01 four-year competing continuation proposal to create a large repository-based sample of cases with recurrent, early-onset major depressive disorder (MDD-RE), and to use positional cloning to identify depression susceptibility genes in regions of significant linkage in our genome scan. The completed four-year project collected 680 families containing 927 affected sibling pairs (ASPs) (MDD-RE diagnostic model) and additional affected relatives (GenRED I). Blinded clinical data and blood specimens for cell culture were deposited in the NIMH repository and are being made public. Linkage fine-mapping has demonstrated genome-wide significant linkage on chromosome 15q; in the 10 cM genome scan, suggestive sex-specific linkage was observed in three regions (6p-q, 8p, 17p), with the result on chromosome 17p approaching genome-wide significance. Six collaborating sites now propose to: (1) Collect (during Years 1-3) an additional 1,350 European-ancestry (EUR) MDD-RE probands (GenRED II) meeting identical criteria (including evidence of having an affected sibling) to create a total repository sample of 2,000 EUR MDD-RE cases, plus cell lines/DMA from available parents, unaffected sibs and male-male ASPs. (2) Initiate a repository-based collection of African-American (AA) MDD-RE probands meeting the same clinical criteria. We will collect 750 AA probands plus available parents and affected siblings, with involvement of young minority co-investigators; AA controls will be available from the repository. A site at Howard University has been added to lead this effort. AA recruitment will continue through Year 4 to build the repository sample. (3) Collect data on childhood abuse and neglect and parental loss, major environmental MOD risk factors; (4) Carry out linkage fine-mapping studies of chromosomes 17p, 1q, 5q, 6p-q, 8p and 18q to maximize evidence for linkage and to narrow candidate regions. (5) Carry out linkage disequilibrium (LD) mapping and intensive gene analysis studies in the 15q candidate region and one additional region in 2,000 EUR cases and 2,000 screened, ethnically-matched controls; and carry out LD fine-mapping studies in the most significant genes in 600 AA cases (the N available early in Year 4) and 1,000 controls, using high-throughput SNP genotyping methods, to identify a depression susceptibility gene. The proposed studies will contribute to the

understanding of this devastating common disorder by identifying susceptibility genes, and by creating a public collection of biological materials and clinical data, as well as over 13 million SNP genotypes, to facilitate further investigation of recurrent MOD and related phenotypes.

### Acknowledgement


- Data and biomaterials were collected in six projects that participated in the National Institute of Mental Health (NIMH) Genetics of Recurrent Early-Onset Depression (GenRED) project. From 1999-2003, the Principal Investigators and Co-Investigators were: New York State Psychiatric Institute, New York, NY, R01 MH060912, Myrna M. Weissman, Ph.D. and James K. Knowles, M.D., Ph.D.; University of Pittsburgh, Pittsburgh, PA, R01 MH060866, George S. Zubenko, M.D., Ph.D. and Wendy N. Zubenko, Ed.D., R.N., C.S.; Johns Hopkins University, Baltimore, MD, R01 MH059552, J. Raymond DePaulo, M.D., Melvin G. McInnis, M.D. and Dean MacKinnon, M.D.; University of Pennsylvania, Philadelphia, PA, RO1 MH61686, Douglas F. Levinson, M.D. (GenRED coordinator), Madeleine M. Gladis, Ph.D., Kathleen Murphy-Eberenz, Ph.D. and Peter Holmans, Ph.D. (University of Wales College of Medicine); University of Iowa, Iowa City, IW, R01 MH059542, Raymond R. Crowe, M.D. and William H. Coryell, M.D.; Rush University Medical Center, Chicago, IL, R01 MH059541-05, William A. Scheftner, M.D., Rush-Presbyterian.


### Publications

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## Study 18 – Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

### Summary

- **Grant Numbers:** N01MH090003
- **PI:** A. John Rush, M.D
- **Study Design & Aims:** STAR*D focuses on major depressive disorder (MDD), which is a common, usually recurrent, and often chronic disorder. STAR*D is prospectively designed to determine the comparative EFFECTIVENESS of different treatment options for participants with MDD. It will evaluate the comparative effectiveness of these treatments when they are used to either augment the previous treatment or as new treatments for participants without a satisfactory response to an initial selective serotonin reuptake inhibitor (SSRI) medication. STAR*D will (1) compare the effectiveness of selected treatment options and, consequently, treatment sequences in reducing patients' symptoms and improving their function, and (2) define the costs and cost offsets of such care.

