Treatment-Resistant Depression Diagnosis in the Outpatient Behavioral Health Setting

Michael Eaton

School of Nursing, University of Missouri-Kansas City

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Faculty Mentor: Dr. Lyla Lindholm, DNP

Preceptor: Dr. Jeanna Wilcox, PhD

Table of Contents

Abstract

Treatment-resistant depression can be challenging to identify in the outpatient behavioral health setting due to a lack of clear diagnostic guidelines. The evidence-based quality improvement project examined current practices in diagnosing treatment-resistant depression in the outpatient behavioral health setting. Data collection on current practices was conducted through a chart review of psychiatric evaluations for patients prescribed antidepressant monotherapy and a direct survey of clinicians. Clinician participation in the survey was voluntary and included any medication-prescribing clinician working in the outpatient behavioral health clinic. This data was analyzed to create an educational offering for clinicians in the outpatient setting regarding the diagnosis and treatment of treatment-resistant depression. After delivering the education, new patient charts were evaluated at the two-month mark to determine if there was a difference in the identification and treatment of treatment-resistant depression. Missed signs of treatment-resistant depression were found in the outpatient setting. Increased accuracy in diagnosing treatment-resistant depression may help improve patient outcomes and the overall quality of care.

Keywords: Treatment-resistant depression, diagnosis, outpatient behavioral health, patient outcomes

Outpatient Treatment-Resistant Depression

Major depression and depressive symptoms represent a significant disease burden to the United States of America and the worldwide population. As of 2013, major depression was the second leading global cause of disability (American Psychiatric Association, 2019). The American Psychiatric Association has established a comprehensive clinical practice guideline for treating major depressive disorder and other depressive presentations (American Psychiatric Association, 2019). This project evaluated the treatment provided in an outpatient behavioral health setting to determine if the treatment is consistent with the evidence-based treatment guidelines. The central focus of this inquiry was on treatment-resistant depression and the treatment plans enacted by outpatient behavioral health providers during outpatient treatment. (See Appendix A).

Significance

The lifetime prevalence of major depression or depressive symptoms is 17.9 % (American Psychiatric Association, 2019), with nearly 1 in every five Americans affected by depression at some point. Patients who fail two antidepressant medications of appropriate dose and duration are described as having treatment-resistant depression (TRD) (Pilon et al., 2019). These patients experience increased disease burden, as they typically experience more depressive episodes than their peers who have depressive symptoms and have responded appropriately to medications (Demyttenaere & Van Duppen, 2019). This increased duration of symptoms, coupled with the experience of poor treatment response, can lead to significantly decreased outcomes concerning both perceived treatment and overall response to treatment (Harris et al., 2020).

With increased episodes of depressive symptoms, patients with TRD experience a significantly higher cost burden associated with behavioral health treatment (Pilon et al., 2019). On average, patients who experience TRD spend $3385 more annually on their behavioral health treatment than similar peers

with adequate treatment of symptoms on antidepressant medications (Pilon et al., 2019). This cost burden represents not only a financial burden but also a time and psychosocial impact burden. Patients who experience TRD are more likely to be hospitalized for psychiatric presentations, utilize emergency room services, and have more outpatient behavioral health visits than patients with treatment-respondent depression (Shrestha et al., 2020).

Perhaps the most significant aspect of the increased disease burden associated with depression is the relationship between TRD and mortality. Evidence suggests that patients who experience TRD have a 35% higher all-cause mortality than their peers with non-TRD (Li et al., 2019). This relationship is also associated with a decreased survival index for those patients who experience TRD (Li et al., 2019). The increased lethality of TRD is of significant concern from a treatment and patient outcomes standpoint.

Evidence suggests that up to half of patients who experience depression will develop TRD (Rush & Jain, 2018). Patients who experience TRD have increased disease burden, higher overall behavioral health costs, and an increased likelihood of death compared to their non-TRD peers (G. Li et al., 2019; Pilon et al., 2019; Shrestha et al., 2020). These factors, taken individually, justify increased scrutiny of the assessment and treatment process associated with depression. The clinical significance of this disease process is overwhelming, and the project's primary goal was a further understanding of current clinical practice standards in the outpatient setting.

Local Issue

The project team leader assumed there was an epidemic of TRD and an opportunity to identify patients who would benefit from targeted treatment interventions. Outpatient assessment and diagnosis of TRD in a diverse metropolitan area may provide insight into TRD management. Quality

improvement in an outpatient behavioral health setting could have a potentially beneficial effect on overall patient outcomes.

Diversity Considerations

Baseline access to healthcare is not equitable across socioeconomic and racial groups (Chandler, Williams, Turner, & Shanahan, 2021). Evidence suggests an implicit bias in healthcare from access and equity of care standpoint (Chandler, Williams, Turner, & Shanahan, 2021). Years of consistent prejudice and systemic racism have fostered an inherent distrust of healthcare organizations and contributed to a decreased likelihood of seeking treatment (Butler, Covington, & Parsh, 2021). Even with the adjustment of biases and the healthcare movement toward equity, the barriers to appropriate behavioral health treatment can remain (Lee, et al., 2021).

Patient populations with an increased history of violence and decreased financial means are more likely to experience symptoms of depression and have poor access to medical and behavioral health treatment (Centers for Disease Control and Prevention, 2021; Butler, Covington, & Parsh, 2021). Furthermore, evidence suggests that poor access to treatment and continued experience of depressive or anxiety-based symptoms increases the likelihood that future generations in this specific environment will experience depression or anxiety symptoms (Centers for Disease Control and Prevention, 2021). Patients of color are also less likely to seek behavioral health treatment. When they seek treatment, they are less likely to receive appropriate treatment than their white counterparts (Chandler, Williams, Turner, & Shanahan, 2021). The project site chosen represented a diverse group of participants and should be representative of the population. There were no identified considerations for impact on the project.

Problem

The landmark sequenced treatment alternatives to relieve depression (STAR*D) study discussed the decreasing likelihood for antidepressant monotherapy to be effective after two trials of adequate dose and duration (Rush & Jain, 2018). The project team leader assumed patients were treated with antidepressant monotherapy against the recommended clinical standards. Clinical practice guidelines support changing from antidepressant monotherapy after two unsuccessful trials of adequate dose and duration (Rush & Jain, 2018). If this problem is present at the project site, an intervention will occur to address the issue.

Another assumption was that the individual clinicians are unaware of current recommendations supporting a change in treatment modalities for patients who fail to respond to two courses of antidepressant monotherapy of adequate dose and duration. A clinician survey was developed to identify knowledge deficits or motivations for specific treatment choices. The survey results allowed for targeted education and discussions regarding current treatment guidelines and strategies to improve patient care.

Purpose

The primary purpose of the proposed project was to achieve improved patient outcomes for patients identified to have treatment-resistant depression. The project identified areas where current practice improvements could be made to help reinforce continued change through clinician education.

A secondary purpose was to achieve consistency in identifying and treating patients who were present with TRD. The project team leader assumed there is no current, consistent approach to treating patients with TRD, and confirmation of this deficiency is the first step in creating a change in practice. If practices are inconsistent with clinical guidelines, targeted intervention, and education may foster a consistent and clinically sound approach.

Review of Evidence

Inquiry

In adults with depression, does documentation align with Clinical Practice Guidelines on diagnosing and treating resistant depression during six months at a community behavioral health clinic?

Literature Search

For this inquiry, the Trip medical database, Cochrane Database of Systematic Reviews, PubMed, and Google Scholar were queried to identify possible sources of evidence. The Trip medical database was used to search for high-level evidence and support material due to its easy-to-use interface and extensive resources for Level I evidence. PubMed accesses the MEDLINE database primarily and contains results for high-quality evidence. Search terms for the database searches and Google Scholar were the same to maintain consistency across the search fields. Search terms were depression treatment, treatment-resistant depression, the disease burden of treatment-resistant depression, clinical practice guidelines for depression, and therapy options for treatment-resistant depression. Exclusion criteria were sourcing older than 2017 or did not provide significant information concerning direct patient assessment and treatment. (See Appendix B).

Identification of the included articles and reports was conducted with a focus on relevant information which addressed TRD directly and applied to the assessment of depression and development of a treatment plan in outpatient behavioral health practice. The initial inclusion of 117 articles for review was produced through initial database queries. That review resulted in 64 articles included for a full review. Of the 40 articles, sixteen represented Level I evidence from all topics, four Level II evidence, six Level III evidence, two Level IV evidence, one Level V evidence, four Level VI evidence, and two Level VII evidence. In total, 40 sources were included in the evidence synthesis (See Appendix C).

Synthesis of Evidence

Six evidence themes were identified during the evidence collection and review stage. The primary theme was Acute Management and Clinical Practice Guidelines. This theme is consistent in each article of evidence discussed as each article contributes to the acute management clinical picture. The next most populated theme was Antidepressant Monotherapy, with nine articles of evidence. This theme represents the *treatment as usual* aspect of depression treatment. Diagnosis differentials and Treatment-resistant disease burden had six articles each. These two themes help establish the types of depressive episodes that may present as treatment-resistant and the overall disease burden associated with TRD. Psychedelic or amnestic treatment options were identified as another theme, and five articles of evidence were collected to support that theme. There is growing evidence for the classic psychedelics in treating depression, and ketamine products already have FDA approval. Lastly, five evidence articles were collected to discuss CBT and blended treatment methods for TRD. The addition of therapy to pharmacotherapeutics has evidence associated with improved outcomes. Each theme helps further support the evidence base for treatment guidance. (See Appendix D).

CBT Blended Treatment

Research indicates that TRD may be effectively treated by adding cognitive-behavioral therapy (CBT) and discontinuing medication, with CBT initiated as a standalone treatment, as demonstrated by studies conducted by J. Li et al. (2018) and Strawbridge et al. (2019). As a course of treatment, it is essential to understand that there are options other than medication for a provider to include in a treatment plan. Referrals can be placed if the provider is not certified to deliver CBT. Dunlop et al. completed a randomized control trial wherein they assigned patients experiencing TRD to one of three monotherapy groups, escitalopram, duloxetine, or CBT (Dunlop et al., 2019). Some patients in each group achieved remission, but those who did not enter a blended treatment phase. Evidence in this phase supported blended treatment, with more patients who had not remitted achieving remission (Dunlop et al., 2019). However, patients who were initially in the CBT monotherapy group and had

escitalopram added to their treatment plan experienced higher degrees of remission (89%) than those patients who were on medication first and had CBT added (53%) (Dunlop et al., 2019). This evidence supports the efficacy of CBT as a monotherapy and a blended treatment. It also helps to establish data that supports trying CBT first, as medication had a higher likelihood of remission when added to CBT monotherapy (Dunlop et al., 2019).

Adding CBT to treatment plans for depression was associated with improved depression scores and reduced relapse or recurrence of symptoms (Ontario, 2017). The addition of CBT was also associated with an increased likelihood of survival as measured by quality-adjusted life years (Ontario, 2017). The cost associated with this treatment was an overall cost saving, despite adding a specific treatment over treatment-as-usual (Ontario, 2017). The delivery method for this intervention can be complicated for some providers to find appropriate practitioners. There is some evidence that adding CBT is associated with a more significant effect size for remission vs. the addition of an augmenting medication (Strawbridge et al., 2019).

The project team leader targeted outpatient behavioral health practices because these locations typically involve several different care disciplines. Especially regarding blended treatment, it can be necessary for the medication provider and the CBT therapist to work in close consort (Mol et al., 2020). Combined treatment is a relatively new model, and evidence suggests that the treatment teams involved in these interventions have found it to be easy to use and more suited for quick delivery (Mol et al., 2020). Though some providers may have found it challenging to deliver this treatment in the past, evidence supports both the overall efficacy and the ease of use in the delivery of this specific intervention.

Psychedelic or Amnestic Medicine

A recent field of study for augmentation agents has been psychedelic and amnestic medications. In 2019, esketamine was first approved by the Food and Drug Administration (FDA) to treat resistant depression in adults (Kim et al., 2019). This medication has been described as both an amnestic and a psychedelic medication, though it is not one of the classic psychedelics (Kim et al., 2019). While this medication has a Risk Evaluation and Mitigations Strategies (REMS) program, it is deemed safe and effective (Kim et al., 2019). The REMS program may make it less likely to be implemented on a larger scale. Currently, esketamine is only FDA-approved as an adjunct therapy option in addition to oral antidepressant medication for the treatment of resistant depression (Daly et al., 2019). Among medication augmentation agents identified in one study, N-methyl-d-aspartate targeting drugs like esketamine had the most significant effect size (Strawbridge et al., 2019). The additional specifier of direct interest to the project team leader is that this medication is specifically approved to treat resistant depression.

One study conducted by Darji et al. (2019) surveyed multiple RCTs to evaluate esketamine against other popular augmentation agents for TRD. The results suggested that esketamine was superior to memantine, riluzole, d-cycloserine, and placebo (Darji et al., 2019). Another literature review evaluated the efficacy of ketamine against other pharmacological and somatic interventions (Papadimitropoulou et al., 2017). This large-scale literature review included 31 RCTs, with 19 RCTs investigating pharmacological interventions and 12 RCTs exploring either ECT or TMS (Papadimitropoulou et al., 2017). Though this analysis revealed a lack of long-term data for ketamine to compare against other interventions, initial results indicate that ketamine had superior efficacy at two weeks but was bested by quetiapine and risperidone at 4, 6, and 8 weeks (Papadimitropoulou et al., 2017). Based on the evidence reviewed, ketamine and the S enantiomer of ketamine are effective augmentation agents for treating resistant depression, though only esketamine has FDA approval for on-

label use (Kim et al., 2019). Esketamine is an effective medication for treating resistant depression and should be considered in treatment plans for TRD.

