Mindpax.me

Managing Bipolar Disorder

Bringing Digital Revolution to Treatment of Severe Mental Illnesses

Table of Contents

We want to empower those struggling with severe mental illnesses by helping them better understand their condition and receiving targeted therapy in time of need.

"Living with bipolar disorder is like riding a roller-coaster in the dark. You never know when the next downturn is going to happen—I would welcome a light on my way."

Max, a 31-year-old psychiatrist, and BD patient

Introduction to Bipolar Disorder

Approximately 45 million people worldwide are experiencing a severe and lifelong episodic illness called bipolar disorder (BD)[1]. It typically manifests itself before 35 years of age as periods of manic and depressive episodes separated by periods of stable phase (figure 1).

BD is considered one of the most frequent causes of disability in youth as, in many cases, it affects the quality of cognitive functioning and overall quality of life[2]. The underlying causes of BD are unclear. However, it is known that the interaction of psychological and social stressful influences with primarily biological and genetic predispositions can contribute to the illness onset.

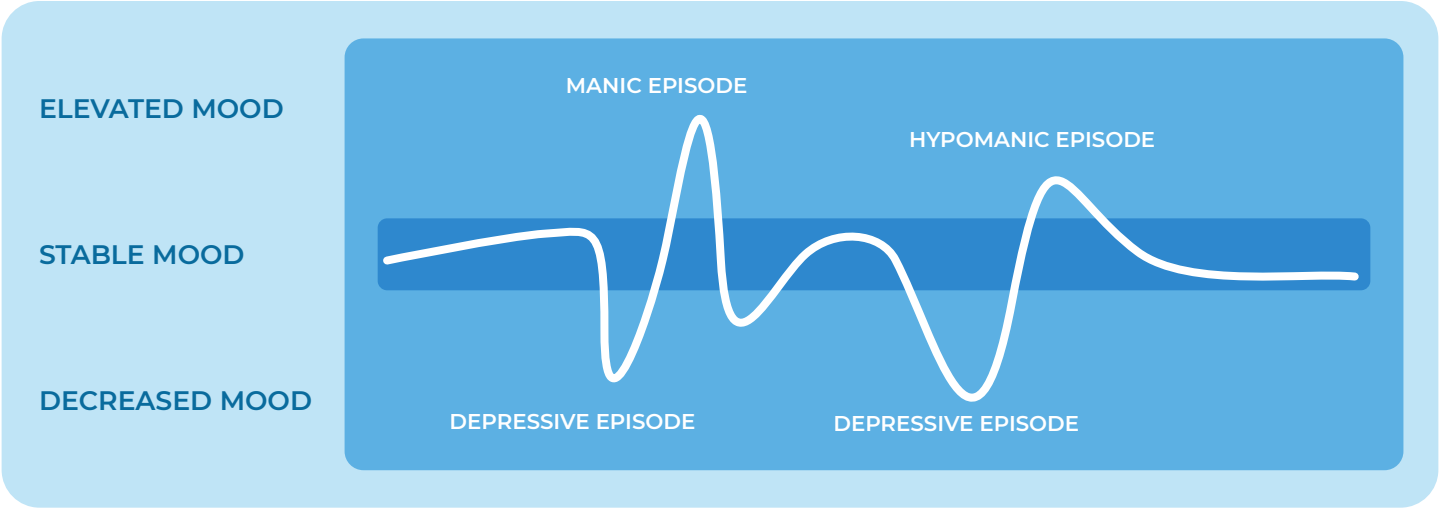


Figure 1: Representation of the clinical course of bipolar disorder (depressive, hypomanic and manic episodes)

Unfortunately, obtaining the correct diagnosis is a long process, and it can often take ten years from the onset of symptoms to the diagnosis of bipolar disorder[3]. The probability of the illness onset is independent of nationality, ethnic origin, or sociodemographic status[4].

Mindpax shines a light on the course of bipolar disorder and enables shared and predictable treatment decisions for our patients, their loved ones and clinicians.

Bipolar Disorder Characteristics

The prevalence of bipolar disorder can vary from 1% of the population to more than 4%, depending on the diagnostic criteria (figure 2).

The Diagnostic and Statistical Manual (DSM), used primarily in the United States, provides a more detailed view of the manifestations and course of bipolar disorder[5]. The recent version of DSM classifies BD into four subgroups: bipolar disorder type I (BD I), bipolar disorder type II (BD II), cyclothymia, and bipolar disorder not otherwise specified[5]. Therefore, the four BD subtypes are estimated to affect 4.4% of the population in the United States[6].

In European countries, it is typically diagnosed according to the International Classification of Diseases (ICD-10)[7, 8].

In contrast with the DSM, ICD-10 does not consider bipolar disorder as a broader spectrum and rather reflects BD I, thus reducing the prevalence in Europe to 1%[9].

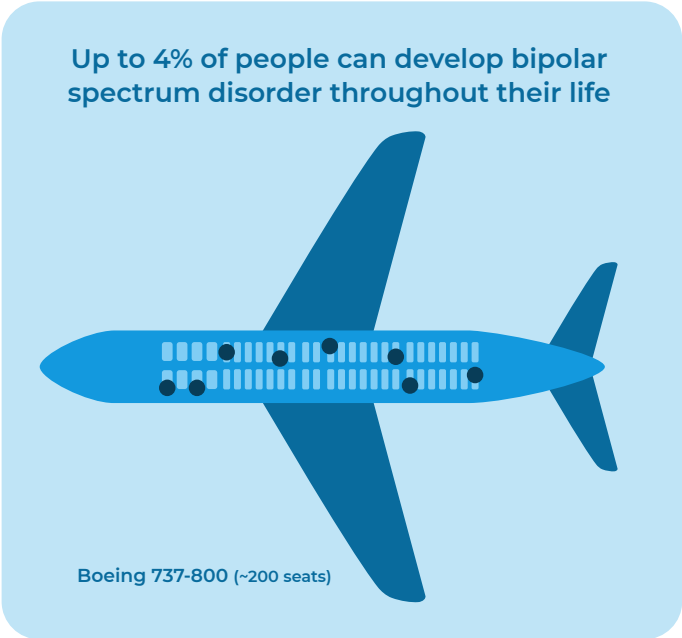


Figure 2: Prevalence of bipolar disorder

Figure 3: Depression/Mania Symptomatology

Therefore, it should be taken into account that the actual prevalence of bipolar disorder may be higher than the reported rate of 1%.

Manic episodes manifest as an elevated mood that is out of proportion to the circumstances. Other symptoms include increased energy, reduced need for sleep, grandiose fantasies and ideas, irresponsible use of funds, promiscuous behavior, or similar things. Mania may also be accompanied by psychotic features such as hallucinations or delusions and can lead to total exhaustion of the individual.

Depressive episodes are characterized primarily by a decline in mood, energy, sleep disruptions, and apathy. Compared to mania, depression typically occurs three times[10] more often and lasts longer[11]. Summary of the main BD symptoms is illustrated in figure 3.

To record the long-term digital imprint of the BD, Mindpax performed the largest-to-date actigraphy study in BD: the AKTIBIPO400 with 369 patients and 18+ months of follow-up time.

"Thank you. Thank you to the team for saving my life, without you, I might not be here today!"