By recruiting a large, widely representative group of outpatients with major depressive disorder, STAR*D will generate information that will be directly applicable to current practice. STAR*D will develop and implement patient/family education materials, as well as practical guidelines for clinicians to follow when implementing evidence-based treatment steps in the care of depressed patients. The National Coordinating Center for the study (University of Texas Southwestern Medical Center at Dallas) will oversee the implementation of the protocol at the 13 Regional Centers. Each Center will coordinate the care at 2–4 clinical settings or clinical sites where clinicians working in both private and public sectors providing either primary or specialty care will enroll and treat study participants. Key collaborating Special Regional Centers include Massachusetts General Hospital (Boston), University of Pittsburgh Medical Center and Western Psychiatric Institute and Clinic (Pittsburgh), University of Pittsburgh Epidemiology Data Center (Pittsburgh) and Columbia College of Physicians and Surgeons (New York).

### Acknowledgement


- Data and biomaterials were obtained from the limited access datasets distributed from the NIH-supported "Sequenced Treatment Alternatives to Relieve Depression" (STAR*D). STAR*D focused on non-psychotic major depressive disorder in adults seen in outpatient settings. The primary purpose of this research study was to determine which treatments work best if the first treatment with medication does not produce an acceptable response. The study was supported by NIMH Contract # N01MH90003 to the University of Texas Southwestern Medical Center. The ClinicalTrials.gov identifier is NCT00021528.


### Publications

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## Study 52 – Genetics of Recurrent Early-Onset Depression 2 (GenRED2)

### Summary

- **Grant Numbers:** R01MH060912
- **PI:** Douglas Levinson; Myrna Weissman; R. DePaulo/James Potash; William Sheftner; R. Raymond Crowe/William Coryell
- **Study Design & Aims:** GenRED2 project included new European-ancestry cases meeting the same criteria as the GenRED study GWAS (Shi, et al., Mol Psychiatry 2011 Feb; 16(2):193-201, PMID: 20125088): subjects with recurrent (≥2 episodes) or chronic (≥3 years) MDD with onset <31 years old and a history of recurrent MDD (onset <41 years old) in a parent or sibling (established by direct interview in GenRED1 and by family history interview in GenRED2) were recruited for GenRED2 by five research groups: Douglas Levinson (Stanford University); Myrna Weissman (Columbia University); R. DePaulo/James Potash (Johns Hopkins); William Sheftner (Rush Presbyterian Medical Center, Chicago); R. Raymond Crowe/William Coryell (University of Iowa).

### Acknowledgement


- Data and biomaterials in this release were collected in six projects that participated in the National Institute of Mental Health (NIMH) Genetics of Recurrent Early-Onset Depression (GenRED) project (1999-2009). The Principal Investigators and Co-Investigators were: New York State Psychiatric Institute, New York, NY, R01 MH 060912, Myrna M. Weissman, Ph.D.; Johns Hopkins University, Baltimore, MD, R01 MH059552, J. Raymond DePaulo, M.D., and James B. Potash, M.D., M.P.H.; University of Pennsylvania, Philadelphia, PA (1999-2005), and Stanford University (2006-2009), R01 MH61686, Douglas F. Levinson, M.D. (GenRED coordinator); University of Iowa, Iowa City, IW, R01 MH059542e, Raymond R. Crowe, M.D., and William H. Coryell, M.D.; Rush University Medical Center, Chicago, IL, R01 MH059541-05, William A. Scheftner, M.D.; and University of Pittsburgh, Pittsburgh, PA (1999-2003), R01 MH060866, George S. Zubenko, M.D., Ph.D., and Wendy N. Zubenko, Ed.D., R.N., C.S.


### Publications

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## Study 88 – Depression Susceptibility Genes and Networks (DGN)

### Summary

- **Grant Numbers:** 5RC2MH089916, 3R01MH090941
- **PI:** Douglas F. Levinson
- **Study Design & Aims:** Data and biomaterials were provided by Dr. Douglas F. Levinson (dflev@stanford.edu). This project was supported by National Institutes of Health/National Institute of Mental Health Grants 5RC2MH089916 (PI: Douglas F. Levinson, M.D.; Co-investigators: Myrna M. Weissman, Ph.D., James B. Potash, M.D., MPH, Daphne Koller, Ph.D., and Alexander E. Urban, Ph.D.) and 3R01MH090941 (Co-investigator: Daphne Koller, Ph.D.). This distribution includes 922 individuals (463 cases and 459 controls) from the largest whole – transcriptome study of MDD to date and the first using RNA-seq. Detail information can be found in the below listed publications.