Differential Diagnosis

Ensuring an accurate diagnosis at the earliest possible stage in psychiatric evaluation is essential. Several etiologies could lead to depressive symptoms. Understanding the difference in possible presentations and discussing differential diagnoses is vital to this process. Nuñez et al. (2018) conducted a chart review and binary regression to examine 194 patients who met the criteria for two separate cohorts of treatment-resistant unipolar depression (TRD-UP, 100) and bipolar depression (BP, 94). The review was intended to determine if TRD-UP would be better described as a prodromal state of BP or if it constituted a specific diagnosis. The researchers determined that multiple clinical features distinguished TRD-UP from BP and should not be considered a prodromal state of BP (Nuñez et al., 2018). This data helps establish that TRD is a distinct and specific condition that can be identified based on current criteria. While TRD is broadly identifiable, a genuinely global consensus definition has not yet been established. A group of experts in Canada was surveyed to create a dimensional model to describe TRD (Rybak et al., 2021). These experts were able to come to an agreement that captures the heterogeneity of TRD. However, this definition has only just been established, and there remains a need to adopt a global standard (Rybak et al., 2021). This definition is progress nonetheless and valuable as a guideline for accurate identification and diagnosis. The project team leader is interested in promoting early and precise diagnosis in treating TRD. Increased education, understanding, and evidence-based clinical guidelines are vital to improve that goal.

TRD Disease Burden

Patients who experience TRD deal with symptoms that do not improve with appropriate treatment from at least two antidepressant courses of adequate dose and duration (American

Psychiatric Association, 2019). These patients are subject to increased disease burden due to extended periods with symptoms and more intense overall symptoms (Pilon et al., 2019). The immediate impact of continuing treatment-as-usual treatment plans when TRD is suspected is the impact on patients and poor patient outcomes (Pilon et al., 2019). Patients who experience TRD have more inpatient hospitalization, more visits to the emergency department, and more time missed from work than peers with non-TRD (Pilon et al., 2019). Patients who experience TRD have almost twice as many workdays missed as their non-TRD peers and nearly six times as many missed days as their non-depressed peers (Amos et al., 2018). The real-world dollar amount of this lost work is $1811 more than non-TRD peers and $3460 more than non-depressed peers (Amos et al., 2018). In addition to being more likely to experience increased healthcare costs and disease burden in the behavioral health system, these patients are subject to a loss of income, which further compounds the financial difficulty of coping with this disease process. While the increased cost to the patient is a direct burden, the increased cost for their insurers may be an increased indirect burden for the patients. Insurers may require increased scrutiny for patients who experience TRD due to higher healthcare burdens (Shrestha et al., 2020). This increased scrutiny could delay care due to the need for prior authorizations and utilization review, limiting timely treatment and intervention (Shrestha et al., 2020). This delay represents a significantly increased overall patient burden and may be avoidable with increased education and awareness of the clinical guidelines. In addition to the increased financial and time commitment, patients who experience TRD also have increased all-cause mortality compared to peers with non-TRD (Li et al., 2019). The increased all-cause mortality is the big picture when discussing mortality and TRD. Patients who experience TRD are more likely to request assistance in dying (Demyttenaere & Van Duppen, 2019). This point is representative of the increased feelings of hopelessness and helplessness experienced by patients with TRD (Demyttenaere & Van Duppen, 2019).

Suicide is a significant risk present in most behavioral health presentations. The risk of suicide is found to be increased in patients who experience TRD (Bergfeld et al., 2018). Patients who experience TRD have a 30% lifetime incidence of at least one suicide attempt (Bergfeld et al., 2018). Bergfeld et al. (2018) conducted a literature review and meta-analysis to try and determine if patients undergoing specific treatment modalities for TRD were more or less likely to have suicide attempts or completed suicides (Bergfeld et al., 2018). This review suggested that the increased likelihood of suicidality was more than likely a conditional trait of TRD and did not seem to be impacted by appropriate TRD-modified treatment plans (Bergfeld et al., 2018). Appreciating the increased treatment burden experienced by patients who experience TRD is paramount in understanding the need for increased scrutiny in treating depression overall. Early and accurate diagnosis may help limit exposure to these burdens and increase the likelihood of remission.

Antidepressant Monotherapy

Antidepressant monotherapy has long been the initial treatment plan for patients with first-episode depressive symptoms (Cipriani et al., 2018). As the STAR*D study suggested, some patients can achieve remission from either one or two antidepressant monotherapy courses of appropriate dose and duration (Rush & Jain, 2018). These medications are very compelling overall and have relatively few tolerability issues. Some medications stand out from the rest regarding tolerability and treatment efficacy when compared head-to-head. However, these differences are typically minor and do not represent clear and consistent evidence for one antidepressant monotherapy over another (Cipriani et al., 2018). Treatment resistance is established after patients fail to respond to at least two courses of adequate dose and duration. Despite available evidence-based recommendations for treatment catered to TRD, some patients are continued on antidepressant monotherapy (Rush & Jain, 2018). This finding is another focus of the project team leader to identify the possible rationale behind continuing treatment-as-usual on patients who could be identified as experiencing treatment resistance. In examining this

phenomenon, Bayes and Parker (2018) conducted a literature review to examine the consistency in treatment across patients with multiple presentations of depression. While there was a high degree of consistency in treatment for initial presentation depression, consistent agreement in treatment modality decreased with more presentations or failure of initial treatment decisions (Bayes & Parker, 2018). This data suggests that while most clinicians can agree on antidepressant monotherapy as the first-line treatment strategy, consensus decreases with each needed alteration of the treatment plan (Bayes & Parker, 2018). The literature also revealed little consistency in the management of TRD (Bayes & Parker, 2018). Understanding the breakdown in evidence-based care discussed in this study is another critical point of interest to the project team leader. While it seems that providers can agree on the first step, it would also appear that further training and education may be necessary to support improved patient outcomes, especially where TRD is present. An evidence-based approach with multiple avenues for altering a given treatment plan to support patients experiencing TRD may help improve patient outcomes and create an increased understanding on behalf of outpatient behavioral health practitioners.

Acute Management and Clinical Practice Guidelines

The overall theme of the research synthesis is the establishment of clinical practice guidelines and evidence-based recommendations for treating TRD. There are two prominent points for discussion in clinical practice guidelines. The initial presentation of depression is an essential first point of contact for every patient who will eventually be described as experiencing TRD. Establishing treatment recommendations for non-TRD is crucial, as appropriate and evidence-based early treatment is the only way to accurately evaluate if depression that fails to remit is truly treatment-resistant (American Psychiatric Association, 2019). If early treatment does not conform to established evidence-based treatment recommendations, it may not accurately predict the risk for TRD (Huang et al., 2020).

This treatment resistance is termed *pseudo-resistance* because it appears resistant to treatment, although it has not been treated with an adequate dose or duration (Voineskos et al., 2020). The American Psychiatric Association (2019) has a thorough and well-researched clinical practice guideline that directs care across the lifespan. Evidence in this guideline is discussed in depth based on the evidence base and strength of the recommendation(American Psychiatric Association, 2019). The professional organization for psychiatry in the United States created and reviewed this clinical guideline. It is a vital source of current practice's most up-to-date and evidence-based treatment guidelines. While it is essential to have an evidence-based source for treating depression, TRD presents a unique challenge separate from the clinical guidelines for non-TRD. Some evidence indicates that patients need to see up to nine different behavioral health providers to report receiving helpful treatment (Harris et al., 2020). This evidence suggests that patients may have negative experiences with at least eight providers while seeking treatment. The sample of patients this data was derived from were patients with major depression, so the difficulties of treating TRD had not yet been factored into this specific overall patient population (Harris et al., 2020).

Evidence suggests that TRD may be associated with a multifactorial degree of causation, previously not considered in the assessment of clinical presentation (Halaris et al., 2021). Nuñez et al. (2022) conducted a systematic review and network meta-analysis of 65 RCTs across 19 augmentation agents to treat TRD (Nuñez et al., 2022). This review was a network meta-analysis and determined that the more significant response and remission rates were associated with T4 hormone therapy and identified second-generation antipsychotic medications (aripiprazole, brexpiprazole, risperidone, quetiapine, and olanzapine/fluoxetine) (Nuñez et al., 2022). Ziprasidone, cariprazine, and mirtazapine were also associated with a greater incidence of discontinuation (Nuñez et al., 2022). This evidence suggests that TRD may be a more complicated and nuanced presentation than previously considered and deserves increased scrutiny.

Evidence Discussion

Analysis of Evidence

Forty articles of evidence were collected, representing six different sub-topics related to TRD and assessment in the outpatient behavioral health clinic. The primary theme was acute management and clinical practice guidelines associated with TRD. Thirty-four articles contributed directly to the evidence discussing acute management. Of those articles, five were Level one evidence articles providing robust evidence for standard clinical practice guidelines for treating TRD. One of the five articles was written by the American Psychiatric Association based on extensive high-level research (American Psychiatric Association, 2019). The evidence is structured to focus primarily on clinical practice guidelines and acute management guidance. Evidence discussing the assessment of TRD is provided to establish a clear and consistent clinical picture of TRD and to help differentiate between similar presentations. After that, research supporting evidence-based interventions is offered to further support and define some treatment interventions for TRD. Each of these sub-topics helps to support the more prominent theme of the clinical practice guidelines as evidence-based guidance for improved outcomes.

Limitations

The limitations of the body of evidence are few. The scope of the evidence is comprehensive, and the individual sub-topics are meant to support each other. High-level evidence has been identified in each of the sub-topic areas. Each sub-topic area has at least one Level 1 study to support the central thrust of the evidence in that specific sub-topic. The project leader included lower-level evidence in each of these areas, which may represent a perspective of limitation regarding the overall evidence. An effort was made to collect an extensive evidence base to support the general inquiry and inform each sub-topic with diverse information.

One primary limitation is that the clinical practice guidelines are not focused exclusively on TRD. The clinical practice guidelines reviewed are meant to assess and treat depression in general and make recommendations for depressive episodes as they present. This guideline is consistent with a presentation clinicians will likely see in practice. While this lack of focus on TRD could be seen as a limitation, the project team leader feels it mirrors clinical environments more closely than focusing on a specific diagnosis of depression.

Gaps

The primary gap in the evidence is that the evidence is focused mainly on the patient side of the interaction. The project team leader had a central focus on documentation and clinical decision-making on the part of the behavioral health clinician. More research discussing clinical decision-making on behalf of outpatient behavioral health providers is needed to compare the findings of this evidence-based quality improvement project. A better understanding of how providers approach patients with continued depressive symptoms may help improve treatment pathways in outpatient behavioral health care and better understand if documentation and treatment nationwide match findings on the Local Level. The project team leader has focused the EBQI on identifying specific treatment decisions that may or may not contribute to a patient being identified as meeting the criteria for a diagnosis of TRD and receiving appropriate care based on clinical practice guidelines. Without more information from the clinician's perspective, it may be difficult to identify what roadblocks or challenges hinder the successful identification of these patients during an early presentation.

The secondary gap in evidence on the provider side is the number of patients who may meet the criteria for TRD but are not identified as meeting the requirements or patients without evidence-based changes to their treatment plans to support a diagnosis of TRD. No robust data describes the frequency or incidence of patients who may meet the criteria for TRD. However, the project team leader

hypothesized that some patients could benefit from a treatment review. The disease burden in the case of TRD is severe enough that increased focus in this area is essential and needed (Pilon et al., 2019).

Summary of Evidence

The evidence collected details the assessment, diagnosis, and treatment recommendations for TRD. The clinical practice guidelines outline evidence-based treatment options and the strength of the research behind each of those options (American Psychiatric Association, 2019). Evidence for individual interventions was also collected and reviewed to further outline and support these interventions. Lastly, evidence discussing the disease burden experienced by patients diagnosed with TRD was examined to further cement the importance of early and accurate diagnosis and treatment. The project team leader has outlined an inquiry to quantify the number of patients who may be undertreated or benefit from additional interventions focused on TRD.

Theory

The ability to incorporate future findings and adapt to new evidence, coupled with the understanding that there are likely myriad causative factors at play in depressogenic effects, makes the foundational theory for the project the Complex Adaptive Systems theory. This theory guides the understanding of a diagnostic and interventional approach to TRD. This theory is chosen as a more complex theoretical model. It is not focused on the physiological systems involved in TRD but rather on the human choices in the assessment and intervention for TRD (See Appendix E.)

Early accurate identification is the identified concept for application to the project. It is the best diagnosis made at the earliest moment after a patient has had two appropriate trials of antidepressant monotherapy without relief from symptoms (Rush & Jain, 2018). Applying the theory to the chosen concept of early accurate identification to evaluate for the possibility of alteration in outcomes may help improve understanding of the inquiry.

The Complex Adaptive Systems Theory has been increasingly used in healthcare-related projects due to the focus on how systems interconnect within larger systems and influence each other. This theory will describe and evaluate how each system within the project interacts with and influences each other. Understanding the complicated ways patients and clinicians interact may increase understanding and predictability of outcomes.