Female, 45-year-old patient with BD

Risk of Suicide

More lives are lost due to suicide every year than death in car accidents[12, 13]!

Average suicide rate in BD patients is appx. 1% annually. The risk of suicide in patients with BD is 20 to 60 times higher than in the general population (figure 4)[14, 15]. The increased occurrence of committed suicides in bipolar disorders comes with a much higher ratio of committed suicides to the number of attempts [15]. The suicidal ideas and attempts occur mostly during severe depressive episodes (78 – 80%) as stated in figure 5[16]. The cycling subtype of bipolar disorder has also been identified as a risk factor for suicide attempts, with a 54% higher risk for attempted suicide and higher intent and lethality compared to non-rapid cyclers[17].

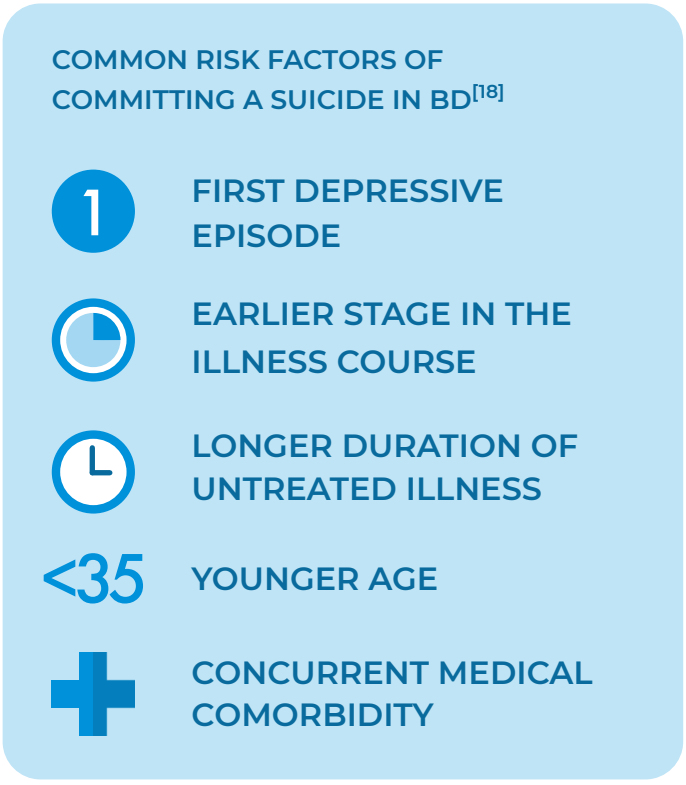


Figure 6: The most common risk factors of committing a suicide in BD

Figure 4: Ratio of risk of suicide in BD population compared to non BD population

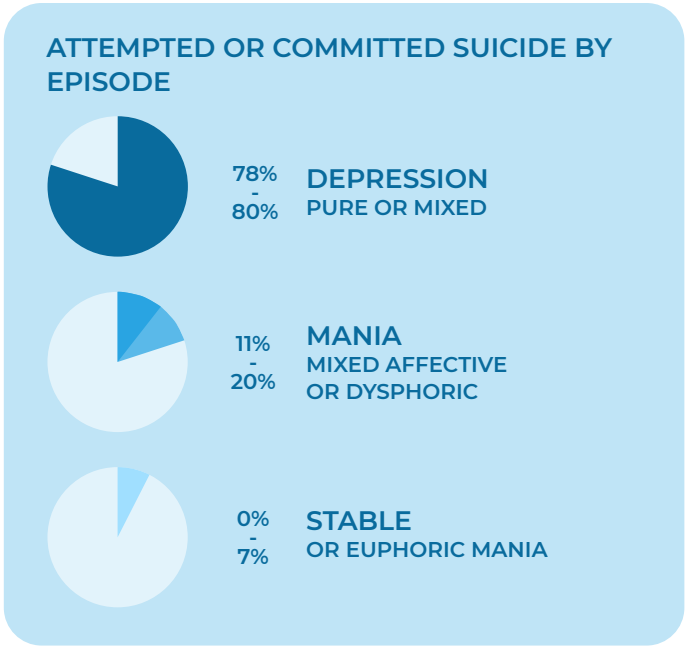


Figure 5: Occurence of attemted or commited suicide by episode

The ability to identify the patients at risk (figure 6), and the ongoing clinical assessment are essential to limit the suicidal risk. Short-term interventions to manage acute suicidal risk include rapid hospitalization, medication, and close clinical supervision. Long-term interventions include medication, psycho-therapy, and psychoeducation.

Bipolar disorder carries the highest risk of suicide compared to other psychiatric illnesses[18].

By helping BD patients to maintain a steady clinical state in the long term, Mindpax has the potential to reduce the risk of suicide.

Circadian Rhythm and Bipolar Disorder

Circadian rhythm is a ~24-hour biorhythm controlled by molecular clockworks within the brain, and it resets daily to precisely 24 hours by exposure to the light-dark cycle[22] (figure 7).

Sleep disturbances and circadian rhythm dysfunction are widely demonstrated in patients with BD. Patients diagnosed with BD manifest sleep timing delay, irregular sleep-wake schedules, and profound inter-daily differences in sleep duration, which has also been shown in our past study[23] and many scientific works of others.

Those circadian deviations are projected into impaired social rhythmicity, i.e., periodicity in daily routines, which is accompanied by periodic motor activity and can be detected using actigraphy. Concurrently, disruptions in mood and, thus, episodes of BD are directly related to disturbances in the regularity of routines[24]. Additionally, it was shown that motor activity is associated with future mood and energy[25].

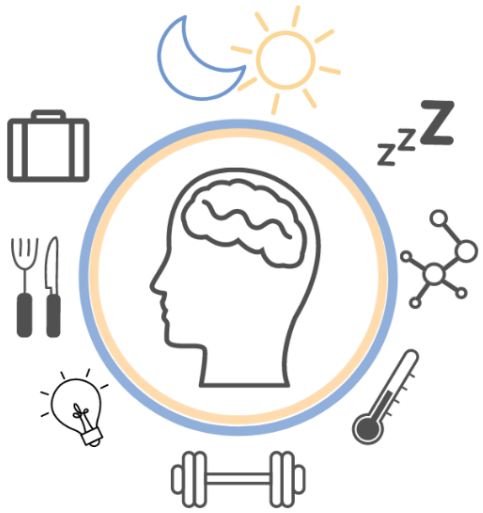


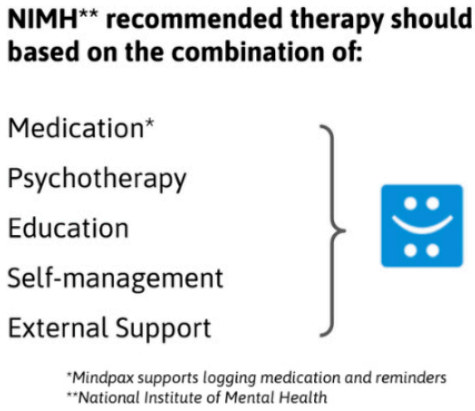
Figure 7: Mood disorders are often associated with disrupted circadian responses, such as sleep and hormone secretion. Also, disruption of circadian rhythms via jet lag, night-shift work, or exposure to artificial light at night, can have negative effects on the affective symptoms in BD patients [22, 23] .