### Acknowledgement


- Data was provided by Dr. Douglas F. Levinson. We gratefully acknowledge the resources were supported by National Institutes of Health/National Institute of Mental Health grants 5RC2MH089916 (PI: Douglas F. Levinson, M.D.; Co-investigators: Myrna M. Weissman, Ph.D., James B. Potash, M.D., MPH, Daphne Koller, Ph.D., and Alexander E. Urban, Ph.D.) and 3R01MH090941 (Co-investigator: Daphne Koller, Ph.D.).


### Publications


- Mostafavi S, Battle A, Zhu X, Potash JB, Weissman MM, Shi J, Beckman K, Haudenschild C, McCormick C, Mei R, Gameroff MJ, Gindes H, Adams P, Goes FS, Mondimore FM, Mackinnon DF, Notes L, Schweizer B, Furman D, Montgomery SB, Urban AE, Koller D, Levinson DF. Type I interferon signaling genes in recurrent major depression: increased

expression detected by whole-blood RNA sequencing. Mol Psychiatry 2013 Dec 3 (in press). PMID: 24296977

- Battle A, Mostafavi S, Zhu X, Potash JB, Weissman MM, McCormick C, Haudenschild CD, Beckman KB, Shi J, Mei R, Urban AE, Montgomery SB, Levinson DF, Koller D. Characterizing the genetic basis of transcriptome diversity through RNA-sequencing of 922 individuals. Genome Res 2014 Jan; 24(1):14-24. PMCID: PMC3875855

# Study 20 – Treatment of Adolescents with Depression (TADS) & Substance Use and Other Outcomes Following Treatment for Adolecent Depression (SOFTAD)

## Summary

- **Grant Numbers:** N01 MH80009 & R01 MH070494
- **PI:** John S. March & John Curry, Ph.D.
- **Study Design & Aims:** The TADS project was supported by Contract N01 MH80008 from the National Institute of Mental Health (NIMH) to Duke University Medical Center (Dr. John S. March, M.D., MPH, Principal Investigator), coordinated by the Duke Clinical Research Institute (DCRI), and conducted in 13 academic and community centers in the United States. The NIMH-funded Treatment for Adolescents with Depression Study (TADS) is a multi-site clinical research study examining the short- and long-term effectiveness of an antidepressant medication and psychotherapy alone and in combination for treating depression in adolescents ages 12 to 17. The SOFTAD project was funded by grant R01 MH070484 from the NIMH. Principal Investigator is Dr. John F. Curry, Ph.D., Department of Psychiatry and Behavioral Sciences and Duke Clinical Research Institute.

## Acknowledgement

- TADS (Treatment for Adolescents with Depression Study) was supported by Contract N01 MH80009 from the National Institute of Mental Health to Duke University Medical Center (John S. March, Principal Investigator). The authors would like to thank the members of the TADS Team. TADS is coordinated by the Department of Psychiatry and Behavioral Sciences and the Duke Clinical Research Institute at Duke University Medical Center in collaboration with the National Institute of Mental Health (NIMH), Rockville, Maryland. The Coordinating Center principal investigators are John March, Susan Silva, Stephen Petrycki, John Curry, et al.
- SOFTAD (Substance Use and Other Outcomes Following Treatment for Adolescent Depression) was funded by grant R01 MH070494 from the National Institute of Mental Health to John Curry, Ph.D. We are indebted to Benedetto Vitiello, M.D. who coordinated administration of SOFTAD at NIMH. We thank participants and the site staff who recruited them, including Margaret Price, Stephanie Frank, and Sue Baab. We acknowledge the many contributions of the late Dr. Elizabeth Weller, a dedicated clinical scientist.

### Publications

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## Study 73 – Combining Medications to Enhance Depression Outcomes (CO-MED)

### Summary

- **Grant Numbers:** N01 MH090003-02
- **PIs:**

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| Madhukar Trivedi, M.D. (Corresponding PI) | The University of Texas Southwestern Medical Center |
| Andrew A. Nierenberg, M.D. | Massachusetts General Hospital |
| Bradley Gaynes, M.D. MPH | University of North Carolina at Chapel Hill |
| Mustafa Husain, M.D. | The University of Texas Southwestern Medical Center Southwestern Medical Center |
| Sheldon Preskorn, M.D. | Clinical Research Institute - Kansas |
| Kevin Kerber/Elizabeth Young | University of Michigan |
| William Gilmer, M.D. | Northwestern University |
| Patrick McGrath, M.D. | Columbia University |
| Edward Friedman, M.D. | University of Pittsburgh |
| Sid Zisook, M.D. | University of California at San Diego |
| Jeff Mitchell, M.D. | Laureate Psychiatric Clinic and Hospital |
| Lori Davis, M.D. | Tuscaloosa VA Medical Center |
| Ira Lesser, M.D. | Harbor-UCLA Medical Center |
| Andrew Leuchter, M.D. | UCLA Neuropsychiatric Institute |
| Richard Shelton, M.D. | Vanderbilt University |
| Susan Kornstein, M.D. | Virginia Commonwealth University |