Methods

Primary IRB

The project was conducted at a community behavioral health outpatient clinic. These clinics are part of a community behavioral health network and utilize the University of Missouri - Kansas City IRB. An application to conduct research at the site was processed before implementing the project. The IRB determined that this project did not constitute human subjects research and was considered a quality improvement project.

Ethics

While the project initially focused on chart review, the ultimate focus was on the behaviors of the providers, specifically their departure from evidence-based practice guidelines for treating depression and TRD. The ethics involved include ensuring that every clinician is reviewed the same and that they are each aware of the implications of the review. The clinicians were emailed as a collective group, and the explanation was provided to the entire group, so there was no focus on one clinician.

Cultural Considerations

The clinic was in an urban area, and many patients came from underserved populations. One of the considerations is to account for the multiple sociodemographic features particular to this group of patients. These features are likely to have an impact, though that impact was not immediately evident in

the project outcomes. There was no identifiable cultural consideration between the two cohorts observed in the evidence-based quality improvement project, as both groups were observed at the same clinic.

Funding and Cost

The project had a primary expense related to providing gift cards to compensate the outpatient clinicians for participating in the clinician self-survey and post-survey. Gift cards for $20 were purchased and delivered to the participating clinicians upon project completion. The project team leader assumed the expense. The project team leader completed chart review and data compilation as part of the project and was not compensated. (See Appendix F)

Settings and Participants

The setting was a behavioral health outpatient clinic in Kansas City, Missouri. The clinic is part of the safety-net health system for the underserved community, though the patient population is diverse and representative of the diverse community the clinic serves. Clinicians employed at the outpatient behavioral health clinic are from multiple disciplines, including Advanced Practice Registered Nurses (APRNs), attending physicians, and resident physicians.

The primary participants were behavioral health providers, physicians, and APRNs currently employed in the clinic who consented to participate in the study. Clinician participation in the survey portion of the project was voluntary upon explanation and discussion of the criteria. An introductory email was sent to a comprehensive list of clinicians at that clinic upon the onset of the project to introduce the project and discuss the goals.

Passive participants were patients who met the criteria for the chart review, and their participation was limited to the assessment of psychiatric evaluations, which had already been

completed and documented. The sampling method for the chart review was conducted based on defined criteria, and all patients who met the criteria were included in the sample. The inclusion criteria for patients in the initial cohort of chart review was that they were prescribed antidepressant monotherapy for depressive symptoms. No specific diagnosis was required as the project focused on interventions and not specifically on the type of current depressive etiology. The exclusion criteria included any patient already on adjunctive medication treatments for depression. Psychiatric evaluations older than a year before the project's initiation were excluded from consideration.

Evidence-Based Practice Intervention

Chart Review and Intervention

The intervention consisted of a chart review for patients on antidepressant monotherapy to determine if there is documentation supporting a diagnosis of TRD. The project also had a clinician survey component to determine a baseline for knowledge among the psychiatric clinicians at the project site. With data collected from the chart review and the clinician survey, an educational offering focused on identifying and treating TRD was developed and delivered to the clinicians in the outpatient setting. The educational offering was a bullet point review created with specific information for identified deficiencies in the self-survey. The educational offering also outlined critical findings from the initial chart review to demonstrate areas of potential improvement. At the end of the education period, a second chart review was conducted for patients on antidepressant monotherapy, and those charts were assessed for evidence of TRD.

Procedure

The initial step was the first chart review, which identified all psychiatric evaluations for the previous year. The project site used an electronic medical record, and the functionality to identify outpatient psychiatric evaluations were contained within that system. Outpatient behavioral health

patients prescribed antidepressant monotherapy at their initial psychiatric evaluation were identified and included in the review. An individual chart audit of each psychiatric evaluation in the defined one-year period accomplished this aim. The project leader completed this task from a list generated by the electronic medical record administrator. Once the cohort of patients was identified, the project leader conducted an individual review to assess the history and presentation for evidence that the patient may have TRD. The primary point of the assessment was a history of failure of two separate antidepressant monotherapy trials of adequate dose and duration. This step in the project identified patients in the cohort who may benefit from a change in their current treatment plan due to a history consistent with TRD. (See Appendix G).

As the initial chart review commenced, the individual clinicians were surveyed using Research Electronic Data Capture (REDCap). This survey was meant to identify the current knowledge base for clinicians in treatment decisions related to TRD. The survey was ten questions dealing with three primary focus points, identification of TRD, treatment preferences for depression, and individual practice decisions. The clinician survey provided perspective from the clinicians making treatment decisions. This data helped to identify opportunities for improved patient outcomes by focusing on knowledge deficits or biases present in the clinicians, which could affect their decision-making process.

The next step in the project was to analyze the data collected from the first two steps. There was an identified incidence of patients treated with antidepressant monotherapy despite meeting the criteria for TRD. The initial chart review reviewed 2,347 individual psychiatric evaluations for initial inclusion. Of the 2,347 psychiatric evaluations reviewed, 549 met initial inclusion due to being prescribed antidepressant monotherapy for an undefined depressive episode. Secondary inclusion was focused on any evidence in the psychiatric evaluation indicating a history of failure in at least two antidepressant monotherapy trials. Of the 549 charts reviewed for secondary inclusion, 163 contained evidence of a prior failure of at least two antidepressant monotherapy trials.

The survey results helped to focus on an educational intervention for the next step in the project. The education addressed the needs identified in the survey and delivered basic information regarding TRD and current clinical practice guidelines associated with the assessment and treatment of TRD. The education occurred at the start of the third month of the project, which allowed two months to complete the first two steps and synthesize the data to determine the needed content for the educational offering.

The fourth step in the process was to perform a second review of psychiatric evaluations, with the same criteria from the first chart review, looking for patients on antidepressant monotherapy and assessing for evidence of TRD. This step identified the incidence of patients who may benefit from changing their treatment plans. This second chart review was as much identical to the first as it could be to determine if there was a change in the ratio of patients who were identified to be experiencing treatment-resistant depression. Improvement in the balance might indicate that an increased number of patients have been identified earlier in the process as meeting the criteria for TRD. Likewise, if the ratio were to be higher after the intervention, it could mean that the intervention has been unsuccessful or has not had adequate time to achieve the desired effect. This step provided the measure, either way, for the efficacy of the intervention.

The last step in the process was to analyze and discuss the results. The project team leader conducted the initial analysis based on observed and obtained data. The initial chart review contained 549 psychiatric evaluations which met the initial inclusion criteria of being prescribed antidepressant monotherapy for any depressive presentation. The second chart review was identified as the post-intervention group. This group of psychiatric evaluations was collected between November 1, 2022, and February 28, 2023. This cohort had 167 psychiatric evaluations, which met the initial inclusion criteria.

Facilitators, Barriers & Sustainability

No financial barriers were encountered for this project as it was primarily based on a review of existing documentation. Financial needs were anticipated by the project leader and provided as needed throughout the execution of the project. Barriers may have existed in the patient charts' continuity of data and history. Initial barriers to determining accurate accounts were incomplete medication history records and poorly defined previous medication trials. Many of the charts reviewed contained insufficient information to determine the presence of past medication trials, and those that included the data did not always have extensive information on past trials. Regarding the medical records reviewed, this was the most prevalent barrier to fully understanding the problem from the perspective of the project leader.

A central facilitator in this process was that the clinical site is a teaching hospital with a tradition of fostering inquiry and supporting research on the part of clinicians. This aspect allowed for more resources and was apparent in the level of professional support which the project leader experienced. The use of electronic medical records in the clinic was a significant facilitator for the project's timely completion, as it made identifying psychiatric evaluations in the target period more attainable. The medical record is maintained by trained and skilled administrators who were able to assist in gathering the targeted information associated with the psych evals.

The feasibility of the proposed project was high. The project was a chart review to determine if current practices are consistent with evidence-based guidelines for treating depression and, in some cases, treatment-resistant depression. This project required time and access to behavioral health charts for patients prescribed antidepressant medications and diagnosed with depressive episodes. Lastly, this intervention produced a change that may be lasting with continued focus and awareness. Change is difficult to predict, but the level of intervention required is low. Continued education and reinforcement will foster sustainable change. Sustainability during the project depended on the project team leader

maintaining the chart review in the initial stages and compiling the data. Goals were identified early on and sustained throughout the completion of the project.

Evidence-Based practice model, Change Process

The evidence-based practice model was the Iowa Model of Evidence-Based Practice to Promote Quality Care (Schaffer et al., 2013). This model was chosen due to its interdisciplinary approach and team-based decision-making process (Schaffer et al., 2013). The evidence-based practice framework will be based on all available evidence, explicitly focusing on the STAR*D study for treatment-resistant depression (Rush & Jain, 2018).

The organizational change model for implementing the intervention at the project site was Duck's change curve (Duck, 2002). Focusing on the individuals involved and discussing the clinician's perspectives to help motivate change locally was an essential aspect of the project. This project uses a five-step model; the steps were included directly in the steps as the project proceeded.

The clinician survey at the start of the project contained questions about current practice models and understanding of the treatment recommendations for TRD. The survey was meant to determine a baseline understanding and to gauge the level of interest in change or perceived need for change. The second clinician survey at the end of the project also contained questions focused on practice standards, specifically if they have changed after the intervention and if the project intervention had anything to do with that change.

Project Design

The project was an evidence-based quality improvement project with two cohorts of patients for chart review and one cohort for provider survey and designated provider on the chart. The project was designed to have an initial assessment of current practices regarding identifying and treating

resistant depression within the clinic and an initial knowledge base for the clinicians. Once data was collected in the initial phase, a short educational offering was created and administered, discussing current evidence-based practice guidelines. This educational offering was designed based on identified needs in the clinician survey. Upon completing the survey, the second cohort of chart reviews started at the two-month mark. This second cohort identified psychiatric evaluations in a four-month post-intervention period (See Appendix H).

Validity

The internal validity of the project was the relationship between the dependent and independent factors, in this case, the accurate identification of treatment-resistant depression (dependent) and the clinician's education (independent). The relationship is implicit regarding the role of the behavioral health clinician and the diagnosis of behavioral health conditions. The external validity of the proposed project is high. The project site is a large outpatient behavioral health setting in a central Metropolitan area. While the clinic is expected to have a high population of patients with limited financial means, the ratio of uninsured and underinsured patients is not likely to be a factor that would impact the ability to transfer the intervention to the healthcare community. The project team leader did not review patient demographics and identifying information, so the only inclusion factor will be that the patient is currently prescribed antidepressant monotherapy.

Outcomes

There could be confounding factors in the data, given that there was not routine and extensive documentation of how long previous trials of antidepressant monotherapy lasted and if the dose would be sufficiently high to expect a response. Additional research and focus on all aspects of this topic are still needed as there is an opportunity for an improved understanding of how clinicians approach depressive episodes.

The intervention delivered was a one-page PDF sent to the clinicians by email for review on their own time. The individual, self-guided review was chosen as the most feasible means of delivery. Gathering all the participants in the same place for a presentation would be difficult and likely impact participation. The educational offering was a mix of an introductory presentation of TRD, clinical recommendations for TRD, and some insight from the initial chart review. A focused review of findings from the initial chart review, intended to promote self-reflection and possibly practice change, was included for group review. The second chart review, consisting of psychiatric evaluations gathered over four months from November 1, 2022, to February 28, 2023, was identified as a post-intervention group.

Measurement Instruments

Rush & Jain (2018) outlined recommendations for identifying depression resistant to first-line treatment recommendations. The measurement instrument for this study is modified from the recommendations made in the STAR*D study of 2006 (Rush & Jain, 2018). Though the STAR*D study supports a third trial of antidepressant medication in some cases, there is a growing body of evidence that suggests that changes from antidepressant monotherapy should be made after the failure of two trials of adequate dose and duration (American Psychiatric Association, 2019; Limandri, 2018; Nuñez et al., 2022). This measure is evidence of two prior courses of antidepressant monotherapy of adequate dose and duration. This measure was determined by patient self-report based on documentation in the psychiatric evaluation completed upon intake for each patient. (See Appendices I and J).

Quality of Data

Data gathered during this project was descriptive and focused on the type of treatment provided and the recorded data history. For the chart review portion of the project, an initial goal of 200 individual patients was the target. The initial chart review resulted in 549 psychiatric evaluations, which met the initial criteria. The initial chart review was open to patients who had started outpatient

treatment at any point before the start of the project, extending back one year. The clinician survey occurred immediately after the initial chart review and included only clinicians employed at the project site. Data gathered from the clinician survey was descriptive of baseline levels of understanding for treatment-resistant depression. A secondary chart review with the same inclusion criteria as the initial chart review started in the third month of the study. This chart review was limited to new patients prescribed antidepressant monotherapy since the educational offering. The second cohort for review was taken over four months and found to contain 167 psychiatric evaluations that met the initial inclusion criteria. There are no identified published benchmarks for data of this type.

Analysis

A survey of the clinician knowledge base was created to provide a baseline measure of reported knowledge in diagnosing and treating treatment-resistant depression. Analysis of this data was based on descriptive statistical data. The initial survey also contained questions identifying respondents as either APRNs or physicians. This metric was meant to determine if there was an observable difference between the two groups and was not a focus of the project. Extensive statistical analysis was not completed on these results as they are not the focus of the project but are meant to serve as a benchmark for the chart review data analysis. A chi-square test was completed on the raw data because the outcome of interest was a categorical variable (missed signs of treatment-resistant depression). There are two independent groups to compare. The initial chi-square statistic was 18.65 with one degree of freedom, which produced a p-value of < 0.001.