Mindpax uses actigraphy monitoring as one of the key inputs to its personalized system. It enables providing the patients with individualized feedback on their daily regime, and thus we aid patients in avoiding risk factors leading to clinical worsening.

Treatment of Bipolar Disorder

BD treatment aims to achieve as high as possible levels of psychosocial function, mitigate the severity of mood swings, and accomplish a health-related quality of life for patients with BD.

According to the current guidelines for BD treatment[26], combining and personalizing multidisciplinary treatment approaches is recommended based on the nature of the stage of the illness and individual responsiveness to each treatment option. The gold-standard treatment includes pharmacotherapy, cognitive behavioral therapy (CBT), interpersonal and social rhythm therapy (IPSRT), and psychoeducation, including self-management and external support.



By combining multiple patient-centric approaches, implemented in an automated personalized system with long-term illness monitoring, we provide both parties in the patient-clinician team with maximum support to achieve top-quality treatment.

"I currently have a 3rd-degree disability pension. I used to have a full-time job, then more part-time jobs, but now I don't have a job. I still keep one flexible freelance job, but it is tough due to my condition, especially these days when I am depressed."

Female, 50-year-old patient with BD

Economics of Bipolar Disorder

The economic burden of BD to society is enormous. According to the World Health Organization (WHO), BD is one of the leading causes of disability in the world (as measured by DALYs).

Research indicates that bipolar disorder carries higher reported "all-cause" direct health care costs than depression, asthma, diabetes, and even coronary artery disease[19]. Costs for the U.S. presented in figure 8, include the direct costs of treatment (20 - 30%), such as medical expenses with psychiatric care, more frequent psychiatric interventions, comorbidity treatment expenses, ER visits, and indirect costs (70 – 80%) from reduced employment, productivity, and functioning. As presented in figure 9, the direct costs are four times more expensive in patients with BD ($20k) compared to people without a mental disorder ($5k)[20].

Drivers for the direct costs include frequent psychiatric interventions (ER visits and hospitalizations), the presence of comorbidities, and both suboptimal medication adherence and clinical management. Indirect costs include mainly the patient's inability to work, the cost of their caregivers, and premature death (figure 10).

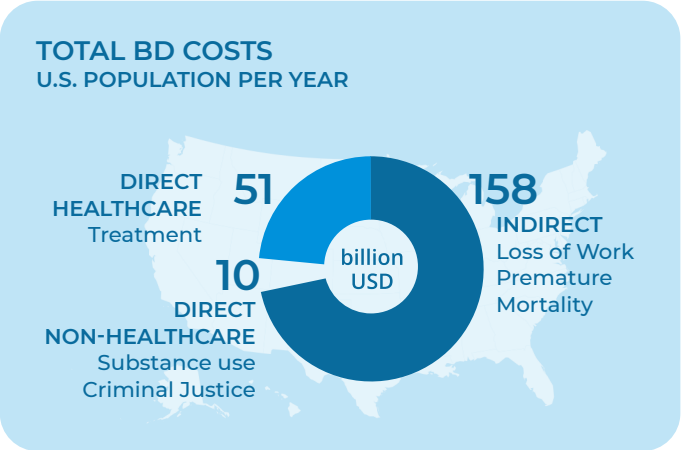


Figure 8: Total BD costs in US population

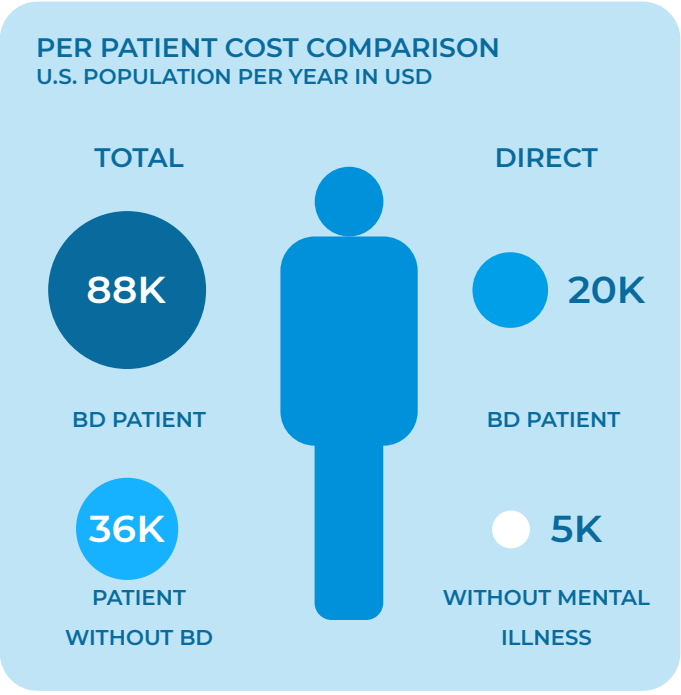


Figure 9: Comparison of healthcare cost in US

Figure 10: Interesting facts about BD costs in US

Long-term strategies for BD management need to be introduced to improve patient outcomes and reduce the overall economic burden. The main target of the treatment management should be a reduction in the recurrence of mood episodes and improvement in the stability of the patient's psychiatric symptoms, general well-being, general functioning, and quality of life.

Mindpax fills the gap in general maintenance treatment solutions for BD and significant psychiatric diseases. Providing continuous long-term digital care has the potential for a considerable cost benefit.

"We tried all available meds, antidepressants, antipsychotics, mood stabilizers, and combinations. I have been hospitalized twice with mania and twice with depression. I also had two years of intensive psychotherapy with a clinical psychologist. The positive change is that the system monitors my sleep now. In the past, I wrote down my sleep and mood every day. I don't have to do that anymore. I also believe that the system may bring valid information about the treatment's success. Another benefit is the feeling that someone can monitor my mood swings, and my doctor will be able to use it to manage my disease."

Adam, a 30-year-old patient with BD

Introduction to Mindpax System

Mindpax system provides therapeutic feedback through visuals of social rhythm stability and gives targeted psychoeducation to patients to help them better self-manage their condition. The information can be additionally provided to clinicians as a clinical decision support tool to help them make more informed therapy decisions.

Improved and shared therapy decisions are critically important, as bipolar patients are generally poorly managed and have limited therapeutic options, which are often impacted by external events and triggers.