- **Study Design & Aims:** Study 73 (CO-MED) was a multisite, clinical trial of persons with depression comparing the effectiveness of randomly assigned medication treatment. The study was supported by NIMH Contract N01 MH090003-02 to the University of Texas Southwestern Medical Center. The ClinicalTrials.gov identifier is NCT00590863. A study of Depression (CO-MED). The overall aim of CO-MED is to enhance remission rates for outpatients with chronic or recurrent nonpsychotic major depressive disorder (MDD) as defined by DSM-IV TR, treated in primary or psychiatric care settings.
- Current evidence indicates that remission, the goal of treatment, is found in only about one-third of representative depressed outpatients treated for up to 14 weeks with an initial SSRI. In addition, even for those who do respond or remit, over one-third relapse

in the subsequent 12 months. Combinations of antidepressants are used in practice at the second or subsequent steps when relapse occurs in the longer term, or, in some cases, even acutely as a first step when speed of effect is a clinical priority. Whether such combinations could potentially offer higher remission rates, lower attrition, or greater longer-term benefit if used as initial treatments as compared to monotherapy remains to be examined.

- CO-MED will test whether two different medications when given in combination as the first treatment step, compared to one medication, will enhance remission rates, increase speed of remission, be tolerable, and provide better sustained benefits in the longer term. Results of this study will inform practitioners in managing the treatment of patients with chronic or recurrent MDD.

### Acknowledgement


- Data used in the preparation of this article were obtained from the limited access datasets distributed from the NIH-supported "Combing Medications to Enhance Depression Outcomes" (CO-MED). This is a multisite, clinical trial of persons with depression comparing the effectiveness of randomly assigned medication treatment. The study was supported by NIMH Contract # N01 MH090003-02 to the University of Texas Southwestern Medical Center. The ClinicalTrials.gov identifier is NCT00590863.


### Publications

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## Study 83 – Incomplete Response in Late Life Depression: Getting to Remission (IRL GREY)

### Summary

- **Grant Numbers:** 5R01MH083660-05
- **PI:** Charles F. Reynolds, M.D., University of Pittsburgh (Responsible PI) Eric Lenze, M.D., Washington University School of Medicine, St. Louis Benoit Mulsant, M.D., University of Toronto
- **Study Design & Aims:** The primary aims of this study are to:
    1. Assess the efficacy of aripiprazole augmentation for the acute and continuation treatment of TRLLD.
    2. Assess the tolerability of aripiprazole in TRLLD with a focus on adiposity and akathisia/restlessness.
- The secondary/exploratory aims of this study are to:
    1. Examine anxiety, medical burden, and executive impairment as moderators of aripiprazole augmentation efficacy in TRLLD.
    2. Examine genetic predictors (phase 1) and moderators (phase 2-3) of treatment outcomes, while controlling for drug exposure.

### Acknowledgement


- Data and biomaterials collected for project "Incomplete Response in Late Life Depression: Getting to Remission (IRL GREY)". This project was supported by ClinicalTrials.gov Identifier: NCT00892047 and 5R01MH083660-05 from the National Institute of Mental Health (NIMH). Principal Investigators are: Charles F. Reynolds, M.D., University of Pittsburgh (Responsible PI); Eric Lenze, M.D., Washington University School of Medicine, St. Louis; and Benoit Mulsant, M.D., University of Toronto.


### Publications

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## Study 84 – Predictors of Antidepressant Treatment Response: The Emory CIDAR; Predictors of Treatment Response, Relapse, and Recurrence in Major Depression

### Summary


- **Grant Numbers:** P50MH077083, R01MH080880
- **PI:** Helen Mayberg, W. Edward Craighead
- **Study Design & Aims:** The goal of the studies were to identify factors that may predict MDD treatment response in a randomized, three arm trial, by comparing the effectiveness of a selective serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor (SNRI), and cognitive behavioral therapy in 344 randomized patients with Major Depressive Disorder (MDD). Primary outcome measure after 12 weeks of treatment was the 17-item Hamilton Depression Rating Scale. The Hamilton Anxiety Rating Scale and the Quick Inventory of Depressive Symptomatology-self report were also collected at every time point.
- Collected predictors of remission included functional magnetic resonance imaging (fMRI) scans, personality assessments and a dexamethasone-corticotropin releasing factor test before and after treatment as well as sociodemographic and other clinical variables.
- Additional Emory investigators who contributed to this study were Boadie Dunlop, Elisabeth Binder (Emory/Max Planck Institute Munich), Joseph Cubells, Xiaoping Hu, Mary Kelley, Clint
- Kilts (now University of Arkansas for Medical Sciences), Becky Kinkead, Michael Owens, Drew Westen, Thaddeus Pace (now University of Arizona), Charles B. Nemeroff (now University of Miami), and James Ritchie.