Results

Setting, Intervention Course

The setting was an outpatient behavioral health clinic in an urban environment. The intervention course was completed over a six-month period beginning in September 2022 and ending at

the end of February 2023. The baseline chart review cohort was collected from psychiatric evaluations which were completed before the start of the project, going back one year.

Baseline Cohort

The first cohort of psychiatric evaluations reviewed contained 2,347 psychiatric evaluations. Of the cohort, 549 met the inclusion criteria of being prescribed antidepressant monotherapy during their initial review. Of those 549 psychiatric evaluations that met initial inclusion criteria, 163 (29.6%) met secondary inclusion criteria, containing evidence in the chart of at least two prior failures on antidepressant monotherapy. This cohort was considered the baseline group. This data showed that almost a third of patients seen in the outpatient clinic during the review period and presented with symptoms of TRD were treated with antidepressant monotherapy, despite evidence suggesting that it is not likely to be effective.

Intervention Cohort

The second cohort chart review was collected between November 1, 2022, and February 28, 2023. This cohort was considered the intervention group, as all psychiatric evaluations were performed after the education intervention. A four-month review window was chosen due to the time constraints of the quality improvement project and to collect the largest sample size possible during the allotted timeframe. The second cohort contained 850 total psychiatric evaluations to review. Initial inclusion criteria were applied, and 167 patients were prescribed antidepressant monotherapy as the defined group. Of the 167 patients prescribed antidepressant monotherapy for presentation with a depressive episode, 32 (19.2%) met secondary inclusion criteria, containing evidence in the chart of at least two prior failures on antidepressant monotherapy. These data show a significant decrease in the percent of patients prescribed antidepressant monotherapy for a presentation more consistent with TRD. (See Appendix N).

Change with Intervention

A chi-square test for independence was performed because the outcome of interest was a categorical variable (missed signs of treatment-resistant depression). There were two independent groups (Group 1 and Group 2) to compare. A chi-square test was performed to determine whether the second cohort was statistically significant in improvement. A chi-squared value of 18.65 and 1 degree of freedom yielded a $p < 0.001$. Therefore, showed a statistically significant finding since the observed frequency of treatment-resistant depression patients in the second cohort was less than the expected frequency at baseline, 19.2% and 29.6% respectively (See Appendix O).

Clinicians

The initial clinician survey assessed the baseline confidence level by clinician self-report. Nine individual clinicians participated in the survey, including five physicians, and four APRNs. There were questions targeting treatment decisions related to TRD, and the data collected was for background and not directly relevant to the project outcomes or execution. Clinicians felt confident they had a thorough understanding of treatment guidelines for TRD, on average rating their understanding as 7.5/10. They were also primarily able to identify the evidence-based augmentation agents choosing second-generation antipsychotic medications over first-generation antipsychotic medications or Depakote.

Discussion

While these results are not meant to serve as definitive proof of the intervention's relevance, they provide some data to suggest that the rate at which signs of treatment-resistant depression are missed may be higher than expected. This finding is considered the major success of the evidence-based quality improvement project. It also provides evidence that a low-intensity intervention can impact the quality of patient care to a significant degree. Further research on the incidence of TRD missed in the population of outpatients seeking treatment at community behavioral health clinics could help to

cement the need for comprehensive increased focus on the basics of behavioral health care and treatment of treatment-resistant depression.

The results were found to be statistically significant, which indicates that there was a factor that influenced the outcome. The primary intervention was the educational flyer emailed to the outpatient behavioral health clinicians two months into the project. A secondary intervention factor is assumed to be that knowledge of the project's existence was a likely factor in increasing awareness of TRD and focus on TRD guidelines and management.

Successes

The immediate success of the project was that the second cohort considered the intervention group, had a decrease in observed patients with missed symptoms of TRD. This result means that more patients were prescribed evidence-based treatment for TRD, which has been associated with an increased likelihood of improved patient outcomes. This evidence-based treatment will lead to improved long-term patient outcomes. With continued improvement and maintenance of the changes accomplished so far, the patients in this clinic are likely to experience less financial burden for their healthcare, miss fewer workdays due to depressive episodes, and experience a decreased lifetime suicide risk. This project demonstrated that increased awareness and education focused on TRD can improve patient outcomes throughout a short intervention window. The intervention was straightforward and focused on the basics of TRD.

A secondary success of the project is that the cost and time commitment associated with the project makes it a repeatable and high-impact option. While the educational tool used in this project was tailored to information from the first chart review and first clinician survey, the project leader does not feel that including specific information was an impactful factor. The educational offering was

focused on the basic evidence-based clinical practice guidelines for TRD and can be a standardized offering across future project sites.

A tertiary success of the project was the amount and quality of initial clinician buy-in associated with the project. The project generated a reaction via the clinician survey and a conversation, which may have impacted the project's outcomes regarding the increased awareness of TRD and treatment recommendations. Due to the lack of published data on missed diagnosis and treatment of TRD, the results of this project were not compared to other studies.

Limitations

Internal Validity Effects

The study design was a standard baseline and intervention, two cohort design common to quality improvement projects. This design is simple and effective, making it reliable and easy to implement. This design was chosen to help assess if there was a statistically significant change after the implementation of the intervention. In this case, there was a statistically significant change after implementing the intervention. This finding could support the conclusion that the intervention directly caused the difference, though there are too many confounding factors to consider. In this project, there was a primary intervention, the educational offering delivered to clinicians at the two-month mark. However, there was an unintended secondary intervention, awareness that the study was being conducted. This awareness may have triggered additional awareness of TRD guidelines and acted as a secondary intervention.

The clinician survey was targeted to collect data on baseline confidence in treating TRD. The clinician survey could include more questions related to any perceived bias on the part of the clinician, as well as questions focused on clinical knowledge and treatment options. There remains the possibility

that factors related to clinician bias or assumptions may be present and unidentified. An expanded background data set would help provide a complete picture of the clinician basis.

Documentation completion was a factor in the internal validity of this project. The project's basis relies on the assumption that data was not collected if it is not charted. The element of missing information in the charting is an unknown quantity and may have an impact on the actual outcome of the project. However, the presence of this unknown quantity is likely to be affected to a similar degree in both groups. It would likely have a negligible overall impact on the outcomes.

External Validity Effects

The most prominent factor for external validity impact is the ability to generalize the findings to the population of the United States. This improvement initiative is generalizable to similar urban environments across the United States. Similar socio-economic, demographic, and accessibility factors are likely present in urban settings nationwide. States' laws will differ and could impact access to healthcare. Specific urban environments may have different demographic backgrounds, affecting the project in unknown ways. The availability of trained and appropriate psychiatric clinicians will also vary across urban settings. The presence of medical training programs is likely to increase access to behavioral health treatment for that population. In contrast, cities without medical colleges may have a significant disadvantage in access to treatment.

The electronic medical record (EMR) was a contextual factor for the external validity of the project. This factor may be limited as an EMR is considered the standard of practice. While the EMR allowed for a rapid and efficient review of available medical records and identification of appropriate psychiatric evaluations, not all clinics across the country may have access to an EMR, which will affect the repeatability of the project and the consistency from site to site.

Sustainability of Effects

The sustainability of the effects of this project is challenging to determine. There are factors about the patients and how they tolerate medication changes, adhere to recommendations, and continue treatment. Multiple spheres of influence for different providers affect the effort required to sustain a positive practice change. Providers in the outpatient behavioral health clinic with more set-in patterns, who have been practicing in a defined way for many years, will find it more difficult to sustain change. In contrast, a provider with less experience may not be so set in a pattern but may be impacted by a demanding workload. Overall the sustainability of the project is high due to the ease with which refreshers can be delivered and the ready access to augmentation agents for best clinical practice.

Efforts to Minimize Limitations

The project leader set out to complete the project and learn of the limitations and challenges as the project was completed so that future iterations could be better aware of the constraints and prepare accordingly. The limitations in the charted information were endemic across both cohorts, and this topic was discussed with the director of psychiatry. Collecting a thorough history, including past medication courses, will help resolve this limitation.

A better understanding of the approach to practice for outpatient behavioral clinicians would help decrease the limitations on the provider side. With a better understanding of some of the treatment practices, a more comprehensive change plan can be created and may help to sustain the intervention forward more definitively.

Interpretation

Expected & Actual Outcomes

The project leader theorized that TRD was underdiagnosed and undertreated in the outpatient behavioral health setting. Previous research on the topic has not been extensively collected or examined

in published studies. The incidence of TRD in the community has not been consistently identified in the psychiatric literature. The project leader sought to determine if baseline rates of TRD identification and appropriate treatment would change by implementing a relatively low-effort intervention to increase awareness. The project outcomes identified that observed rates of patients prescribed antidepressant monotherapy with documented signs of TRD after the intervention decreased from the expected rate at baseline. This finding indicates that the baseline rate of 29.6% observed in the baseline cohort is a quickly impacted baseline and not an accurate baseline for experienced providers.

Intervention Effectiveness

The efficacy of the intervention was likely two-fold. The primary intervention was intended to be the direct education provided to the outpatient behavioral health clinicians directly. The unintended secondary intervention was the increased awareness of TRD associated with the implementation of the project. The combination of both interventions was effective enough to create a statistically significant change in the identified rates of the patients with missed signs of TRD.

Intervention Revision

Future revisions of the intervention include the removal of the educational offering entirely. With increased focus on a questionnaire for the participating clinicians, and reduction of the educational offering, the impact of the secondary intervention can be measured to determine the individual efficacy of that approach, which would help to further gauge the effectiveness of the primary intervention by comparison. Delivery of the educational offering outside of the framework of an evidence-based quality improvement project will be an effective way to limit the impact of the secondary intervention if clinicians are unaware that there is a chart review project underway.

Expected and Actual Impact

The expected impact for accurate identification and treatment of TRD can significantly impact patient outcomes and improve the effectiveness of behavioral health interventions. The effect of the change observed in the evidence-based quality improvement project could be measured in the future or added to future iterations of this project at additional sites. Clinical measures to understand the presence of future depressive symptoms and episodes, as well as measures of the quality of life experienced by these patients with identified TRD, would help to support the implementation of projects aimed at increasing awareness of TRD.

Conclusions

Practical Usefulness

This project has identified patients not initially treated with evidence-based practice when presenting signs of treatment-resistant depression in the outpatient behavioral health clinic. The intervention's practical usefulness pertains to increasing clinicians' baseline knowledge in outpatient practice and improving patient outcomes. The educational offering for clinicians consisted of reviewing evidence-based guidelines for treatment-resistant depression, identifying TRD in the patient population based on clinical evidence, and reviewing current practices observed in the clinic. This educational offering was delivered, and the intervention cohort observed a decrease in patients with missed signs of treatment-resistant depression.

Further Study

Further study in the diagnosis and identification of TRD is needed. The exact incidence of TRD is unknown, and more research into the specifics regarding diagnosis, medication trials, and referral is necessary. With expanded research into TRD, there is likely to be increased awareness of the outpatient clinician approach and available treatments. Increased focus on collecting accurate historical data is needed, providing further insight into the degree to which TRD may be missed in the general population.

In the execution of this project, incomplete or unrecorded medication history was a significant limitation in determining the history of treatment-resistant depression.

Dissemination

The quality improvement initiative has been shared within the Doctor of Nursing Practice Spring 2023 cohort at the University of Missouri-Kansas City School of Nursing. After initial discussion in the academic setting, the compilation, review, and EBQI experience will be disseminated within healthcare systems and organizations. The EBQI will be submitted for publication in the *Journal of the American Psychiatric Nurses Association*.

A poster presentation discussing the evidence-based quality improvement project was also accepted for display and discussion at the Psych Congress Elevate conference in Las Vegas, Nevada. The poster will be part of the symposium on current research and EBQI projects in psychiatry. The project leader will present the poster and be present to facilitate discussion and answer questions.

Impact to Healthcare

This project identified that there was a statistically significant decrease in the observed frequency of patients with missed signs of treatment-resistant depression after the delivery of a short educational offering focused on TRD. This improvement initiative may be generalized to a portion of the population and represent a significant opportunity to focus on increased awareness for evidence-based treatment for TRD. Also, an opportunity exists to improve clinicians' knowledge and understanding when identifying depression, anxiety, and TRD daily in outpatient behavioral health clinics nationwide.