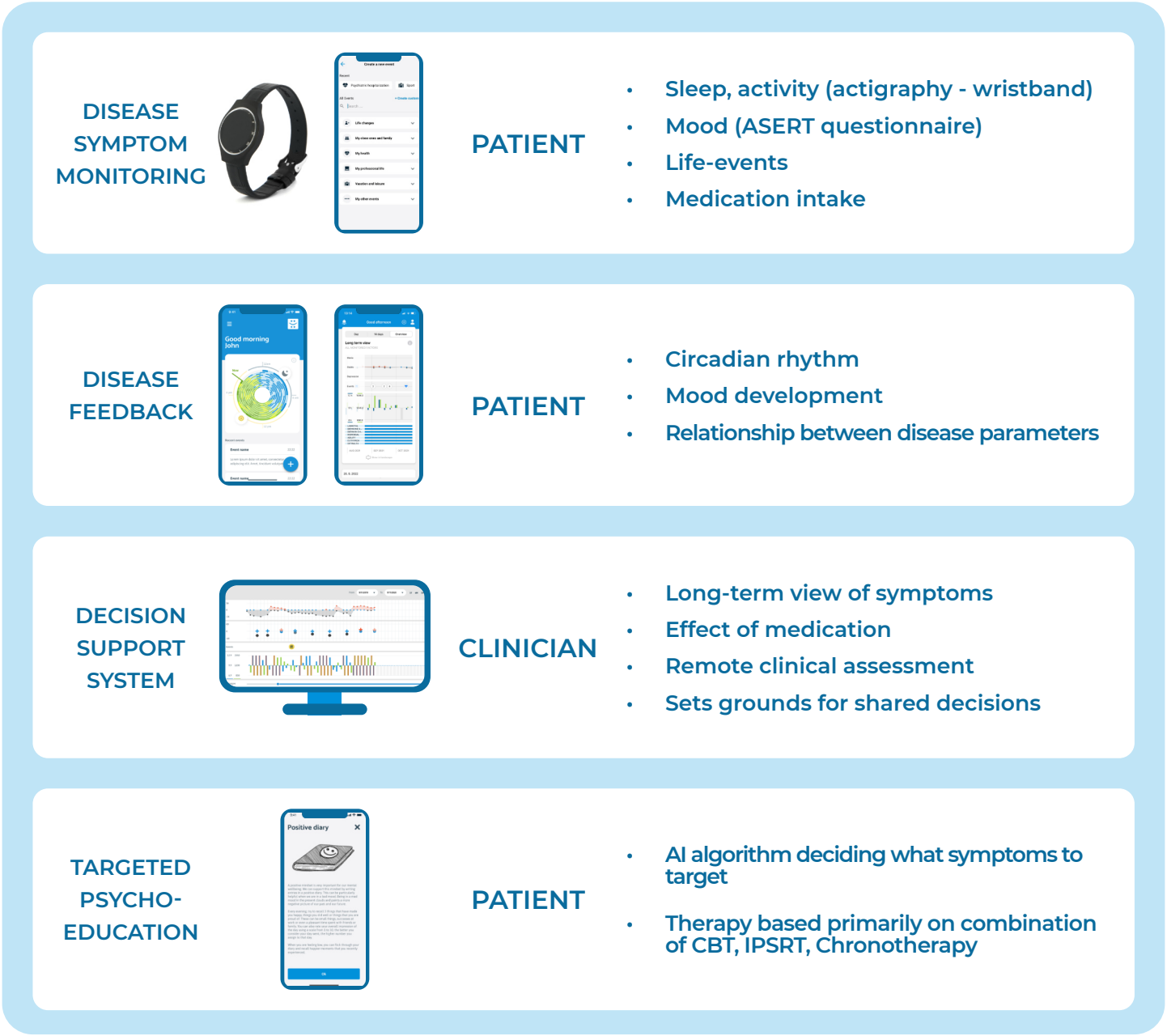


Figure 11: Mindpax System digital therapy pathway

We use data-driven algorithms based on our sizable long-term study to provide patients personalized feedback when and where they need it.

"... In fact, I am in a manic episode now, but thanks to your system and my husband's patience, we have managed not only to flatten the mania-mood curve, but it is already reversing in recent days. Thank you from all of my heart."

Female, 47-year-old patient with BD

Why and How Does Mindpax Help?

Since BD is a chronic disorder with varying incidences and severity of manic and depressive relapses, treatment options center around controlling and maintaining a stable balance of moods and mitigating the frequencies and severity of BD episodes. The Mindpax system for BD has been developed based on clinical guidelines, the latest available research findings, and our proprietary IP. Mindpax's most relevant previous results are:

- **Circadian rhythm's inter-daily stability (IS) is a very promising actigraphic parameter in determining manic or depressive events**[27][28]**.**
- **BD patients show more changes in sleep duration, circadian rhythm, motor activity, and inter-daily sleep variability compared to healthy controls.** They manifest delayed and prolonged sleep, irregular sleep/wake schedules with reduced overall levels of motor activity, and profound inter-daily differences in sleep duration, when compared to healthy controls[29].
- **ASERT self-report questionnaire is a reliable tool for monitoring symptom severity and relapse detection**[29]**.** The ASERT items were highly associated with both MADRS and YMRS. Furthermore, the model for scale-based relapse detection showed high detection accuracy for both depression (AUC=0.880) and mania (AUC=0.844).

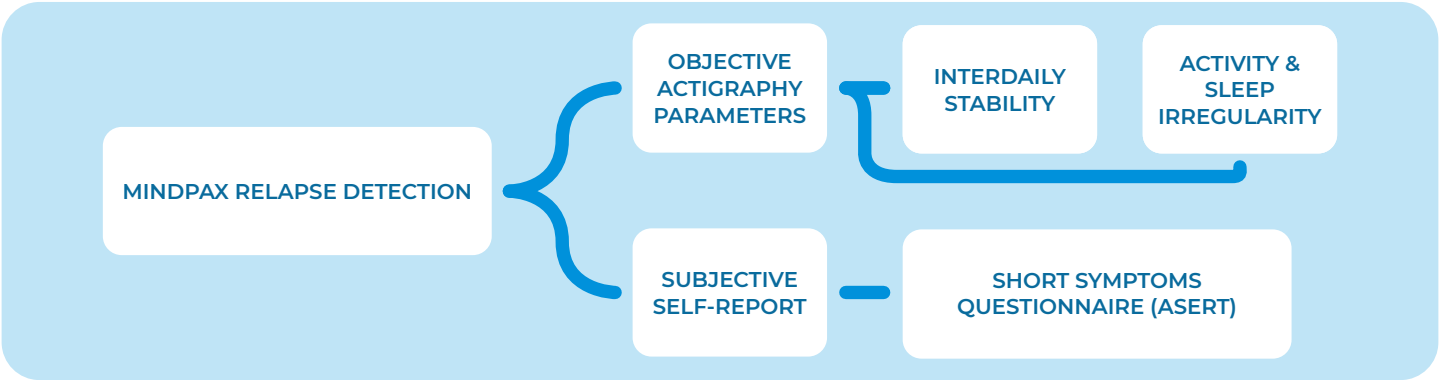


Figure 12: Mindpax relapse detection is based on objective parameters and subjective self-report

The ASERT self-report and the long-term actigraphy data are very informative about a patient's current clinical state and diagnosis and require no clinician involvement. We use them in our closed-loop system to maximize the clinical benefit to the patient, as well as to cut costs.

Is there a connection between the clinical state, mood and sleep/activity in BD?
Is it universal across patients?
Does it hold in the long-term?
We undertook the largest clinical research of its kind to find out.

Mindpax Bipolar Disorder Research & Findings

In table 1, we introduce two large Mindpax studies focusing on bipolar disorder, which result in one of the most extensive and detailed datasets available worldwide in the context of long-term symptom and activity monitoring of mood disorders. This database, as outlined in figure 13, is still expanding.

The purpose of the AKTIBIPO400 study was to observe motor activity and, thus, the functioning of the circadian system in patients with BD in relation to their state, relapse, or remission. The ongoing AKTIBIPO VALIDATION study evaluates the clinical benefits of the Mindpax system.

