



Depression and Bipolar
Support Alliance

Major Depressive Disorder

Designing Clinical Trials Which Support Patient-Focused Drug Development

Overview

For people living with major depressive disorder, the past 25 years have seen anemic progress in the development of meaningful new treatments and development has focused on incremental improvements to existing ways of treating the disease. People electing such treatment are frustrated by, and losing hope of a pharmacologic solution. Modest improvement in clinical outcomes is simply no longer enough.

As a nationally recognized and balanced voice for people with the lived experience of major depressive disorder, the Depression and Bipolar Support Alliance (DBSA) has built bridges among numerous diverse constituencies. As such, DBSA has served as a connector to stakeholders, including individuals with the lived experience, family members, clinicians, researchers, and the biopharmaceutical industry. It is from this perspective that DBSA is uniquely positioned to explore how to advance patient-focused drug development for this community.

DBSA believes that meaningful innovation in treatment will be aided by understanding, first and foremost, how those receiving treatment define success, rather than simply relying upon the assessments of clinicians and researchers. Further, DBSA believes that every person deserves the opportunity not just to survive, but to thrive. To do that, we need to ensure true wellness as the end goal for people living with major depressive disorder.

The mean goals for clinical success can no longer be defined by controlling this week's, this month's, or even this year's major depressive disorder episode, but by providing a pathway to a life well-lived as defined by the individual. Because this is not often the defined objective for clinicians or researchers, the potential exists for the patient's definition of success to be obscured in the drug-development process. A holistic approach is necessary to support wellness.

In addition to lacking a focus on total wellness, the accepted measures for evaluating the safety and efficacy of new medicines can be obscured by complications that are unique to clinical trials in depression. Issues such as placebo response and a lack of objective and quantifiable measurement tools necessitate additional acceptable measures to get a full picture of a medicine's potential risks and benefits for people with lived experience.

The goal of this paper is to explore some of the opportunities that exist in today's regulatory environment, and to provide recommendations that can enhance patient-focused drug development for the treatment of major depressive disorder.

Shift towards whole health

The idea of wellness cannot be embraced without considering the whole health of the individual, and, major depressive disorder can disproportionately negatively affect an individual's whole health. The comorbidities associated with depression are not insignificant. The prevalence of major depression among individuals living with heart disease is (15 to 23%), diabetes (11 to 12%), chronic obstructive pulmonary disease (10 to 20%), Parkinson's disease (40-50%), Huntington's disease (40%), multiple sclerosis (10-15%), and Alzheimer's (15-55%). Further, the effect depression has on the positive outcomes of comorbid conditions is well known.



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Depression decreases adherence to clinical regimens, is associated with less healthy lifestyles around diet, exercise and smoking, and is associated with higher mortality.

Unfortunately the delivery of health care is often not designed to treat the whole health of the individual. The medical community struggles with the definition of whole health integration and still protects treatment silos. Added to this puzzle are pharmacologic interventions. Even more challenging than understanding the whole health ramifications of pharmacologic interventions associated with comorbidity is the realization that no one medication typically provides the entire range of symptom relief for major depressive disorder and these interventions have differing risk/benefit tolerances for each individual.

Individuals on the other hand think in terms of their overall health and in terms of how the different components of their health play out among the communities they are participating in—where they live, work, play, and pray.

The table below illustrates some of the whole-health considerations patients evaluate when assessing the risks and benefits of one particular treatment over another for treating major depressive disorder.

Whole-Health Considerations
Patients want options to choose what is best for them.

Symptom Relief	depressed mood • feelings of guilt • work and activities • retardation/psychomotor • agitation • genital • hypochondriasis • loss of weight • insight • anxiety: somatic and psychic • somatic: general and gastrointestinal • suicide • insomnia: early/late/middle
Side-Effect Minimization	psychiatric • cardiovascular • endocrine • metabolic • nervous system • gastrointestinal • dermatologic • respiratory • musculoskeletal • immunologic
Well-Being Gains	autonomy • interest in activities • environmental mastery • personal growth • purpose in life • positive relations with others • self-acceptance • cheerful mood • calm and relaxed • wake-up rested

While symptom relief and side-effect management are already typically captured by the clinical trials, capturing data on well-being remains a gap.

Adding to the challenge for the prescriber treating major depressive disorder is the dilemma that just as each medication is different, so is each patient's clinical reaction. Further, the considerations around medication risks and benefits can often be different. The prescriber may approach the challenge from the clinical perspective—symptom relief—while the patient, on the other hand, may be seeking well-being outcomes.

Another factor that cannot be overlooked is that many patients living with major depressive disorder do not take medications as prescribed. This is especially true among individuals taking anti-depressants.¹



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Understanding some of the underlying causes for this abandonment of pharmacologic interventions is necessary.