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Appendix A

Definition of Terms

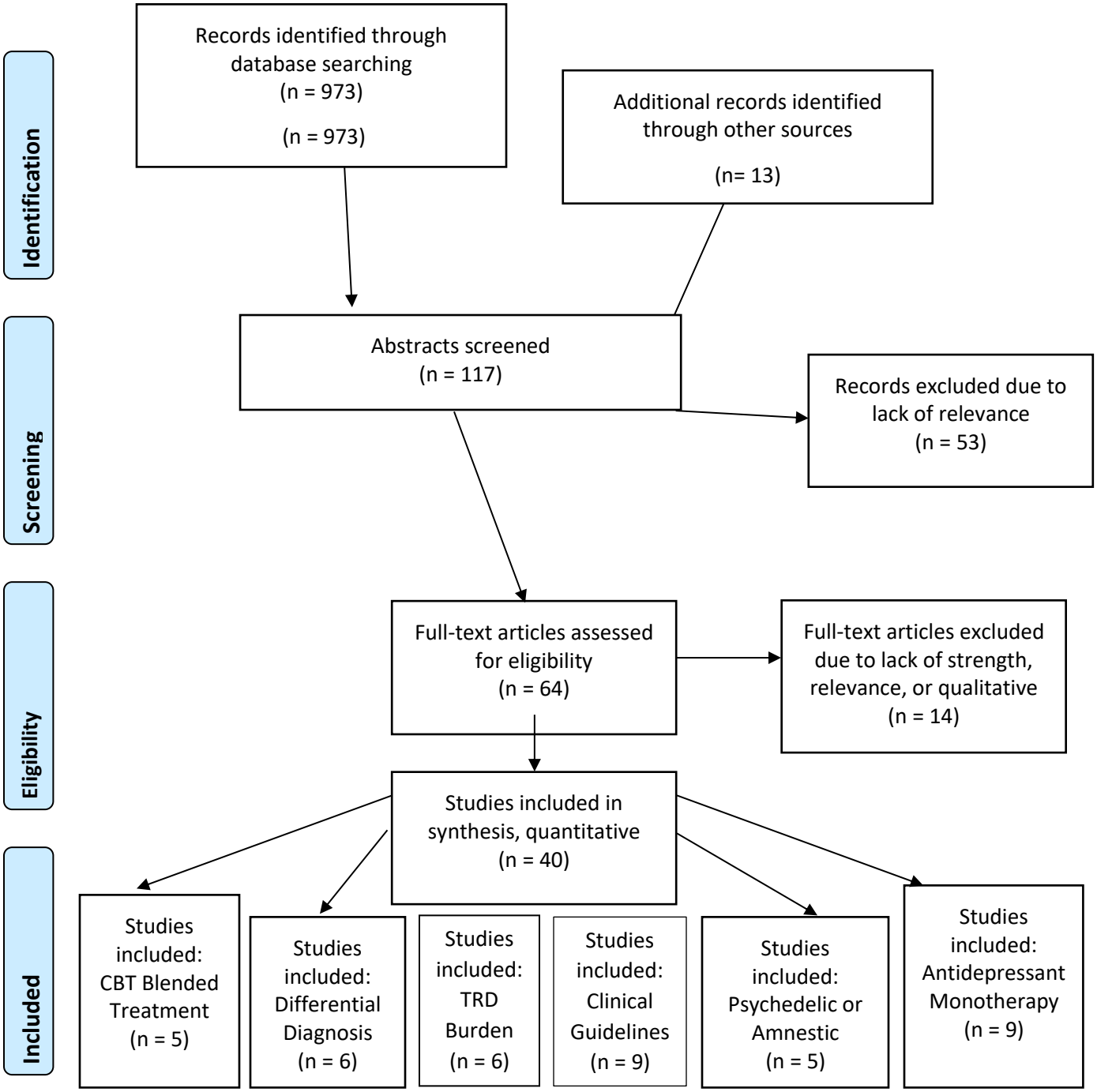
Treatment-resistant depression (TRD), by the most up-to-date definition, is a continuation of symptoms after three adequate trials of antidepressant medication (Rush & Jain, 2018).

Antidepressant monotherapy, for purposes of this research, is defined as a serotonin-selective reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) used as monotherapy to treat depression.

For purposes of this project, an outpatient clinician is defined as a behavioral health clinician working in the outpatient setting with prescriptive medication privileges who works as a physician or advanced practice provider for treating psychiatric conditions.

Appendix B

Adapted PRISMA Flow Diagram



Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses:* The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix C

First author, Year, Title, Journal	Purpose	Research Design[1] , Evidence Level[2] & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
Clinical Practice Guidelines						
Nuñez (2022) Augmentation strategies for treatment-resistant major depression: A systematic review and network meta-analysis. *Journal of Affective Disorders*	EBPG	Systematic Review and Network Meta-Analysis Level 1 - NMA	65 studies and a total of 12 415 individual participants		Network Meta-Analysis of 65 studies and 19 augmentation agents The review suggests the superiority of approved SGAs and Thyroid hormone (T4)	Heterogeneity in TRD definitions, variable trial duration and methodological clinical design of older studies, and a small number of trials per comparison.
Liu (2021) Epidemiology of Treatment-Resistant Depression in the United States. *The Journal of Clinical Psychiatry*	Determine the prevalence of TRD in adult populations	Cross-sectional Study Level 4	574,273 patients across two databases		17,640 (6.0%) and 16,131 (5.8%) had TRD	Low-level study Does it provide a consistent estimate of TRD prevalence
Halaris (2021) Treatment-Resistant Depression Revisited: A Glimmer of Hope. *Journal of Personalized Medicine*	EBPG	Systematic Review Level 1			A comprehensive description of evidence in the diagnosis and treatment of TRD	Extensive research

First author, Year, Title, Journal	Purpose	Research Design[1] , Evidence Level[2] & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
Voineskos (2020) Management of Treatment-Resistant Depression: Challenges and Strategies. *Neuropsychiatric Disease and Treatment*	EBPG	Meta-analysis Level 1			Further work is necessary to understand and adequately treat TRD	Multiple topics discussed with in-depth evidence
Harris (2020) Findings from World Mental Health Surveys of the Perceived Helpfulness of Treatment for Patients with Major Depressive Disorder. *JAMA Psychiatry*	Evaluate perceived helpfulness of treatment for the treatment of MDD	Systematic Review Level 1	80 332 respondents were surveyed in 16 countries		Most patients were helped (93.9%) if they persisted through ten treatment professionals, but only 21.5% continued that long	Patient report of historical data by memory
McAlister-Williams (2020) The identification, assessment, and management of difficult-to-treat depression: An international consensus statement. *Journal of Affective Disorders*	To develop an International Consensus or CPG for difficult-to-treat-depression (DTD)	Qualitative Level 6 – CPG Primarily informed by expert opinion	A literature review was conducted, and an International Group of 15 Psychiatrists with Expertise in Affective Disorders were convened		Recommended change in terminology to difficult to treat depression, from treatment-resistant depression. Debate on the number of antidepressant	Lower-Level Evidence Consisting Mostly of Expert Opinion Did not produce much new information or actionable data

First author, Year, Title, Journal	Purpose	Research Design[1] , Evidence Level[2] & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
					trials needed to meet the criteria. Proposal of numerical staging models for TRD	
American Psychiatric Association (2019) Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts	EBPG Specific to Depressive Episodes	EBPG Quantitative Level 1				Helpful as a reliably evidence-based guide for treatment
Park (2019) Depression in the Primary Care Setting. *New England Journal of Medicine*	Evaluation of Depression treatment in the Primary care setting	Single Quantitative Case example Level 6				Limited use and scope Largely anecdotal
Rosenblat (2019) Treatment effectiveness and tolerability outcomes that are most important to individuals with bipolar and unipolar depression. *Journal of Affective Disorders*	Evaluate treatment efficacy in bipolar depression and unipolar depression	Primary Research Level 6	896 participants completed an online survey		Participants reported multiple prior treatment regimens and a minority of patients said that their current treatment plan was helpful	Online survey
Rush (2018) Clinical Implications of the STAR*D Trial.						

First author, Year, Title, Journal	Purpose	Research Design[1] , Evidence Level[2] & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
Mahlich (2018) Estimating Prevalence and Healthcare Utilization for Treatment-Resistant Depression in Japan: A Retrospective Claims Database Study. *Drugs – Real World Outcomes*	To estimate the prevalence of TRD in Japan	Retrospective cohort study Level 4	1143 pharmaceutically treated patients Japan		137 patients had a failure of more than two antidepressant medications	Lower-level evidence Japan
Wiles, N. (2018) Management of treatment-resistant depression in primary care: a mixed-methods study. *British Journal of General Practice*	Evaluate current treatment as usual practices for treatment-resistant depression in primary care	Quantitative Level 2 – RCT	235 patients randomized to GPs followed for a year at three-month intervals Primary care patients in the United Kingdom	Most patients continued on SSRI monotherapy (*n* = 147/186 at three months, 79% (95% confidence interval [CI] = 73 to 85%) And those measures were similar at the end of the study (9–12 months: 72% (95% CI = 63 to 79%)	Most patients did not have a change in medications, and most did not have depression assessed in the primary care setting	Small sample study The study focused on a primary care clinic and not an outpatient psychiatry clinic
Akil (2018) Treatment resistant depression: A multi-scale, systems biology approach.	EBPG	Systematic Review Level 1				Varied and multi-systems approach

First author, Year, Title, Journal	Purpose	Research Design[1] , Evidence Level[2] & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
Neuroscience & Behavioral Reviews	A dynamic approach to TRD Treatment					The focus could be overbroad
MacQueen (2017) Systematic Review of Clinical Practice Guidelines for Failed Antidepressant Treatment Response in Major Depressive Disorder, Dysthymia, and Subthreshold Depression in Adults. *Canadian Journal of Psychiatry*	EBPG Guidelines specifically for TRD and failed response to medications in the past	Systematic Review Level 1	46,908 citations 3167 screened 21 CPGs applicable to adults with depression		Most CPG reviewed did not provide specific guidance for second-line treatment	The focus was primarily on second-line treatment
Differential Diagnosis						
Rybak (2021) Treatment-resistant major depressive disorder: Canadian expert consensus on definition and assessment. *Depression and Anxiety*	Obtain a consensus opinion on the definition and assessment	Expert Opinion Level 7	14 Canadian Experts Three rounds of Surveys 27 items discussed		Modified Delphi process for consensus agreement	Expert opinion
Nunez, N. (2018) Psychopathological and sociodemographic features in treatment-resistant unipolar depression versus bipolar depression: a comparative study. *BMC Psychiatry*	Comparison of features between treatment-resistant unipolar depression (TRD-UP) and	Qualitative Level 6 – Qualitative Study	Chart analysis of 194 patients at a Mood Disorders clinic McGill University Health Center	Reliability analysis was performed to determine the internal consistency using Cronbach's alpha. Overall, we reached	Treatment-resistant depression constitutes a distinct psychopathological condition and not a prodromal state of bipolar disorder	Small sample study Lower-level evidence

First author, Year, Title, Journal	Purpose	Research Design[1] , Evidence Level[2] & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
	bipolar disorder (BP)			acceptable reliability for all the scales (MADRS: α = 0.91; HAMD-17: α = 0.82; QIDS-C16: α = 0.77). Inter-rater reliability was performed on a sample of 140 patients. Three raters assessed patients (two psychiatrists and a General Practitioner). We found moderate to good agreement (Cohen's kappa range: 0.58–0.85) [34]) (MADRS: 0.60; HAMD-17: 0.58; QIDS-C16: 0.61; CGI-S: 0.72; CGI-Global	Binary Logistic Regression	

First author, Year, Title, Journal	Purpose	Research Design[1] , Evidence Level[2] & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
				Improvement: 0.85) across all scales.		
Limandri (2018) Treatment-Resistant Depression: Identification and Treatment Strategies. *Journal of Psychosocial Nursing and Mental Health Services*	Identification of TRD					
Antidepressant Monotherapy						
Day, E. (2021) A retrospective examination of care pathways in individuals with treatment-resistant depression. *BJ Psych Open*	To explore the nature and extent of treatment gaps experienced by patients with treatment-resistant depression	Qualitative Level 5 – Review of qualitative data	178 Patients identified as diagnosed with TRD across three cities in the United Kingdom	Time from the start of a depressive episode to the first initiation of antidepressant medication > 24 months (95% CI 18–31%) 55% of patients had been prescribed at least three trials of antidepressant	Patients were not started on AD medications in an adequate time frame. Patients were not trialed on adjunctive medications despite indications. Patients were found to have	Low Level of Evidence Qualitative Study Limitations or requirements could influence the study in Nationalized healthcare

First author, Year, Title, Journal	Purpose	Research Design[1] , Evidence Level[2] & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
				medication, and only 38% had been treated with some form of adjunctive therapy	slower medication changes than indicated.	
Marasine (2021) Use of Antidepressants among Patients Diagnosed with Depression: A Scoping Review. *Biomed Research International*	Review medication usage in patients with TRD	Systematic Review Level1	13 articles reviewed from 13 different countries			Language bias as only sources published in English was used
Strawbridge (2019) Augmentation therapies for treatment-resistant depression: systematic review and meta-analysis. *The British Journal of Psychiatry*	Review of augmentation strategies	Meta-Analysis Level 1	28 trials 25 trials looking at pharmacological interventions Three looking at psychological treatment	N-methyl-D-aspartate targeting drugs have the highest effect size (ES = 1.48, 95%CI 1.25–1.71)	All antidepressants were more efficacious than placebo More minor differences were found among active drugs	Limited scope for long-term efficacy
Cipriani (2018) Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major	Compare the efficacy of multiple antidepressant drugs	Systematic Review and Network Meta-analysis Level 1	522 trials comprising 116 477 participants			Useful in describing evidence for efficacy in multiple

First author, Year, Title, Journal	Purpose	Research Design[1] , Evidence Level[2] & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
depressive disorder: a systematic review and network meta-analysis. *Lancet*						pharmacologic agents
Bayes (2018) Comparison of guidelines for the treatment of unipolar depression: a focus on pharmacotherapy and neurostimulation. *Acta Psychiatrica Scandinavica*	Evaluation of current guidelines for unipolar depression	Systematic Review Level 1				
Davies (2018) Pharmacological interventions for treatment-resistant depression in adults. Cochrane Database of Systematic Reviews	Discuss multiple pharmacological interventions for TRD in adults	Systematic Review Level 1				Extensive evidence-based resources for medication management of TRD
CBT Blended Treatment						
Mol (2020) Why Uptake of Blended Internet-Based Interventions for Depression Is Challenging: A Qualitative Study on Therapists' Perspectives. *Journal of Clinical Medicine*	Increase understanding of difficulty with the uptake of Blended CBT	Focus groups and semi-structured interviews Level 3	Three focus groups (n = 8, n = 7, n = 6) and semi-structured in-depth interviews (n = 15) were held throughout the Netherlands			Low-level evidence Not a large enough sample to be meaningful