AKTIBIPO400 Study

	AKTIBIPO400	AKTIBIPO VALIDATION
TIMELINE	2017 - 2021	2021 - 2023
DURATION	18 MONTHS	12 MONTHS
PARTICIPANTS	369 BD PATIENTS + 30 HEALTHY CONTROLS	73 PATIENTS (FROM AKTIBIPO400) + 55 NEW PATIENTS (27 WITH INTERVENTION)
METHODS	LOW INTERVENTION WRISTBAND ASERT APP	INTERVENTION WRISTBAND ASERT APP + PERSONALIZED PSYCHOEDUCATION IMPROVED DATA VISUALIZATION
OUTCOMES	ASERT VALIDATION RELAPSE DETECTION	CHANGE IN QUALITY OF LIFE (Q-LES-Q) LOWER MEAN VALUE OF ASERT LOWER NUMBER OF HOSPITALIZATION DAYS OTHER CLINICAL SECONDARY OUTCOMES

Table 1: Overview of Mindpax studies: AKTIBIPO400 and AKTIBIPO VALIDATION

Mindpax, in collaboration with the National Institute of Mental Health in the Czech Republic, conducted the observational multicenter longitudinal study with more than 300 patients over a period of 4 years. Patients with bipolar disorder participated in a study called AKTIBIPO400 from all over the Czech Republic.

Published Results from AKTIBIPO400

Description	**Actigraphy** measures motor activity at a sample frequency of *30 seconds*	**Self-reported mood** from *weekly* ASERT questionnaire	**Clinical scales** from *monthly* interviews: MADRS & YRMS	Patients can also record **medication** and external **events**
Motivation	**Activity/Rest levels** are usually affected during depression and mania episodes	Captures the patients' **own perspective** on their state on a regular basis	Gives **clinically relevant** measure of disease progression	Necessary to obtain a **complete picture** of patients' situations
Quantity	**523 years** of valid actigraphy data	**27394** completed mood questionnaires	**2684** collected clinical scales	**964 drugs** and **3544 events** recorded by patients **+ 2306 drugs** from doctors/interviews

Figure 13: Schematic overview of Aktibipo400 study

AKTIBIPO400 RESULTS OVERVIEW

- Motor activity can distinguish between BD patients and healthy controls
- Clinical validation of the ASERT questionnaire
- Clinical validation of the relapse detection algorhitm
- DTX personalized psychoeducation module
- High longitudonal patient compliance

- **Classification of patients and healthy controls based on physical activity patterns.** A machine-learning actigraphy-based model could distinguish between inter-episode BD patients and HCs solely based on actigraphic records (accuracy 87.8%). The classification remained valid even when features influenced by employment status were omitted (accuracy 78.7%). The findings suggest that the temporal variability of actigraphic parameters may provide discriminative power for differentiating between BD patients and HCs while unaffected by employment status[28, 29].

Even when not experiencing a clinical episode, BD patients exhibit highly specific physical activity and sleep patterns, distinguishing them from the healthy population. The episodes are specific in terms of sleep/activity, and there is significant inter-individual variability. This inconsistency stresses why long-term BD-specific datasets are necessary to train personalized care models, adapting to the personal characteristics of each patient.

- **Subjective digitally administered BD symptom self-monitoring questionnaire developed by Mindpax (ASERT) is simple and provides substantial clinically relevant additional information to current treatment:**
  - ASERT is a quick (~30s) and acceptable mood monitoring tool administered via a smartphone application with good capability to detect worsening clinicalsymptoms in a long-term monitoring scenario.
  - More frequent and low-cost sampling compared to standard clinical scales representing a golden standard in the field (ASERT X MADRS ($p<0.001$), ASERT X YMRS ($p<0.001$).
  - Ecological validity—home environment
  - High compliance—mean response rate 76%[29]
- **Development of a relapse detection model using generalized mixed-effect models with patient-specific parameters[30]:**
  - Depression relapse: sensitivity 70%, specificity 88%
  - Mania relapse: sensitivity 65%, specificity 89%
- **High patient compliance** (81% of patients stayed over 12 months) with wearing the wristband and completing the ASERT into the research version of the Mindpax system even without personalized feedback and psychoeducation.
- **Using specific activity patterns during clinical episodes, we automatically classified patients' states based on actigraphy**[30] (accuracy of about 75% for a distinction between depression and mania). However, the patterns vary substantially across patients, owing to other non-clinical social and environmental factors and different biological disorder progressions. Thus, stressing the need for Mindpax's ongoing phenotyping research.

We have shown that clinically valid remote monitoring of clinical state in BD is possible in the long term.

AKTIBIPO VALIDATION Study

If you provide BD patients with relevant digital information on their disease course and digitally educate them on how to intervene at times of the clinical worsening, is it enough? Will you improve their clinical state and the quality of life? We conducted the first clinical validation study with the AKTIBIPO400 BD population to find out.

Mindpax is currently running an interventional study called AKTIBIPO VALIDATION. The study aims to validate the clinical benefits of the Mindpax system in the self-management of bipolar disorder. The patient population is divided into two cohorts: a) DeNovo—new participants and b) patients that participated previously in the observational AKTIBIPO400 study. The participants use the Mindpax system. See figure 14 for the schematic representation of the use of the Mindpax system in the study.

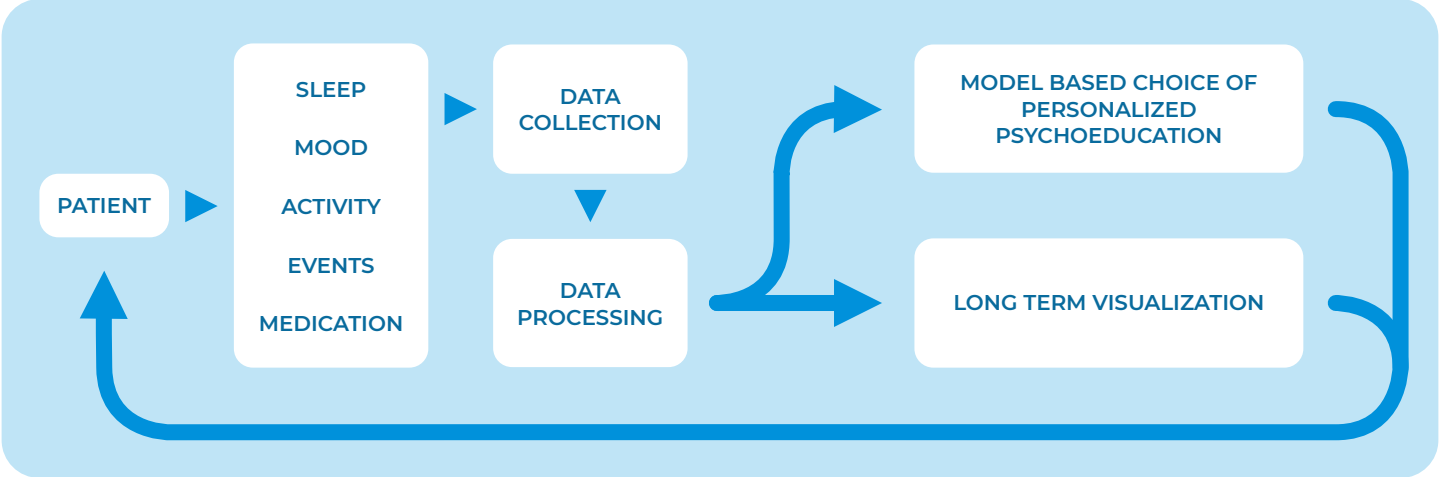


Figure 14: Visualization of the role of the Mindpax system in the AKTIBIPO VALIDATION study

Preliminary Demographic Results from AKTIBIPO VALIDATION

Currently, 100 patients with bipolar disorder are enrolled in the study, of which 60% are women. The average age of the participants is 41 years (SD = 11). The first symptoms appeared, and the illness onset in patients around 23 years of age (SD = 9). One-third of the patients in the study are fully unemployed, a second third are employed full-time, and a third works part-time jobs.

