

The Case for the Patient-Centric Development of Novel Digital Sleep Assessment Tools in Major Depressive Disorder

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Keywords

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Abstract

Background: Depression imposes a major burden on public health as the leading cause of disability worldwide. Sleep disturbance is a core symptom of depression that affects the vast majority of patients. Nonetheless, it is frequently not resolved by depression treatment and may even be worsened through some pharmaceutical interventions. Disturbed sleep negatively impact patients' quality of life, and persistent sleep disturbance increases the risk of recurrence, relapse, and even suicide. However, the development of novel treatments that might improve sleep problems is hindered by the lack of reliable low-burden objective measures that can adequately assess disturbed sleep in this population. **Summary:** Developing improved digital measurement tools that are fit for use in clinical trials for major depressive disorder could promote the inclusion of sleep as a focus for treatment, clinical drug development, and research. This perspective piece explores the path toward the development of novel digital measures, reviews the existing evidence on the meaningfulness of sleep in depression, and summarizes existing methods of sleep assessments, including the use of digital health technologies. **Key**

Messages: Our objective was to make a clear call to action and path forward for the qualification of new digital outcome measures which would enable assessment of sleep disturbance as an aspect of health that truly matters to patients, promoting sleep as an important outcome for clinical development, and ultimately ensure that disturbed sleep will not remain the forgotten symptom of depression.

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Introduction

As the most common mental illness worldwide, depression poses a major public health burden [1]. With estimated 320 to 350 million cases globally, depression is the leading cause of disability due to high lifetime prevalence of up to 20% and often chronic development [2–5]. Up to 85% of individuals who experience a single depressive episode will suffer a recurrent episode within their lifetime [6]. Lifetime prevalence of a suicide attempt in patients with a diagnosis of major depressive disorder (MDD) is 13% [4], and 50–66% of individuals who commit suicide suffered from MDD [7, 8]. The recent COVID-19 pandemic has further exacerbated the rise of MDD, with estimations pointing to 53.2 million additional cases of MDD in 2020 [9]. MDD as diagnosed by

the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, (DSM-5) presents as a cluster of five or more symptoms with a duration of at least 2 weeks, including either depressed mood or loss of interest or pleasure in almost all activities. Additional symptoms such as sleep disturbance, fatigue, or loss of energy are necessary to warrant a diagnosis and as such are part of diagnostic criteria [2].

While sleep disturbance is an important core symptom of depression that negatively impacts patients' quality of life, it is often not adequately treated. The development of interventions that improve sleep symptoms in depression is held back by how challenging it can be to adequately assess sleep symptoms. Subjective and objective sleep measures are not always well aligned, with subjective sleep assessment through sleep logs showing significant differences when compared to polysomnography (PSG) [10]. The development of reliable digital measurement tools could allow for more accurate and easier sleep assessment in clinical trials, ultimately aiding in the inclusion of sleep as an important focal point in public health research, clinical drug development, and treatment of MDD. Improving the availability of low-burden, ecologically valid, and clinically accepted measures of sleep is essential to the broad adoption and recognition of sleep as a meaningful parameter of health in MDD.

The focus of this article was to (1) examine evidence supporting sleep disturbance as a meaningful aspect of health for patients living with MDD, (2) describe existing methods for assessing sleep disturbance in MDD, and (3) finally examine available digital measurement tools as new ways to better understand sleep in MDD. Measurement of sleep disturbance via digital measurement tools is relatively mature compared to other measurement domains, yet their use and impact in mental health clinical trials is limited because they cannot currently be used to support regulatory decision-making. We aimed to address this gap by creating a clear call to action and a path forward for validation and qualification of novel digital sleep assessment tools in MDD.

The Challenge: Sleep as the Forgotten Symptom of Depression

Sleep Disturbance as an Important Symptom of Depression

In total, 92% of patients suffering from a major depressive episode report symptoms of sleep disturbance, with 85.2% experiencing insomnia and 47.5% suffering from hypersomnia [11]. Insomnia symptoms present in

MDD often include difficulty initiating sleep, maintaining sleep during the night with long periods of awakenings, or waking up in the early hours without being able to go back to sleep. Hypersomnia, i.e., extended sleep periods during the night or increased daytime sleeping, is less common but often occurs in younger patients [2, 12] and women [11].