First author, Year, Title, Journal	Purpose	Research Design[1] , Evidence Level[2] & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
Dunlop (2019) Benefits of Sequentially Adding Cognitive-Behavioral Therapy or Antidepressant Medication for Adults with Nonremitting Depression. *American Journal of Psychiatry*	Explore the benefits of adding medications to poor responders to CBT	RCT Level 2	A total of 112 patients who did not achieve remission with a monotherapy entered combination treatment (41 who responded to monotherapy but did not achieve remission and 71 who did not respond to monotherapy)		CBT plus meds group had higher remission than the Meds plus CBT group	New evidence Well-designed level 2 study
Li (2018) Cognitive behavioral therapy for treatment-resistant depression: A systematic review and meta-analysis. *Psychiatry Research*	Increased research to clarify the evidence base for CBT	Systematic Review Level 1		Heterogeneity was insignificant in effect size (I2= 14%, P = 0.28). The pooled RR was 2.01 (95% CI = 1.54 to 2.62, Z = 5.14, P < 0.00001), giving evidence of comparative efficiency of CBT	Remission rates showed that 45 of 174 CBT subjects and 24 of 168 control subjects were reported remitted	Strong design

First author, Year, Title, Journal	Purpose	Research Design[1] , Evidence Level[2] & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
Ontario Health (2017) Psychotherapy for Major Depressive Disorder and Generalized Anxiety Disorder: A Health Technology Assessment. Health Quality Ontario	Review the effect of CBT on Anxiety and Depression treatment	Systematic Review Level 1			Interpersonal therapy, compared with usual care, reduced posttreatment major depressive disorder scores	Large State-Sponsored review
TRD Disease Burden						
Shrestha (2020) Incremental Health Care Burden of Treatment-Resistant Depression Among Commercial, Medicaid, and Medicare Payers. *Psychiatric Services*	Documentation and evaluation of disease burden in TRD	Retrospective Cohort Study Level 3	Adults in the US who had received antidepressant treatment between 2006-2016 commercial, N=27,595; Medicaid, N=5,556; and Medicare, N=1,856		Patients with treatment-resistant depression have substantially higher healthcare utilization and cost burdens compared with patients with treatment-responsive depression	Provides valuable evidence for disease burden
Huang (2020) Investigation of early and lifetime clinical features and comorbidities for the risk of developing treatment-resistant depression in a 13-year nationwide cohort study. *BMC Psychiatry*	To investigate the risk of treatment-resistant depression (TRD) in patients with depression by	Cohort study Level 3	31,422 depressive inpatients were followed up from the diagnostic onset for more than ten years		Seventy percent of patients with multiple psychiatric comorbidities developed TRD during follow-up	

First author, Year, Title, Journal	Purpose	Research Design[1] , Evidence Level[2] & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
	examining their clinical features, early prescription patterns, and early and lifetime comorbidities				Cox Regression Analysis	
Li (2019) All-cause mortality in patients with treatment-resistant depression: a cohort study in the US population. *Annals of General Psychiatry*	Assess all-cause mortality risk for patients with TRD	Cohort Study Level 3	355,942 patients with MDD, 34,176 (9.6%) met the criterion for TRD	TRD was associated with significantly higher mortality compared with non-TRD MDD (adjusted HR: 1.29; 95% CI 1.22–1.38; $p < 0.0001$)	Survival time was significantly shorter in the TRD cohort compared with the non-TRD MDD cohort ($p < 0.0001$) Proportional hazards model and Kaplan–Meier estimate	Large sample size
Pilon (2019) Burden of treatment-resistant depression in Medicare: A retrospective claims database analysis. *PLoS One*	Assess the disease burden of TRD	Cohort Study Level 3	Of 29,543 patients with MDD, 3,225 (10.9%) met the study definition of TRD; 157,611 were included in the non-MDD cohort		Among Medicare-insured patients, those with TRD had higher HRU and costs compared to those with non-TRD MDD and non-MDD	

First author, Year, Title, Journal	Purpose	Research Design[1] , Evidence Level[2] & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
Demyttenaere (2019) The Impact of (the Concept of) Treatment-Resistant Depression: An Opinion Review. *The International Journal of Neuropsychopharmacology*	Expert opinion and observation on the impact of TRD	Expert Opinion Level 7				Expert Opinion
Bergfeld (2018) Treatment resistant depression and suicidality. *Journal of Affective Disorders*	Investigate instances of suicidal behaviors and completed suicide in TRD	Systematic Review Level 1	30 studies included		The overall incidence of completed suicides was 0.47 per 100 patient-years (95% CI: 0.22–1.00), and of attempted suicides, 4.66 per 100 patient-years (95% CI: 3.53–6.23)	A large-scale review of RCTs focused specifically on suicidality data
Amos (2018) Direct and indirect cost burden and change of employment status in treatment-resistant depression. *The Journal of Clinical Psychiatry*	Assess the financial and social-economic impact of TRD	Cohort Study Level 3	6,411 patients in a US Claims database for private insurance		TRD, even compared to MDD, poses a significant direct and indirect cost burden to US employers and may be associated with higher rates of employment status change	

First author, Year, Title, Journal	Purpose	Research Design[1] , Evidence Level[2] & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
Psychedelic or Amnestic Medicine						
Gill (2021) The Effects of Ketamine on Cognition in Treatment-Resistant Depression: A Systematic Review and Priority Avenues for Future Research. *Neuroscience and Biobehavioral Reviews*	Evaluate the effects of ketamine on cognition in TRD	Systematic Review Level 1	Five articles met the inclusion criteria		While few procognitive effects are observed, all studies report no cognitive impairments following subanesthetic administration of ketamine	
Darji (2019) Comparative efficacy between ketamine, memantine, riluzole and d-cycloserine in patients diagnosed with drug resistant depression: a meta-analysis. *International Journal of Basic and Clinical Pharmacology*	Compare the efficacy of multiple augmentation agents for TRD	Systematic Review Level 1	14 RCTs ketamine (5), memantine (3), riluzole (2), and d-cycloserine (4) vs. placebo in drug-resistant depression		Ketamine showed the best efficacy, followed by memantine	Level 1 evidence supporting the effectiveness of ketamine against other agents and placebo
Daly (2019) Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant	To assess the efficacy of esketamine nasal spray plus an oral antidepressant	Double-blind RCT Level 2	705 adults with prospectively confirmed TRD were enrolled; 455 entered the optimization		For patients with TRD who experienced remission or response after esketamine	Large scale double-blinded study focused on the treatment of

First author, Year, Title, Journal	Purpose	Research Design[1] , Evidence Level[2] & Variables	Sample & Sampling, Setting	Measures & Reliability (if reported)	Results & Analysis Used	Limitations & Usefulness
depression. *JAMA Psychiatry*	compared with an oral antidepressant plus placebo nasal spray in delaying relapse of depressive symptoms in patients with TRD		phase and were treated with esketamine nasal spray Two hundred ninety-seven who achieved stable remission, or durable response, entered the randomized withdrawal phase.		treatment, the continuation of esketamine nasal spray and oral antidepressant treatment resulted in clinically significant superiority in delaying relapse compared with an antidepressant plus placebo.	TRD with Esketamine
Kim (2019) Esketamine for treatment-resistant depression - First FDA approved antidepressant n a new class. *The New England Journal of Medicine*	Discuss newly available treatments for TRD	RCT Level 2			Esketamine is FDA approved for the treatment of TRD in adults	

1. State the specific research design or state EBPG. 2 State the Hierarchy of Evidence per the Melnyk 7 level of evidence for an intervention inquiry.

Appendix D

In adults with depression, does documentation align with Clinical Practice Guidelines on diagnosing and treating resistant depression during six months at a community behavioral health clinic?

Evidence Grid

	CBT Blended Treatment	Differential Diagnosis	Antidepressant Monotherapy	Psychedelic or Amnestic Medication	TRD Disease Burden	Acute Management and CPGs
A retrospective examination of care pathways in individuals with treatment-resistant depression (Day, 2021)			X			X
All-cause mortality in patients with treatment-resistant depression: a cohort study in the US population (Li, 2019)					X	X
Augmentation strategies for treatment resistant major depression: A systematic review and network meta-analysis (Nuñez, 2022)						X
Augmentation therapies for treatment-resistant depression:			X			X

systematic review and meta-analysis (Strawbridge 2019)						
Benefits of Sequentially Adding Cognitive-Behavioral Therapy or Antidepressant Medication for Adults with Nonremitting Depression (Dunlop, 2019)	X					X
Burden of treatment-resistant depression in Medicare: A retrospective claims database analysis (Pilon, 2019)					X	X
Clinical implications of the STAR D trial (Rush, 2018)						X
Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts (APA, 2019)						X
Cognitive behavioral therapy for treatment-resistant depression: A systematic review	X					X

and meta-analysis (Li, 2018)						
Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis (Cipriani, 2018)			X			X
Comparative efficacy and tolerability of pharmacological and somatic interventions in adult patients with treatment-resistant depression: a systematic review and network meta-analysis (Papadimitropoulou, 2017)	X		X	X		X
Comparative efficacy between ketamine, memantine, riluzole and d-cycloserine in patients diagnosed				X		X

with drug resistant depression: a meta-analysis (Darji, 2019)						
Comparison of guidelines for the treatment of unipolar depression: a focus on pharmacotherapy and neurostimulation (Bayes, 2018)			X			X
Depression in the Primary Care Setting (Park, 2019)			X			X
Direct and indirect cost burden and change of employment status in treatment-resistant depression (Amos, 2018)					X	X
Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression (Daly, 2019)				X		X

Epidemiology of Treatment-Resistant Depression in the United States (Liu, 2021)						X
Esketamine for treatment-resistant depression – First FDA approved antidepressant n a new class (Kim, 2019)				X		X
Estimating Prevalence and Healthcare Utilization for Treatment-Resistant Depression in Japan: A Retrospective Claims Database Study (Mahlich, 2018)						X
Findings From World Mental Health Surveys of the Perceived Helpfulness of Treatment for Patients with Major Depressive Disorder (Harris, 2020)						X
Incremental Health Care Burden of Treatment-Resistant					X	X

Depression Among Commercial, Medicaid, and Medicare Payers (Shrestha, 2020)						
Investigation of early and lifetime clinical features and comorbidities for the risk of developing treatment-resistant depression in a 13-year nationwide cohort study (Huang, 2020)					X	X
Management of treatment-resistant depression in primary care: a mixed-methods study (Wiles, 2018)						X
Management of Treatment-Resistant Depression: Challenges and Strategies (Voineskos, 2020)						X
Pharmacological interventions for treatment-resistant depression in adults (Davies, 2018)			X	X		X

Psychopathological and sociodemographic features in treatment-resistant unipolar depression versus bipolar depression: a comparative study (Nuñez, 2018)		X				X
Psychotherapy for Major Depressive Disorder and Generalized Anxiety Disorder: A Health Technology Assessment (Ontario Health Tech, 2017)	X					X
Serotonin, psychedelics, and psychiatry (Carhart-Harris, 2018)			X			X
Systematic Review of Clinical Practice Guidelines for Failed Antidepressant Treatment Response in Major Depressive Disorder, Dysthymia, and Subthreshold Depression in Adults (MacQueen, 2017)			X			X