One way to address this challenge is to encourage biopharmaceutical companies to continue to invest in new types of medical treatments with different mechanisms, effects and side effect profiles. Given the difficulty already discussed in thoroughly and objectively assessing new treatments and bringing them to patients, research in the disease has stalled. Patients deserve more options to address their unique and complex needs.

What's important to patients?

With any pharmacologic intervention the effects and side effects of a particular treatment differ for different individuals. Existing therapies are often slow to demonstrate efficacy. When seeking a pharmacologic intervention, patients need to weigh the risks and benefits of that intervention against symptom relief. Added to this challenge is the fact that an intervention may not be consistent in both its symptom relief and side-effects among the patient population. This often results in a frustrating trial-and-error period for both the prescriber, who wants to help his patient, and the patient, who is looking for improvement. Unfortunately, during this trial-and-error period many patients reach a point where they abandon hope in a pharmacologic intervention or any type of treatment.

Further, while today's clinical and drug development environment remains focused on symptom relief, patients have reported this is not what is most important to them. In the paper *Defining a Clinically Meaningful Effect for the Design and Interpretation of Randomized Clinical Trials*, the authors share some valuable insights about what is meaningful to patients. Patients understand why scales such as the Hamilton Depression Rating Scale, Young Mania Rating Scale (YMRS), and Brief Psychiatric Rating Scale (BPRS) are used in clinical trials, but—of those participating in focus groups—none of them thought these scales were useful to them as individuals.²

The paper reports that patients are seeking interventions that help them function in life rather than alleviate their symptoms. Examples include:

- relief from bad decision-making
- ability to work and earn an income
- getting better sleep³

Another common complaint among patients is the lack of information from their prescriber about treatment options. Patients share that they are not given enough time to ask questions about treatment, and that they are dissatisfied with the amount of information they receive about treatment options.⁴

Given the wide variety of medications, the different side-effects associated with them, and the fact that symptom relief is not the greatest benefit, a patient is seeking, it is not surprising that patients don't often take the medication as prescribed.

Advancing patient-centered outcomes

Patients and families want safe, meaningful, and affordable treatment outcomes. Exploring a path forward requires understanding the role the different stakeholders play in the ecosystem.



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The Food and Drug Administration’s (FDA) stated mission is to “assure the safety efficacy and security of human...drugs.” In addition, the “FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable.”

The biopharmaceutical industry is tasked with research, development, and bringing to market new pharmacologic interventions. Public and private insurers determine which interventions to include in their plans and the subscriber cost-sharing algorithm.

Next generation scales

Adapting clinical trial measurement tools to include wellness outcomes as defined by people with major depressive disorder has the potential to greatly improve treatment. Significant strides forward have been made through the work of the PRO Consortium’s Depression Working Group.

In a paper published in 2015, the group shared their research around a new major depressive disorder scale to measure treatment effectiveness relating to symptoms. The work of the consortium was supported by the FDA and adhered to FDA PRO Guidance and best practices. The Symptoms of Major Depressive Disorder Scale (SMDDDS) measures symptom improvement along a thirty-five item scale, and provides more depth than current scales. The table below provides a sampling of the new SMDDDS measurements.⁵

New SMDDDS	More Depth
negative mood	anger, frustration, crying
negative affect	feeling lonely
sleep disturbance	oversleeping
cognition	intrusive thoughts, intensive thoughts, difficulty remembering
anxiety	feeling overwhelmed
low motivation	not wanting to get out of bed, lack of drive
eating	overeating

DBSA applauds and recognizes the effort of the consortium and the FDA in developing the SMDDDS, and is encouraged by the release of the research as a significant step forward. One area of major note is a movement toward patient-reported outcomes. This is a major shift from the current scales that are entirely clinician-reported. However, the scale’s emphasis is still symptom improvement based.

Including endpoints that matter to patients

A next logical step is the inclusion of measureable well-being outcomes that are sensitive, patient-centric, and captured in real-time. It should be noted that the SMDDDS does include patient-reported outcomes, but, with a seven-day reporting cycle, the scale is reliant on recall. This methodology opens the possibility that the participant’s mood has changed between the time of the event and the reporting—creating the potential for inaccurate data capture. It is understandable that in the time-frame of an existing clinical study these longer-term outcomes may be difficult to effectively capture, but manufacturers should be encouraged to continue



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real-world outcomes studies to better understand these potential benefits and to publish results so that physicians have the information they need to ensure a productive dialogue with patients.

Several scales such as the Ryff Scale of Psychological Well-Being, the Sheehan Disability Scale, and the WHO- 5 Well-Being Index measure well-being domains. The focus of these scales is improvement in environmental autonomy from an interpersonal relationship and work/school perspective. Because these scales do not focus on the reduction of a given symptom, their use of global questions more accurately reflects each individual's unique experience living with major depressive disorder, and whether or not the treatment is bringing improvement to their lives. Manufacturers should consider these scales as additional measures in long-term studies.