Like patients with a primary diagnosis of insomnia, patients with MDD often experience changes in sleep architecture, including disturbances in REM sleep and sleep continuity [13]. Patients with MDD have been found to have a shorter total duration of sleep, longer sleep latency, longer wake after sleep onset, higher frequency of awakenings during the night, and lower sleep efficiency than healthy controls [14]. The severity of sleep symptoms is associated with overall symptom severity; patients with severe MDD exhibit shorter total sleep time, reduced nighttime sleep, and lower sleep efficiency than patients diagnosed with mild to moderate MDD [14].

A bidirectional relationship between sleep disturbances and depression has been theorized, with evidence pointing to insomnia increasing the risk of later development of depression and treatments targeting sleep disturbance often leading to a reduction in depression symptoms [13]. The presence of sleep problems during childhood predicts the later development of depressive symptoms [15].

Sleep Matters to Patients

Qualitative evidence shows that sleep matters to patients with MDD. A cross-cultural systematic review of qualitative studies on depression found that sleep problems appeared among the top three most frequently mentioned distressing symptoms in Western and non-Western countries [16]. Sleep was found to be the second most common feature, only behind depressed mood in non-Western populations [16]. One reason for this is that disturbed sleep has a strong negative impact on quality of life and even poses a risk factor for suicide [12]. This was elaborated on in a qualitative study, with patients describing a close relationship between sleep problems and suicidal ideations or suicide attempts, pointing to the negative effects that disturbed sleep had on their everyday lives [17]. Sleep problems are often exacerbated through MDD treatment as disturbed sleep is a commonly reported pharmaceutical-treatment-emergent adverse effect [18]. For example, in a qualitative study with MDD patients treated with atypical antipsychotics, excessive sleep and low energy were among the side effects most often considered highly burdensome by patients. However, clinicians interviewed for the same study pointed to

other treatment emergent adverse effects such as weight gain but did not include sleep symptoms [19].

This finding is an example of how patients and clinicians may differ in what they consider important symptoms [20, 21] as they tend to hold differing assessments of what being cured from depression actually means. While clinicians put their focus on the reduction of depressive symptomology and an improvement in functioning, patients are much more concerned with a return of positive affect [22, 23]. Patients are often interested in learning to manage depression, whereas clinicians focus more on symptom reduction [24]. This becomes evident when discussing factors that help in management of depression as patients mostly focus on categories within their own control, such as sleep, diet, meditation, and physical activity [25]. In line with this finding, individuals with MDD highlighted the importance of effectively managing insomnia in depression during an externally led patient-focused medical product development meeting [26]. When asked about their experience, patients with MDD identified fatigue as a very disruptive symptom, notably experiencing no relief from it and expressing dissatisfaction with their treatment [27]. Further research should thus aim to include the patient voice as direct input from patients on the meaningfulness of the symptoms experienced in depression can allow to better tailor the basis for clinical decision-making in trial and care settings to focus on treatment success from the patient perspective.

Sleep Is Not Adequately Addressed by All Treatments

In clinical practice, treatment of both depression and sleep disturbance in concert remains challenging as antidepressants have vastly differing effects on sleep [12, 16–18]. While tricyclic antidepressants and other antidepressants such as trazodone or mirtazapine can have a sedative effect, MAOs, serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors are known to induce insomnia [18]. This leads to sleep disturbances being a common refractory symptom, often remaining even after successful pharmacological treatment for the mood symptoms of MDD [18]. Thus, despite sleep disturbance being a diagnostic symptom of MDD, it is frequently not resolved by depression treatment, which is particularly worrisome as persistent sleep problems in patients increase the risk of relapse and recurrence [12]. These findings point to the necessity of including patients directly into research on their care as they are best suited to speak for themselves when it comes to aspects of health that are most meaningful to them.