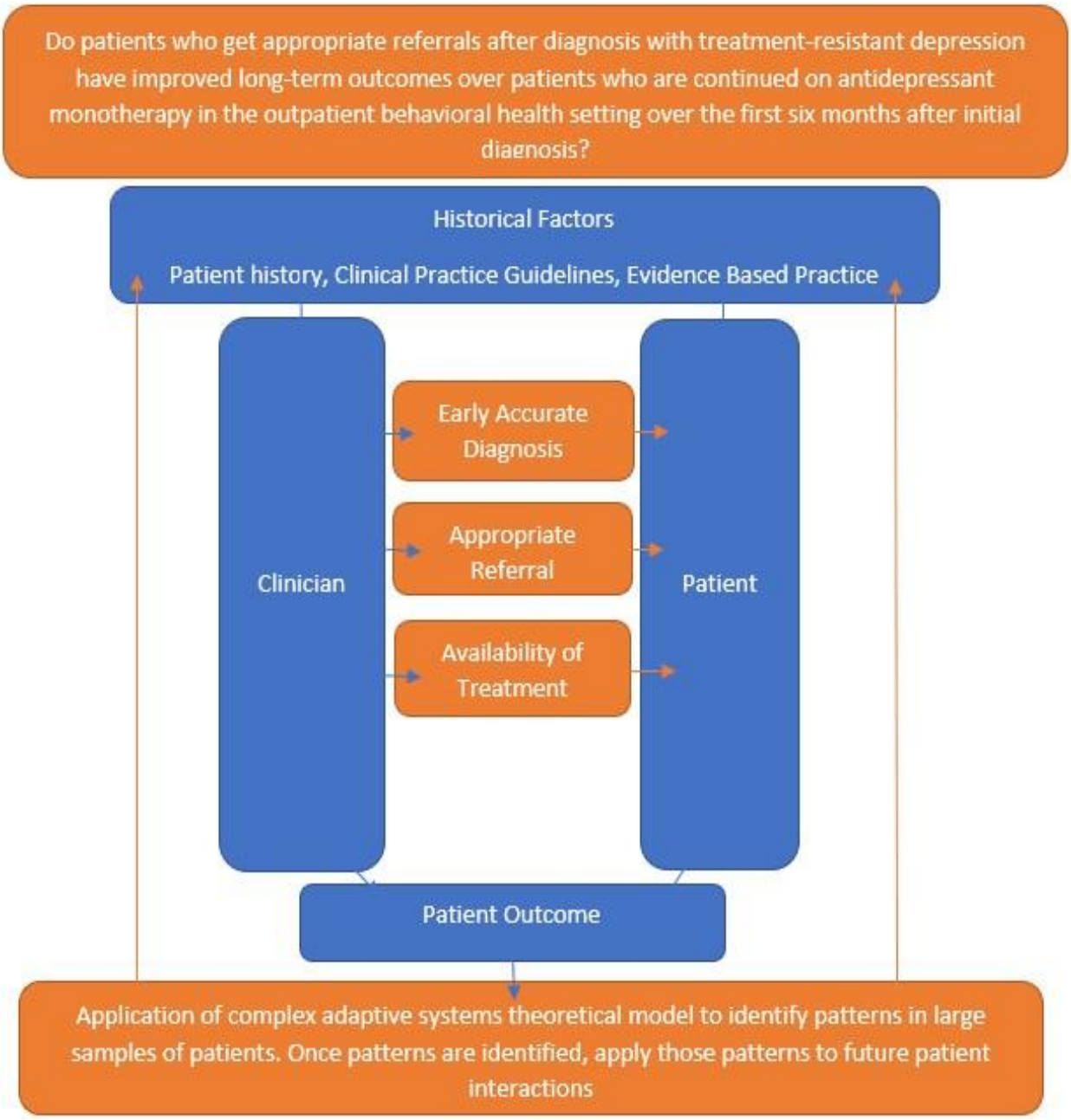
The Effects of Ketamine on Cognition in Treatment-Resistant Depression: A Systematic Review and Priority Avenues for Future Research (Gill, 2021)				X		X
The identification, assessment, and management of difficult-to-treat depression: An international consensus statement (McAllister-Williams, 2020)						X
The Impact of (the Concept of) Treatment-Resistant Depression: An Opinion Review (Demyttenaere, 2019)					X	X
Treatment effectiveness and tolerability outcomes that are most important to individuals with bipolar and unipolar						X

depression (Rosenblat, 2019)						
Treatment resistant depression and suicidality (Bergfeld, 2018)					X	X
Treatment resistant depression: A multi-scale, systems biology approach (Akil, 2018)						X
Treatment-Resistant Depression Revisited: A Glimmer of Hope (Halaris, 2021)						X
Treatment-Resistant Depression: Identification and Treatment Strategies (Limandri, 2018)		X				X
Treatment-resistant major depressive disorder: Canadian expert consensus on definition and assessment (Rybak, 2021)		X				X
Use of Antidepressants among Patients Diagnosed with Depression: A			X			X

Scoping Review (Marasine, 2021)						
Why Uptake of Blended Internet-Based Interventions for Depression Is Challenging: A Qualitative Study on Therapists' Perspectives (Mol, 2020)	X					X

Appendix E

Theory to Application



Appendix F

Cost Table

	Projected Cost	
Researcher	90 hours * $30 per hour	$2700
Clinician Honorarium for Participation	Eight clinicians * $20 gift cards	$160

Appendix G

Logical Flow of Outcomes to Analysis

	State Outcome or Demographics	Measurement	Tool Validity	Permission Needed	Statistical Analysis Test
Primary Outcome	Increased identification of TRD	Fewer patients from Cohort 2 with missed identification of TRD		NA	
Secondary Outcome	Increased clinician knowledge and confidence in treating TRD	Fewer patients from Cohort 2 with missed identification of TRD		NA	
Demographics		[redacted]			Descriptive for each group. Comparison statistics for two independent groups.

Appendix H

Logic Model

OVERARCHING GOAL:	Improve identification of TRD in the outpatient behavioral health clinic	LOGIC MODEL DATE:	05/11/2022

INPUTS →	OUTPUTS →		OUTCOMES	
Mobilized Resources	Activities and Interventions	Specific processes to measure	Short-term outcomes and measures	Long-term outcomes reflecting program objectives
• Outpatient behavioral health clinic staff • Clinical practice guidelines and recommendations for best practice related to TRD	• Chart review to identify patients who may meet criteria for TRD but may have not been accurately diagnosed • Clinician self-survey for knowledge of TRD • Educational offering to outpatient behavioral health clinicians to target areas of opportunity for learning	• Identification of TRD when evidence is present • Level of knowledge and awareness as relates to TRD	• More patients being identified as having TRD when presenting with evidence of more than two prior antidepressant monotherapy courses • Improved clinician awareness	• Improved patient outcomes related to TRD and depressive episodes

ASSUMPTIONS (root cause analyses, prior learning/experience)	EXTERNAL FACTORS (barriers/facilitators)
• There are patients who present for outpatient behavioral health treatment who meet criteria for TRD, but are not identified as meeting criteria for TRD	• Resistance to change • Poor history collection • Polypharmacy

REMEMBER: THIS IS JUST A SHAPSHOT OF YOUR CURRENT UNDERSTANDING OF HOW THINGS OUGHT TO WORK!
Adapted from University of Wisconsin Extension Program Development and Evaluation resources: http://www.uwex.edu/ces/pdande/evaluation/evallogicmodel.html

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Appendix I

Measurement Tools

Chart review: A measurement tool for chart review is a modified approach first described in the STAR*D clinical trial (Rush & Jain, 2018). This model is considered a basis for current clinical practice. The tool is meant to identify patients with documented evidence of at least two prior trials of adequate dose and duration. These patients were identified from a cohort already identified as currently prescribed antidepressant monotherapy.

Clinician survey: Measurement for the clinician survey will be self-reflection, scored from 1 to 10 points, and consist of not more than 15 items meant to evaluate the clinician's knowledge base for identifying and treating treatment-resistant depression.

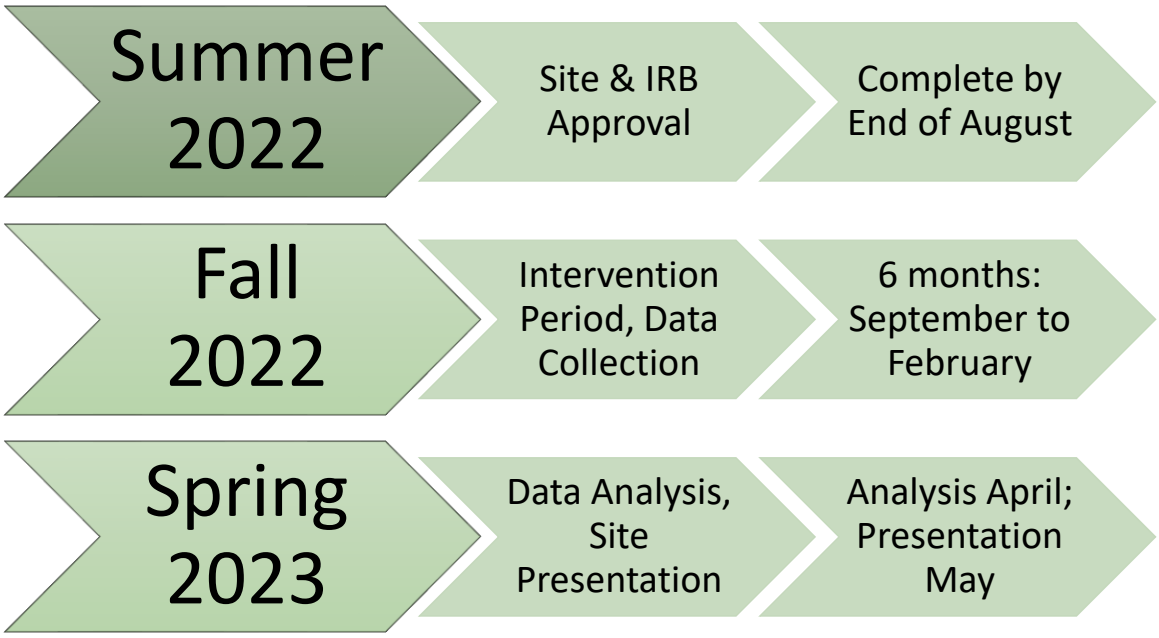
Appendix J

Permission for Tools

The tools used in this project proposal are not published or proprietary and will not require different permissions.