	ValM1 (M0)	DeNovo (M-3)	ALL
PARTICIPANTS	73	27	100
SEX (FEMALE)	58.9%	63.0%	60.0%
AGE* (*p - t test = 0.049)	42.49 +-9.92	37.38 +-12.96	41.15 +-10.97
EMPLOYMENT (FULL/PART/NONE)	34.3 37.7 30.0	43.5 8.7 47.8	36.6 29.0 34.4
BD ONSET AGE	22.5 +-8.9	22.2 +-10.0	23.2 +-9.2

Table 2: Demographic data of the AKTIBIPO VALIDATION study population

Preliminary (Unpublished) Results from AKTIBIPO VALIDATION

AKTIBIPO VALIDATION PRELIMINARY RESULTS OVERVIEW

- The link between stable regime and the quality of life confirmed
- Improvement in the quality of life
- Improvement in mood stabilization an depressive symptoms
- Qualitative results (patient satisfaction, data compliance, effect of personalization on compliance)

- **A stable regime is connected to a better life quality**
  The results showed a strong connection between long-term stability of sleep regime and quality of life, showing that patients with lower variability in daily routine also show significantly higher quality of life. When combined with the available literature on sleep and affective disorder, it may present a plausible focus for treatment and suggest the validity of the Mindpax approach. The causal relationship needs to be evaluated in further study.

  In the preliminary analysis, a statistically significant connection was observed between the quality of life as measured by Q-les-Q and long-term variability in sleep duration (r=0.45, p=0.028) and sleep timing (r=0.50, p=0.021). These results are also supported by other features (like L5 time and Acrophase) (unpublished).

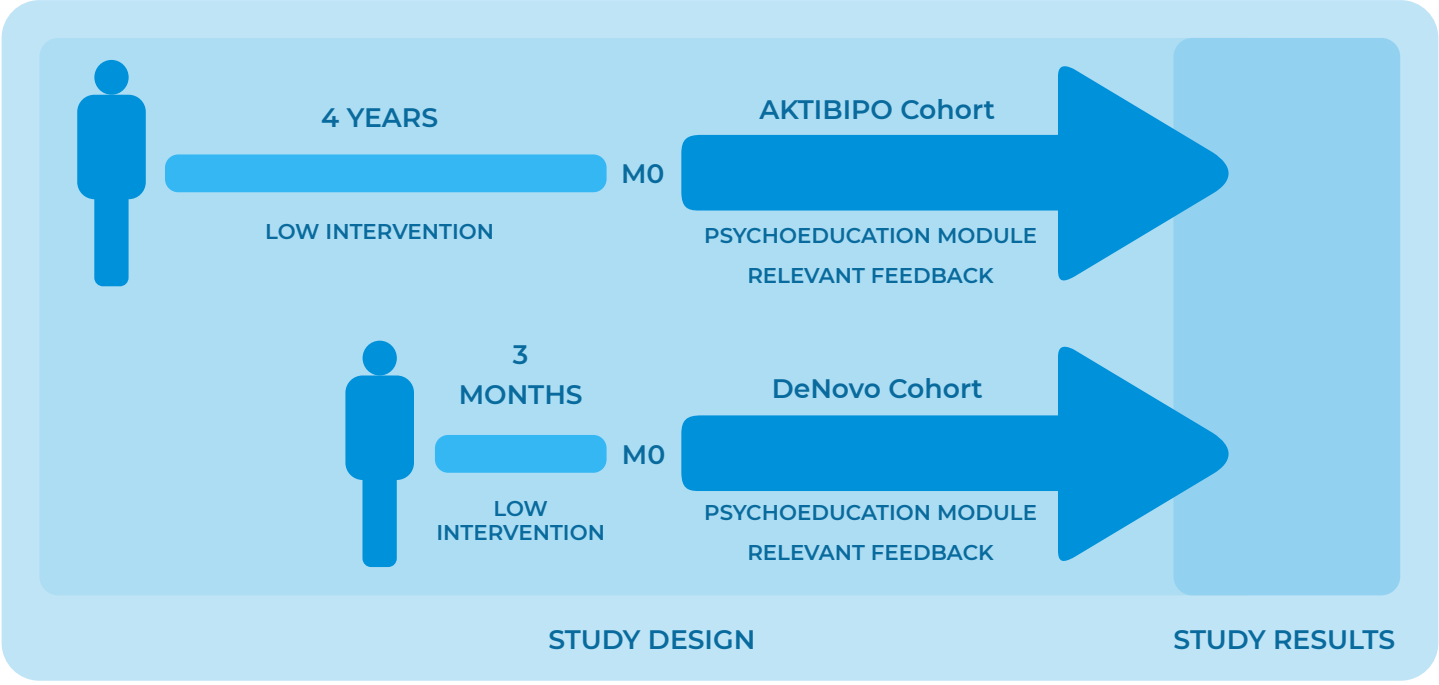


Figure 15: Description of patient cohorts in AKTIBIPO VALIDATION

First readout of the original cohort of past AKTIBIPO400 patients revealed their preselected character (likely driven by their past participation in our clinical programme): the patients showed high quality of life, low disability and overall good health. We thus added the DeNovo study arm, including patients with no past experience with our system to estimate the effect on the general BD patient population.

DeNovo N = 27 AKTIBIPO N= 73	DeNovo M(-3)		DeNovo M0 vs M(-3)			AKTIBIPO M0 vs DeNovo M0		
	MEAN	SD	MEAN	SD	P-VAL	MEAN	SD	P-VAL
QlesQ	38.3	7.3	44.3	10.0	**0.007**	44.8	11.4	0.852
WHODAS	46.5	24.3	38.6	21.0	**0.028**	38.4	29.3	0.435
MADRS	7.9	7.1	4.7	4.4	0.059	5.4	5.9	1.000
YMRS	3.6	5.1	6.1	8.3	0.241	2.7	4.3	0.808
ASERT DEP	5.1	3.0	4.1	3.3	0.080	5.3	4.2	0.615
ASERT MAN	3.0	2.0	3.0	2.4	0.871	1.1	1.7	**0.001**
MID SLEEP VAR	1.5	0.7	1.7	0.6	0.390	1.3	0.9	**0.025**

Table 3: Preliminary results of the AKTIBIPO VALIDATION study

- **Improvement in the quality of life and the disability score**
  The preliminary results show that the DeNovo patients at the entry to the low-interventional part of the study (M-3) report significantly lower quality of life (QlesQ) and higher disability score (WHODAS) compared to the AKTIBIPO patients at enrollment (M0) as stated in table 3.