Technology exists today to capture well-being in real time. Many wellness trackers including one provided by DBSA (which includes WHO-5 Well-Being Index domains) enable real-time collection and documentation of an individual's mood and sense of well-being.

Below are two different examples of a shift from clinician-reported symptom reduction domains to global, patient-reported, well-being domains.

Symptom-based clinician reported

Feelings of Guilt (Scale 1-4)

- Absent
- Self-reproach
- Ideas of guilt or rumination over past
- Present illness is punishment
- Hears accusatory voices

Well-being patient-reported

Well-Being PRO (Scale 1-6)

When I look at the story of my life, I am pleased with how things have turned out

Global symptom-based question

Since starting the trial, I have experienced anxiety.

Global well-being based question

Since starting the trial, I feel more in charge of my life.

Recommendations

As was noted previously, patients feel that they do not have enough information about treatment options and outcomes with their clinicians. This is unfortunate, since it is known that shared decision-making between clinicians and patients improves outcomes that often result from a desire to engage with clinicians and take medications as prescribed.⁶ But what happens when patient/clinician engagement is present, and patient-identified outcomes are noted, but the doctor lacks sufficient information to explore all of the treatment options with the patient? DBSA encourages FDA to consider the following:



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- Cross-sector partnership to develop a global question unique to individuals with major depressive disorder that FDA requires all manufacturers to include in New Drug Applications that more effectively measures patient perspectives (e.g. Patient Global Impression Scale, or PGIC). This would allow for collection of patients' perspective on how they are doing with their disease while on a certain medicine. Inclusion of the data in the product labels would provide an opportunity for physicians to have more comprehensive conversations with their patients tied to their personal treatment goals.
- FDA should also work to adapt the acceptable terminology that can be used to discuss the risks and benefits of new medications. Information that directly aligns with outcomes in a clinical trial (such as anhedonia) isn't understandable to patients and it hampers their ability to be an active participant in decision-making about their care.

While patient reported outcomes data are often included in clinical trials as secondary endpoints, elevating these PROs, requiring more of these endpoints to be included, and greater consideration by FDA of these endpoints in their evaluation process may lead to more understanding of the risks and benefits of new medicines in a disease where outcomes are often difficult to measure reliably.

Implementing 21st Century Cures

When President Obama signed the 21st Century Cures Act in December, 2016, new impetus was provided to patient-focused drug development. For example, within six months of approval of a 505(b) application, the FDA is required to issue a statement articulating how patient-experience data was used during the review and approval process. The agency is also required to provide guidance on the process of obtaining and using that data with regards to identifying what is most important to patients in these areas: "burden of disease, burden of treatment, and benefits and risks in the management of the patients' disease."

Implementing these policies will further strengthen the need for strong industry and patient advocacy organizations' partnerships. Deepening these relationships can be a win-win for both groups. Industry can demonstrate their commitment to developing medications that meet the desired outcomes of the patient community, and patients are empowered to have a voice in the development of new treatments—ensuring that these medications are actually going to meet their needs.

Convening the stakeholders

DBSA has demonstrated leadership in both strengthening relationships with industry and in engaging with the FDA. In December, 2014, DBSA submitted comment to *Docket Number [FDA-2014-N-1698]—Food and Drug Administration Activities for Patient Participation in Medical Product Discussion*. This comment was related to the inclusion of depression in the FDA's list of conditions to be studied for best practices concerning patient engagement as part of the FDA Safety and Innovation Act (FDASIA) section 1137. This activity was followed by meetings with various stakeholders within the FDA (2015) and testimony (2016) at two different FDA hearings on topics relating to depression.

DBSA's engagement strategy was further deepened in Q4/2016 with a series of meetings with two groups: Professional Affairs and Stakeholder Engagement and the Division of Psychiatry Products. As a result of this positive engagement, the FDA has encouraged DBSA to move forward with an externally-led scientific workshop in 2017. The FDA recognizes that, as a convener, DBSA is in a position to bring together the patient, family, clinician, researcher, payer and industry communities to



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examine how to include patient-defined and -reported well-being domains as measureable endpoints to be included in clinical trials.

In tandem, the FDA has encouraged DBSA to submit an LOI for an externally-led, patient-focused drug development meeting. It is intended that output from the scientific meeting can be tested by DBSA within their community. What is learned from this scientific workshop and the DBSA constituency surveys will serve as the foundation for an externally-led, patient-focused drug development meeting to be held in in 2018.

DBSA is proud of the work to-date in engaging both industry and the FDA to hear and include the voice of those living with major depressive disorder in the development and approval of new pharmacologic treatments. Through continued engagement and collaboration, DBSA believes that great strides towards truly patient-centric treatment innovation can be achieved.

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