The Status Quo: Standard Sleep Assessment Tools

Sleep symptoms can, and are, assessed in MDD clinical research. However, these tools demonstrate several limitations, either not adequately assessing sleep symptoms or assessing symptoms in a non-performant way or placing a high degree of burden on participants, sites, and sponsors. In this and the following sections, we will outline these current tools, their limitations, and the consequences for clinical research in MDD.

With depression being a multifaceted disorder, a meta-epidemiological study of randomized control trials in MDD found a diverse set of 88 different patient-reported outcome (PRO) measures used in a sample of 49 studies. The most commonly used PROs were found to be the Patient Health Questionnaire-9, the Beck Depression Inventory I and II, and the Inventory of Depressive Symptomatology – Self Report [28]. All of these questionnaires include at least one question on sleep, with the Inventory of Depressive Symptomatology – Self Report including items on onset insomnia, middle insomnia, morning insomnia, and hypersomnia [29]. In addition to PROs, clinician-reported outcomes play an important role in both mental health care and research. The Hamilton Depression Rating Scale [30] is the most commonly used clinician reported scale. It is reliable [31] and captures sleep latency, middle insomnia, and terminal insomnia; however, atypical symptoms such as hypersomnia are not addressed. When focusing on sleep symptoms, studies will often include specific sleep scales, such as the Pittsburgh Sleep Quality Index, the Insomnia Severity Index, or the Insomnia Symptom Questionnaire.

While these subjective measures are commonly used in clinical development, with 32% of clinical trials in MDD using PROs as primary endpoints and 67% employing a PRO as a secondary endpoint [28], the gold-standard of sleep assessment is still considered to be PSG undertaken in a sleep laboratory [32]. However, PSG assessment in a sleep laboratory requires expert sleep technicians and administrative support, patients to travel to and spend the night in a sleep center, invasive testing procedures, and is expensive, thus posing a high burden on patients, clinicians, and researchers. This creates a barrier to access of proper assessment and leads to corresponding health disparities in both clinical studies as well as in access to health care. For example, individuals who are receiving inpatient care, immobile, and low resourced often experience disproportionate challenges and are less likely to participate in PSG assessment [33]. These limitations also place a barrier to long-term assessment of sleep, making it difficult to objectively measure sleep changes over the long term and in ecologically valid settings [34].

Comparisons between objective and subjective measures of sleep show mixed results. Severity of the sleep disturbance may influence the reliability of subjective sleep reports, with patients suffering from more severe symptoms having more trouble correctly estimating their sleep [35]. Subjective measures of sleep have been shown to differ significantly when compared to PSG-collected sleep parameters in a sample of patients with a major depressive episode and insomnia. Actigraphy measures on the other hand showed overall good correlations with PSG-derived measures of sleep [10]. However, validation of the algorithms used to derive actigraphy-based sleep measures requires studies to have been carried out specifically in an MDD population, such that we can ensure that accuracy, precision, and sensitivity to change are sufficient to support clinical development, especially when used to collect data in real-world settings. These findings put into question the reliability of subjective reports as accurate outcome measures [36–39]. Collectively, existing evidence suggest there is an opportunity to improve how sleep is assessed in patients with MDD. More accurate and accessible measures will support more reliable, equitable, and impactful research and care.

The Opportunity: Digital Health Technologies

Digital Sleep Assessment and Depressive Symptoms

The assessment of sleep disturbances through varying digital tools can predict depression symptoms. For example, sleep disturbance and variability in daily activity patterns and circadian rhythm as measured by passive audio collections have been found to be linked with depressive symptoms [40]. When using a machine learning model on actigraphy and light exposure data, reduced sleep efficiency and low levels of physical activity were found to be important features predicting depression in a sample of elderly adults [41]. These findings are of particular importance as geriatric individuals living alone are at high risk of remaining underdiagnosed for depression, and digital measures may contribute in closing this gap in diagnosis, though it must be noted (as the authors themselves point out) that these results are based on a relatively small study, and further work is required to assess generalizability in a wider population. Notably, sleep irregularity as measured through digital tools shows a close link to depression symptoms. In an assessment of passive and active digital data collected in a student sample during the COVID-19 pandemic, actigraphy-based measurement of sleep variance was closely associated with clinical measures of depressive

symptoms [42]. A similar link between sleep regularity and mood appeared in a study conducted in patients with mood disorders. Patients with highly unstable mood showed more irregularity in their wake-sleep patterns; sleep onset and offset patterns appeared to be disrupted [43].