  The possible causes are the stabilization effect of the Mindpax system even in the low-intervention program, as well as potential selection bias of the AKTIBIPO cohort (the ability of the patients to conform to a long-term AKTIBIPO400 study in the past). However, the effect of the low-intervention program is supported by the fact that DeNovo patients show dramatic and significant improvement in the primary outcomes already after using the low-intervention program for three months, bringing them close to the state of the AKTIBIPO patients at enrollment.

  Marked differences remain in the clinical parameters such as self-assessment of manic symptoms (ASERT man) and variability of sleep regime (mid-sleep var).

- **Improvement in mood stabilization and depressive symptoms**
  Another important result of the AKTIBIPO VALIDATION study is a significant stabilization of self-reported mood after nine months in the AKTIBIPO cohort. After nine months of using the Mindpax app with feedback, 69% of patients from a preliminary readout reported a decrease in depressive symptomatology (-0.8 ASERT points from the mean value of 5.0 at baseline, signrank test p=0.008) and 53% of patients showed a stabilization of their mood (signrank test p=0.021).

  On the other hand, there is also a significant increase in ASERT manic score, which is not present in the clinical YMRS scale. We observed a nonsignificant decrease by 1 point from the baseline mean value of 3. The slight increase in ASERT manic score can be interpreted as a relief from the depressive symptoms.

- **Feedback-driven high data compliance**
  Compliance with the Mindpax app has increased throughout the study. In the first three months, the ASERT questionnaire was filled in by only 39% of active patients, and after nine months, by 85% of active patients. The completeness of actigraphic data has also increased (from 46% to 76%). Improvements can be interpreted as the more effort patients put into the app, the more beneficial the system is to them. Patients who see their regime's regularity and mood development may combine it with personalized education.

  Interesting is the comparison with the DeNovo patients. The actigraphic data compliance was 73% within the first three months and increased to 78%. Their compliance with the ASERT questionnaire at the study enrollment was 87%, and it didn't change even after three months in the study. The higher compliance in the DeNovo group at their inclusion in the study may be interpreted as a higher novelty of the whole system for the DeNovo group. Additionally, we see that when introduced with appropriate feedback, compliance is almost identical in both groups.

In the AKTIBIPO VALIDATION study, we turn the patient's focus to the long-term stability of the sleep and activity routine and help them maintain a stable clinical state through patient-targeted micro educational messages.

Qualitative Analysis of the Mindpax System for Bipolar Disorder

MINDPAX SYSTEM OVERVIEW

- High satisfaction with mindpax system
- 1444 psychoeducation sent
- Individual psychoeducation increases compliance
- High perceived usefulness of psychoeducation

- **Satisfaction with Mindpax app after nine months**
  Patients in the Aktibipo Validation study are overall satisfied with the Mindpax application. After nine months of using the Mindpax app, 66% of patients are very satisfied or satisfied. Less than 10% of the patients are unsatisfied. It is interesting that even unsatisfied patients keep using the Mindpax app. The main concern of the unsatisfied patients was technical difficulties connected to the app use.

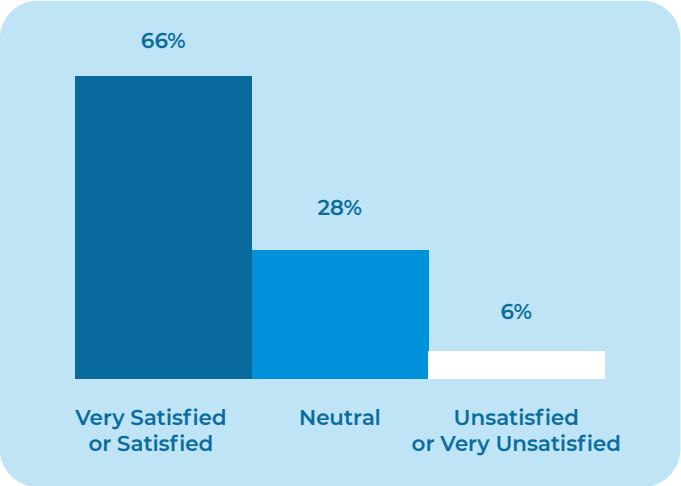


Figure 16: Results of patient satisfaction evaluation with the Mindpax system after 9 months of using

- **Psychoeducation in numbers**
  Our preliminary results show that patients in the study received a total of 1444 psychoeducation materials, of which 923 targeted mood changes (704 for depression and 219 for mania). We sent 296 messages based on sleep changes (187 for shortened and 109 for prolonged sleep).Materials educating about the increase in activity were received by 94 patients, and 120 were educating about a decrease in activity. Eleven patients were warned about the risk of mixed symptoms and encouraged to seek professional help.

  Most educational messages are being sent out for the depressive symptoms (mood low), which is to be expected as this is the condition predominant over time in BD patients.

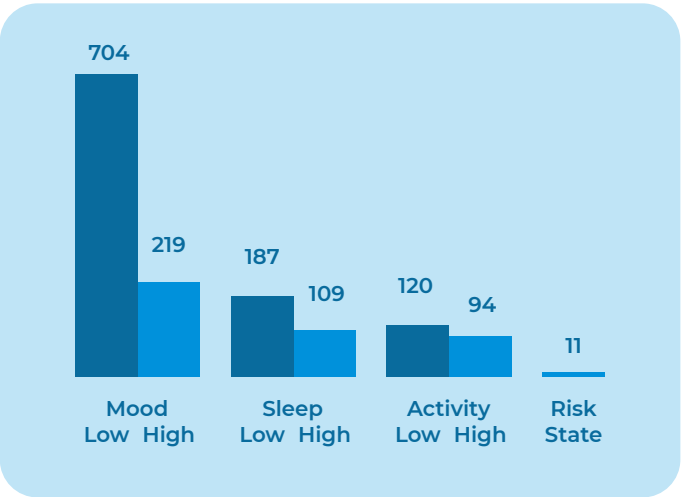


Figure 17: Amount of personalized psychoeducations sent during the AKTIBIPO VALIDATION study

- **Regularity of psychoeducation reading after 3/9 months**
  Patients in the AKTIBIPO VALIDATION study do generally read received psychoeducation. After three months in the validation study, 68% of patients read all or at least more than half of the psychoeducation, and 18% read none or one/two psychoeducation during three months. The number of psychoeducation readings increased significantly after nine months of the study. 91% of patients read all or more than half of psychoeducation, and only 9% read less than half. There were no patients in our study who didn't read at least a few psychoeducation after nine months.