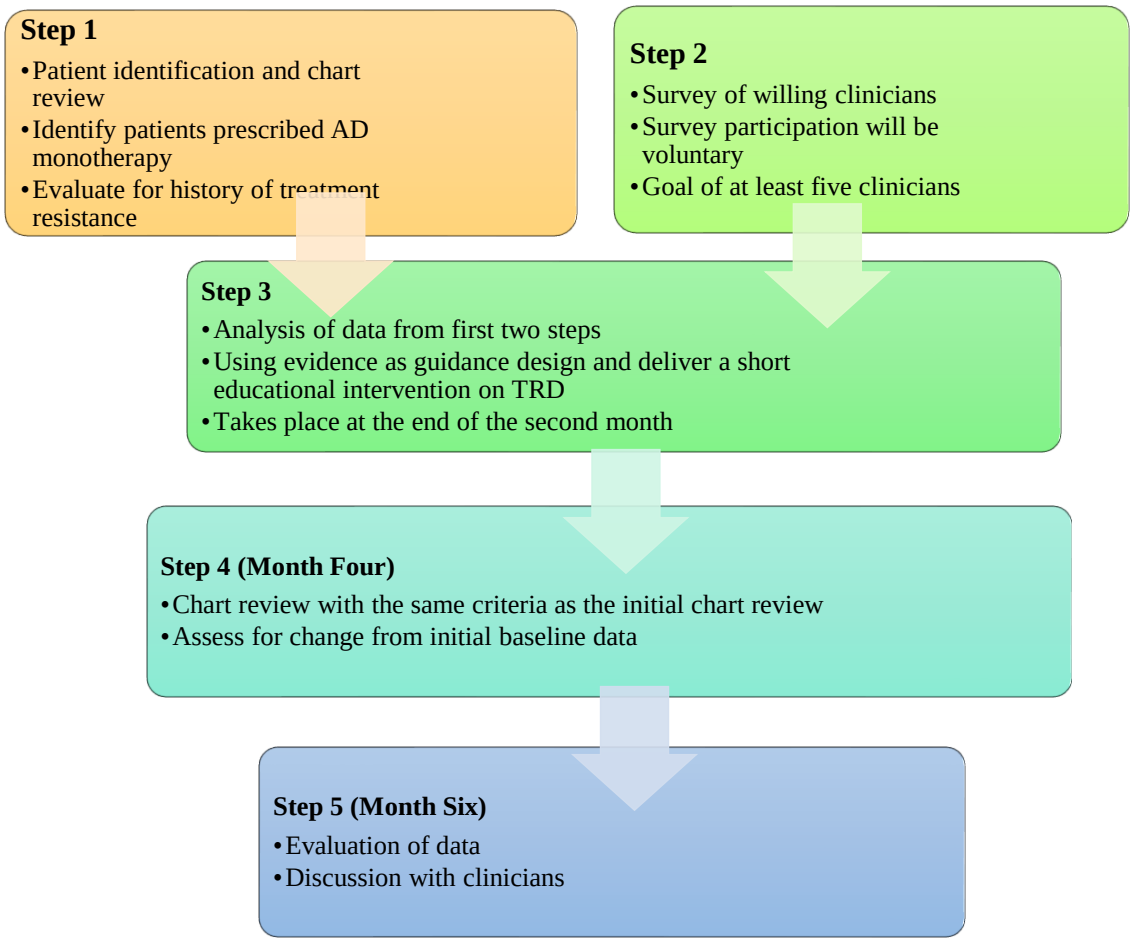
Appendix K

Project Timeline



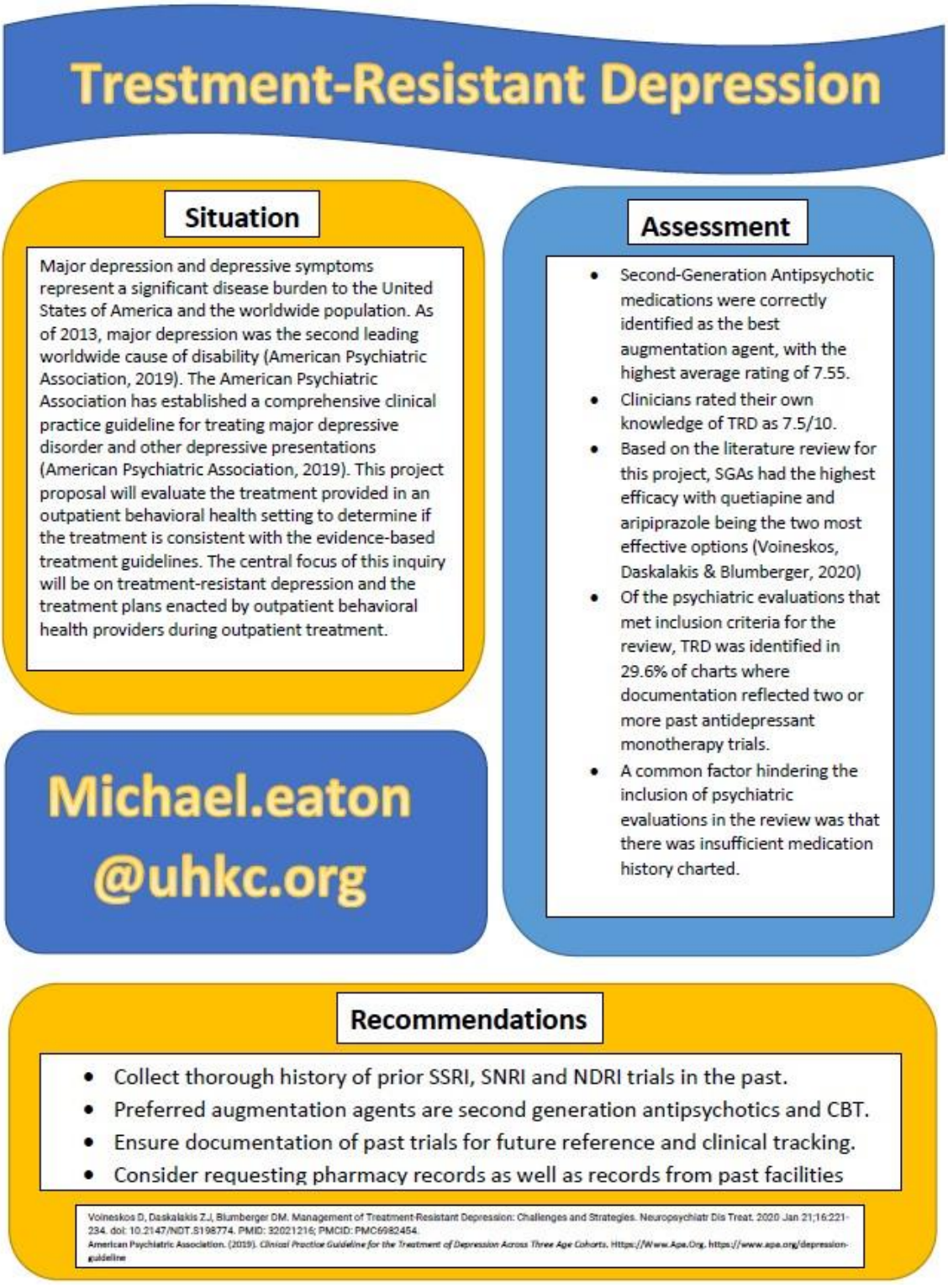
Appendix L

Intervention Flow Diagram



Appendix M

Intervention Materials



Appendix N

Data Collection Template

Total Number of Charts reviewed	Prescribed Antidepressant monotherapy	Evidence of Two Prior Courses of antidepressant monotherapy
Cohort One 2,347	549	163
Cohort Two 850	167	32

First Clinician Survey

Column1	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	Question 7	Question 8	Question 9	Question 10
Participant 1	8	3	7	2	2	9	0	1	5	7
Participant 2	8	8	3	2	2	6	0	2	8	9
Participant 3	7	10	10	7	3	8	1	0	5	9
Participant 4	9	9	9	4	8	10	0	0	9	10
Participant 5	7	10	9	3	6	10	1	0	7	10
Participant 6	7	9	8	6	2	10	3	3	9	10
Participant 7	9	5	10	4	3	10	1	1	9	10
Participant 8	7	8	8	5	5	8	1	4	9	10
Participant 9	6	5	8	3	6	10	2	0	7	10
SUM	7.555555556	7.444444444	8	4	4.111111111	9	1	1.222222222	7.555555556	9.444444444
MD/DO	8.2	6.8	7.4	3.6	3.4	9	0.8	1.4	8	9.2
APRN/PA	6.75	8.25	8.75	4.5	5	9	1.25	1	7	9.75

Appendix O

Statistical Analysis Table

Observed Frequencies

	Treatment-Resistant Depression	**No Treatment-Resistant Depression**	**Total**
Group 1	163	386	549
Group 2	32	135	167
Total	195	521	716

Expected frequency = (row total * column total) / grand total

Expected Frequencies

	Treatment-Resistant Depression	**No Treatment-Resistant Depression**	**Total**
Group 1	137.97	411.03	549
Group 2	57.03	109.97	167
Total	195	521	716

Chi-squared = ((163 - 137.97)^2 / 137.97) + ((386 - 411.03)^2 / 411.03) + ((32 - 57.03)^2 / 57.03) + ((135 - 109.97)^2 / 109.97)

Chi-squared = 18.65, One degree of freedom

P-value = < 0.001

Significance level = 0.05

Appendix P

UMKC eCompliance

IRB #2092289 KC

Human Subjects Research Determination Form (Including QI Projects) #380068

Submission date: **07/10/2022**
Submitted by: **Lindholm, Lyla Jo**

1. Human Subjects Research Determination

1. Project Investigators

Role	Investigator	Department	Consent personnel role	Primary contact
Principal Investigator	Lindholm, Lyla Jo	Nursing - General	Authorized to Obtain Consent	☑
Student Investigator	Eaton, Michael (UMKC-Student)	Nursing Practice - DNP	Participate in the Process	☑

2. Contact Information

Principal investigator

Lindholm, Lyla Jo

Job title PROF, AST CLINCL
Department Nursing - General
Division School of Nursing & Health St
Business unit University of MO-Kansas City

Primary contact

Lindholm, Lyla Jo

Job title PROF, AST CLINCL
Department Nursing - General
Division School of Nursing & Health St
Business unit University of MO-Kansas City

Eaton, Michael (UMKC-Student)

Job title Graduate
Department Nursing Practice - DNP
Division School of Nursing & Health St
Business unit University of Missouri

3. Project Title:

Treatment-Resistant Depression Diagnosis in the Outpatient Behavioral Health Setting

4. Describe the purpose of your project.

Note: If you are using an investigational invitro diagnostic device on biospecimens, you must complete the IRB application, even if the biospecimens are unidentified.

To review and evaluate the current practices for evaluating, diagnosing, and treating treatment-resistant depression in one outpatient behavioral health setting to improve practice, specifically accurate diagnosis and treatment. The evaluation will be through chart review and a clinician survey. This provides the baseline data in the PDSA quality improvement cycle and information for the development of an education module to improve care at the site.

5. What do you intend to do with the data collected?

Compile, analyze, and share the data internally to improve practice. Also, the findings will be used to develop an educational module with a post-education chart review and clinician survey, using the same tools as pre-education (baseline data). This comprises the evaluation cycle after intervention in the PDSA model.

Also, the quality improvement experience will be shared external to the site.

6. Quality Improvement Activities VS Human Subject Research Determination

A. Do you consider the activities you will perform to be Quality Improvement instead of human subject research?

If yes, you will be prompted with additional questions.

● Yes ○ No

B. The following questions are required to make a Quality Improvement determination.

i. Is this a student-led QI project?

● Yes ○ No

*Please be sure to add your advisor to section 1(1) of this form.

ii. Describe the quality improvement project in detail. Make sure to include specifics about what it is you are trying to improve.

Treatment-resistant depression can be difficult to identify in the outpatient behavioral health setting due to a lack of clear diagnostic guidelines, and this challenge exists at the current practice site and triggered a quality improvement initiative. The proposed evidence-based quality improvement project will examine current practices in the diagnosis of treatment-resistant depression in one outpatient behavioral health setting to improve the management of treatment-resistant depression. Data collection on current practices will be conducted through a chart review of patients prescribed antidepressant monotherapy and a direct survey of clinicians. Clinician participation in the survey will be voluntary and include any medication-prescribing clinician working in the outpatient behavioral health clinic.

Analysis of this data will be used to create an in-person brief, less than 1 hour, and in-person or online educational offering for clinicians regarding the diagnosis and management of treatment-resistant depression based on current evidence-based guidelines. A chart review and the clinician survey will be repeated at 6 months to determine if there is an improvement in the identification and management of treatment-resistant depression. Increased accuracy in the diagnosis of treatment-resistant depression fosters positive patient outcomes and overall quality of care.

Chart Review and Survey:
Chart review: The measurement tool for chart review is a modified approach first described in the STAR*D clinical trial (Rush & Jain, 2018). This model is considered a basis for current clinical practice. The tool is meant to identify patients with documented evidence of at least two prior trials of adequate dose and duration. These patients will be identified from a cohort of patients who

have already been identified as currently prescribed antidepressant monotherapy. The project leader will conduct the chart review.
Clinician survey: Measurement for the clinician survey will be self-reflection, scored from 1 to 10 points, and consist of not more than 15 items meant to evaluate the clinician's knowledge base for identifying and treating treatment-resistant depression. It will be administered either via paper or online and takes about 5 minutes to complete.

iii. Describe the location and/or population being evaluated by the quality improvement project.

If the activity you are proposing involves working with an entity in which you have a financial conflict of interest, please make sure you have disclosed this in your Outside Interest Disclosure Form with the COI office.

The location will be the outpatient behavioral health clinics at University Health. The population being evaluated is outpatient psychiatric providers who prescribe medication.

iv. Do you have permission to conduct this QI project in the location proposed?

● Yes ○ No

v. List the source of funding for the QI project.

Student funded

vi. **Read each statement and mark if the following is relevant to this project:**

☑ The purpose is to measure performance or determine the effect of a process change.

☑ Data are being gathered solely for administrative purposes within the context of normal efforts to examine or improve services, or operations.

☑ The individuals where the planned activity will take place could potentially benefit from the project.

☑ The data is intended to be used by and in the entity where the project is taking place.

☑ The project will involve a sample of the population ordinarily seen/present the institution where the project is taking place.

☑ The risks to individuals involved in the project is no greater than what is normally involved in their daily lives.

☐ The purpose of the project is a submission to a National or State registry/database that is mandated for improving the delivery of clinical care.

vii. **Please review the following items listed below. If you mark any of the following, your project will not be considered quality improvement, and an IRB application will be required.**

☐ The project is a clinical investigation as defined by the FDA, including randomization and/or placebo controls.

☐ The project is designed for the purpose of expanding knowledge base of a scientific discipline or scholarly field of study.

☐ The project is externally sponsored and is based on support of a research paradigm.

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Appendix Q

Barber, Cheri

To: Eaton, Michael (UMKC-Student)

Cc: Lindholm, Lyla J.; Pankau, Debra C.

Good afternoon Michael,

Congratulations ! The DNP faculty have approved your project proposal *Treatment-Resistant Depression Diagnosis in the Outpatient Behavioral Health Setting.* We look forward to the positive impact this project will have for on the behavioral health population.

Kind regards,
Dr. Cheri Barber

Cheri Barber, DNP, RN, PPCNP-BC, FAANP
Clinical Associate Professor
DNP Program Director
PNP Programs Coordinator
UMKC School of Nursing & Health Studies
HSB 5407
2464 Charlotte Street
Kansas City, MO 64108
816-235-6355 x1
NFLP Project Director
barberch@umkc.edu

"The meaning of life is to find your gift. The purpose of life is to give it away." -William Shakespeare

UMKC School of Nursing and Health Studies

Appendix R

Executive Summary

Evidence-based quality improvement project completed at an outpatient behavioral health clinic in a major metropolitan area. The project is focused on the identification and treatment of treatment-resistant depression (TRD) in the outpatient behavioral health population. Treatment-resistant depression has the potential to interfere with the lives of millions of Americans each year. Early and accurate treatment is essential in improving behavioral health outcomes for patients experiencing these symptoms.

The main research question is on documentation and how charted history aligns with treatment decisions. In adults with depression, does documentation align with Clinical Practice Guidelines on diagnosing and treating resistant depression during six months at a community behavioral health clinic? A focused chart review for psychiatric evaluations completed in the outpatient setting was completed, and the results were compiled for analysis. Clinicians were only aware of the quality improvement project after the baseline cohort of chart reviews was completed.

The methodology for the quality improvement project was a completed pre-post-intervention design where an educational offering focused on TRD was delivered to the clinicians at the outpatient clinic after the baseline cohort of chart reviews was completed. A second cohort of chart reviews over four months was completed once the educational offering was delivered. The charts were reviewed based on two phases of inclusion criteria. The first phase of inclusion was all patients who were prescribed antidepressant monotherapy for any depressive episode. The second phase of inclusion criteria examined the psychiatric evaluations for any documented depressive episode. The resulting analysis provided a metric for missed signs of TRD.

Findings indicated that patients in the baseline cohort had missed signs of TRD at a rate of 29.6%. Patients in the post-intervention cohort had missed signs of TRD at a rate of 19.2%. Using a chi-square analysis with one degree of freedom provided a p-value < 0.001. This was a statistically significant finding, and the data illustrates that a low-effort intervention can have a clinically significant and impactful outcome.

The application of this EBQI to the greater outpatient population at large would have a significant impact on the behavioral health outcomes for patients experiencing symptoms of TRD. The intervention is low-cost and does not require a significant amount of planning and teaching for successful execution. While most clinicians are aware of TRD and some of the evidence-based treatments, increased awareness focused on the topic can have a major impact on the early and accurate identification of TRD so that evidence-based interventions can be delivered.