Even severity of depressive symptoms can be predicted through digital assessments. By combining data collected through consumer-grade wearables with patient-reported health data, the Prediction of Severity Change-Depression (PSYCHE-D) model was able to predict increase in depression severity with good sensitivity and specificity. Sleep features as measured through the wearable device were among the most helpful objective predictors of change in depression severity [44]. In a study conducted in three European countries using consumer grade wearable data to assess the association of objectively measured sleep and depressive symptoms, 14 sleep features were identified that were linked to severity of depressive symptomatology [45]. These findings point to the value of continuous digital sleep assessment data collection in the detection and prediction of a worsening of depressive symptoms, with disturbed sleep features being closely linked to later increase in symptomatology.

Digital Sleep Assessment in Clinical Development

As of today, sleep assessment through actigraphy has been used as an outcome measure in an array of clinical trials examining sleep disturbance in depression. A common approach is the investigation of the effect of targeted sleep treatment in patients suffering from a primary diagnosis of MDD. One such example is the use of sleep actigraphy as a primary outcome in a study investigating the effect of the co-administration of ramelteon with an antidepressant in a sample of patients with a diagnosis of MDD and sleep-onset insomnia [46]. Another notable clinical trial explored the effect of targeted pharmaceutical treatment for insomnia on suicidal ideations in patients with MDD. Actigraphy was used as an additional secondary outcome to patient-reported sleep indices, and a reduction in suicidal ideations was correlated with an improvement of insomnia symptoms. Delayed sleep time and low levels of activity as assessed with actigraphy were linked to higher levels of suicidality [47, 48].

Sleep actigraphy assessments have also been found useful in trials targeting sleep through non-pharmaceutical treatments. Actigraphy assessment of sleep was used as a secondary outcome exploring the use of acupuncture as a treatment for insomnia in patients with a diagnosis of MDD. The participants in this study

reported residual insomnia despite stable treatment with antidepressants [49]. Interventions aimed at perinatal depressive symptoms are often based on non-pharmaceutical interventions and can profit from a close look at the link between sleep disturbance and depressive symptomology in pregnancy. One example is the use of sleep actigraphy as a secondary outcome measure for an intervention based on mindfulness therapy in pregnancy. As high levels of psychological distress are associated with poorer maternal and child health and the development of postnatal mood disorders, early assessment and intervention are particularly important in this group [50, 51]. A similar approach was taken for the LIFE-ON project, which is both an observational and interventional study of sleep disturbance as a prospective factor for the development of perinatal depression, employing sleep actigraphy assessment [52]. Another important value of passive digital assessment tools lies in the option to accurately measure symptoms in populations that might not be able to give accurate subjective reports, for instance, in a study with depressed nursing home patients. The effect of pain treatment on sleep was measured with ongoing actigraphy, showing that sleep onset latency, sleep efficiency, and early morning awakenings were reduced through pain treatment. Accurate subjective reporting of these sleep parameters would have been difficult to assess with self-reports due to the patients suffering from dementia in addition to depression, thus underlining the importance of objective measures in vulnerable populations that might not be able to speak for themselves [53]. As wrist-worn actigraphy sleep assessment allows for a low-burden continuous data collection, it is also well suited in prospective studies. One such study is the MEDACIS multicenter clinical trial, which explored the link between depressive symptoms, anxiety, and sleep/wake disturbances after acute coronary syndrome [54].

One important point to note is that, for both subjective and objective assessment, strong placebo effects are often seen in clinical sleep research [55] and that mental health symptoms can further exacerbate the impact of the Hawthorne effect [56]. Further research is required to investigate whether low-burden, passive digital assessment, in a participant's home environment, can reduce these effects.