### Acknowledgement


- NIMH Study 84 (Site 276) was funded by two independent NIMH grants. The principal investigators for the Emory CIDAR center grant were supported by funding from the National Institute for Mental Health grant P50MH077083 (Helen Mayberg). Additional funding was obtained for long-term follow-up of study participants via R01MH080880

(W. Edward Craighead). Additional Emory investigators who contributed to this study were Boadie Dunlop, Elisabeth Binder (Emory/Max Planck Institute Munich), Joseph Cubells, Xiaoping Hu, Mary Kelley, Clint Kilts (now University of Arkansas for Medical Sciences), Becky Kinkead, Michael Owens, Drew Westen, Thaddeus Pace (now University of Arizona), Charles B. Nemeroff (now University of Miami), and James Ritchie.

### Publications

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## Study 108 – Sustaining Remission of Psychotic Depression

### Summary

- **Grant Numbers:** 5U01MH062446, 5U01MH062518, 5U01MH062565
- **PI:** MEYERS, BARNETT
- **Study Design & Aims:** Psychotic depression (PD) is a severe disabling disorder with considerable morbidity and mortality. Between 19% and 45% of inpatients with major depression have psychotic features, with greater prevalence in older patients. Although electroconvulsive therapy has well-established efficacy in the treatment of PD, its use is limited by several factors. As a result, the pharmacologic treatment of PD is common. Expert guidelines recommend the combination of antidepressant and antipsychotic medications in the pharmacologic treatment of PD. The recently completed Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) was the first NIMH-funded randomized controlled trial (RCT) to examine the efficacy and tolerability of newer antidepressant and antipsychotic medications in the acute treatment of younger and older persons with PD. The combination of sertraline and olanzapine was significantly more efficacious than olanzapine combined with placebo. Both treatments were equally well tolerated, but were associated with clinically significant weight gain and elevation of lipids. Older persons, however, had significantly less weight gain than younger persons. Little is known about the continuation treatment of PD. Of particular concern, it is not known whether antipsychotic medication needs to be continued once an episode of PD responds to pharmacotherapy. This issue has profound clinical relevance. On the one hand, the unnecessary continuation of antipsychotic medication exposes a patient to adverse effects, such as weight gain and metabolic disturbance. On the other hand, premature discontinuation of antipsychotic medication has the potential risk of early relapse of a severe disorder. The primary goal of this Renewal application, therefore, is to assess the risks versus benefits of continuing olanzapine in younger and older patients with PD, once the episode of depression has responded to treatment with sertraline and olanzapine. This goal will be addressed through a 36-week double-blind RCT, in which placebo is substituted for olanzapine in half the study group, following a period of sustained remission. We hypothesize that sertraline+olanzapine will be more efficacious than sertraline+placebo in preventing relapse of PD. This study provides the unique opportunity to systematically assess the effect of antipsychotic discontinuation (as opposed to switching from one antipsychotic to another) on olanzapine-related

weight gain and metabolic disturbance. Additional innovative aims of the study are to examine age and genetic polymorphisms as predictors/moderators of treatment variability, potentially leading to more personalized treatment of PD, and to employ population pharmacokinetics to determine the magnitude and consistency of exposure to study drugs. Olanzapine is selected because it is the only atypical antipsychotic with established efficacy and tolerability in the treatment of both younger and older adults with PD . This research will be transformative, by providing clinicians with a much-needed evidence base to guide the continuation treatment of one of the most disabling and lethal psychiatric disorders.

## Acknowledgement


- Data and biomaterials were collected as part of the National Institutes of Health-funded study 'Sustaining Remission of Psychotic Depression' (5U01MH062446, 5U01MH062518, and 5U01MH062624). Study sites were Weill Medical College of Cornell University and New York Presbyterian Hospital, Westchester Division, NY (PIs: Drs. Barnett Meyers and George Alexopoulos); the University of Massachusetts Medical School and UMass Memorial Health Care, Worcester, MA (PI: Dr. Anthony Rothschild); Western Psychiatric Institute and Clinic, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA (PI: Dr. Ellen Whyte); and the Departments of Psychiatry, University of Toronto and University Health Network, Toronto, Canada (PI: Dr. Alastair Flint). The investigators are very grateful to the patients who participated in and contributed to the study.


## Publications