Equally, MDD and depression are known to present with many other comorbidities [57], which in turn are themselves associated with disrupted sleep, for example, hypertensive disorders [58]. Improved sleep assessment tools will hopefully help us understand this complex web and establish sleep outcomes as important tools in clinical research for MDD and its comorbid conditions.

The development of novel digital sleep assessments tools is promising as they have been used successfully in both depression prediction as well as in clinical development studies in recent years. It is particularly encouraging that patients with depression show high acceptance and compliance in long-term digital data collection, allowing for longitudinal studies with high retention [59]. As digital assessments allow for continuous passive collection of objective data, they are valuable tools for prospective studies, they allow to include data from underserved populations, and can serve as complementary tools bolstering the accuracy of subjective measures.

Conclusion: The Opportunities for Digital Health Technologies in MDD

Depression as the most common mental illness and leading cause for disability worldwide poses a major public health burden, and development of proper treatment options is vital and pressing [1]. This need has even been exacerbated by the recent COVID-19 pandemic, which while leading to an increase in depression cases, has also substantially hindered treatment. However, when it comes to developing interventions for MDD, it is important to reflect on what we as researchers call successful treatment. Common clinical trial endpoints like remission and response may not completely reflect what matters to patients in clinical care. This can lead to refractory sleep disturbance symptoms remaining even after successful treatment, and the effects of antidepressants on sleep can sometimes even be counterproductive. This is despite MDD patients cross-culturally experiencing sleep disturbance as having a high impact on their quality of life. As sleep disturbances are connected to later recurrence and even suicidal ideations, proper treatment appears even more pressing. There is thus a real need for clinical trials to incorporate meaningful measures of functioning and quality of life that are important to patients. Given the importance of sleep in the diagnosis of MDD, meaningfulness to patients, and relevance to long-term treatment effect, measuring sleep in the development and evaluation of therapies should be prioritized.

However, standard tools for measuring sleep such as PSG or subjective reports have a number of drawbacks, including cost, burden, and insensitivity. More importantly, use of these tools has not synergistically improved our understanding of sleep symptoms in MDD or how they are impacted by potential treatments, leading to the

current situation where sleep is frequently not improved or even worsened through interventions despite its well-established relevance in MDD. The development of novel digital measures is promising as these new tools could allow for more accurate and wide-spread sleep assessment in depression; nonetheless, further standardization, validation, and qualification are needed to enable wide-spread use in regulatory decision-making. A patient-focused approach in the development of these novel standardized measures is of paramount importance, enabling features of sleep that are most meaningful to patients with MDD to be included as a basis for decision-making in clinical development. It is also important that we invest into further analytical and clinical validation to ensure that real-world digital sleep outcome measures are fit for purpose in MDD [60, 61]. Many algorithms commonly used for digital sleep assessment such as Cole-Kripke [62] were first developed in healthy sleepers; thus, we need to show that these algorithms, variations thereof, or novel digital measures are performant in assessing the specific types of sleep disturbance that are seen in MDD populations. Initial analytical validation studies have shown that when compared to PSG, commonly used DHTs have “significant limitations in quantifying sleep and wake, relative to PSG” [63], underlining the point that extensive investment is required in robust evaluation of DHTs in MDD. This investment must include efforts to define specific measurable concepts, the relation of these concepts to specific patient groups, disease stages and severities, as well as clinical validation to define thresholds for a clinically significant change on an individual and cohort levels.

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Digital health technologies hold the potential to close the gap between meaningful sleep symptoms and our ability to measure them as a basis for decision-making in clinical development. Engaging patients into defining measures that matter [64], ensuring that novel measures are fit for purpose for use in MDD, and working with regulators to qualify these measures will ensure that sleep does not remain a forgotten symptom in MDD.

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Conflict of Interest Statement

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Author Contributions

N.P. and I.C. created the initial concept. N.P., S.A., J.B., T.S., Y.Z., I.C., and K.L. were involved in design and research. N.P. created the first draft of the manuscript. N.P., S.A., J.B., T.S., Y.Z., I.C., and K.L. contributed to revisions and approved the final manuscript and agree to be accountable for all aspects of the work.

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