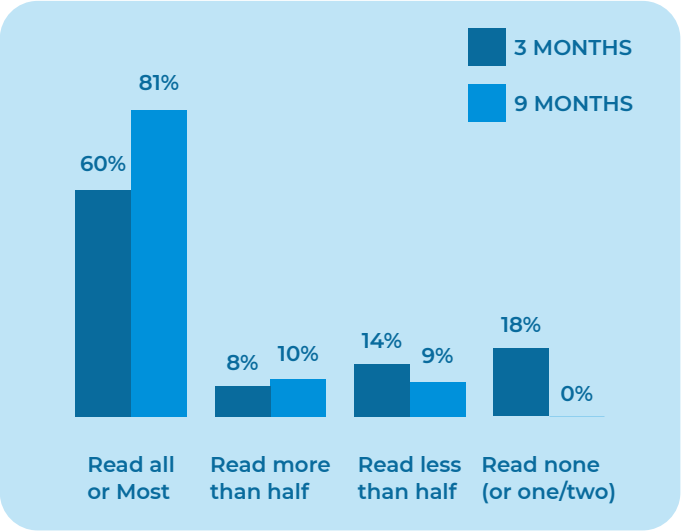


Figure 18: Percentage of psychoeducations read by the patients during the AKTIBIPO VALIDATION study

- **The usefulness of psychoeducation**
  Patients who participated in the AKTIBIPO Validation study for three months and more found psychoeducation valuable and interesting in 50%. They found it partly useful and partly useless in 33%, and only 17% of patients found psychoeducation useless and uninteresting at the beginning of the study. The perceived usefulness rises after nine months (up to 60%). We believe this might be due to the disorder-relevant and personalized content of psychoeducation that patients receive after three months.

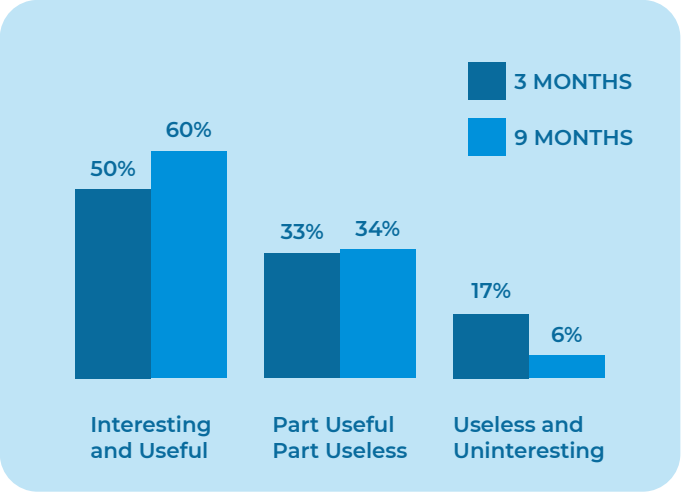


Figure 19: Results of system psychoeducation usefulness evaluation by patients participating in the AKTIBIPO VALIDATION study

Along with regularly reading the psychoeducation, compliance with wearing the actigraphy wristband and reporting the ASERT self-assessment questionnaires does not decrease over time in the study. This point supports the feasibility of the long-term maintenance solution that Mindpax represents.

Summary of Findings

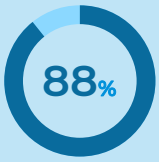
Monitoring and Diagnostics

Relapse detection

Correct detection from self-report

Using the clinically validated, quick, digital, self-administered questionnaire ASERT can help patients to detect warning signs of relapse in time

BD classification & actigraphy



Detection of BD and HC from actigraphy

Activity patterns measured via wristband can distinguish BD patients from healthy controls, then they can facilitate diagnostics

Risk factor detection

1400+
cases

<100 patients in 9M

Different sleep and activity profiles during remission, depression and mania help patients and clinicians with better understanding of individual manifestation of BD symptoms. Detection of changes in mood state (assessed by ASERT) and motor activity is a tool for targeted personalized psychoeducation.

Digital Therapy

▲15%
improvement
in quality of life

After 3 months

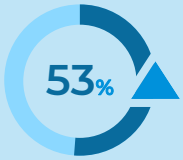
Patients newly introduced to the Mindpax system (DeNovo) show dramatic and significant improvement in the quality of life and disability scores already after using the low-intervention programme for 3 months.

Depressive symptoms

Patiens with substantial reduction in depressive symptoms

Patients in the AKTIBIPO cohort of the validation study with personalized psychoeducation showed clinically significant decrease in depressive symptomatology after 9 months.

Symptoms stabilization



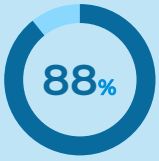
Patiens with substantial signs of stabilization of symptoms

Patients in the AKTIBIPO cohort of the validation study with personalized psychoeducation showed clinically significant improvement in stabilization of self-reported mood.

Summary of Findings

Compliance and adherence

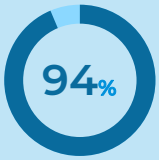
Study compliance



At 9 months readout

High patients' compliance in the validation study proves long-term viability of the solution (only 12% drop out rate after 9 months).

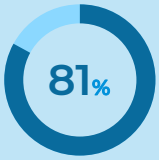
Patient satisfaction



Find the psychoeducation useful

Patients are overall satisfied with the Mindpax system for BD.

Patient adherence



Read all or almost all educations

Patients find psychoeducation useful and interesting and are more compliant to psychoeducation after personalization is introduced.

Conclusion

Providing BD patients with Mindpax System, including disorder-relevant feedback and personalized psychoeducation, indicates a dramatic improvement in multiple key factors including significant improvement and stabilization in self-perceived, weekly reported disorder symptoms.

This outcome is likely due to the system's empowerment effect of using a BD-specific health monitoring app as well as its educational effect enabling patients to manage their behavior better and thus stabilize the disorder course.

As the preliminary results of the AKTIBIPO VALIDATION study show, the Mindpax system manages to engage and maintain high compliance in long-term use - a key asset for an application aimed at long-term maintenance treatment.

"I would like to feel better in the future and get BD under control. With the Mindpax system, I perceive as positive that I can see the data myself, I can realize in retrospect when there was a clear euphoria and when I was depressed. I can orient myself better in my mental disorder."

Female, 51-year-old patient with BD

References

[1] GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. https://doi.org/10.1016/S0140-6736(18)32279-7

[2] World Health Organization. (2008). The global burden of disease: 2004 update.

[3] Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry. 2003;64:161–174.

[4] Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RMA, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry. 2007;64:543–52.

[5] (APA) American Psychiatric Association (Ed.). (2013). Diagnostic and statistical manual of mental disorders: DSM-5 (5th ed). Washington, D.C: American Psychiatric Association.

[6] Merikangas, K. R., Jin, R., He, J. P., Kessler, R. C., Lee, S., Sampson, N. A., ... & Zarkov, Z. (2011). Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Archives of general psychiatry, 68(3), 241-251.

[7] Carvalho, A. F., & Vieta, E. (Ed.). (2017). The treatment of bipolar disorder: integrative clinical strategies & future directions. Oxford: Oxford University Press.

[8] World Health Organization. International Statistical Classification of Diseases and Related Health Problems. ICD-10. 10th revision, Fifth edition, 2016. Geneva: World Health Organization, 2015. https://apps.who.int/iris/handle/10665/246208.

[9] Rowland, T. A., &Marwaha, S. (2018). Epidemiology and risk factors for bipolar disorder. Therapeutic Advances in Psychopharmacology, 8(9), 251–269. doi:10.1177/2045125318769235

[10] Kupka, R. W., Altshuler, L. L., Nolen, W. A., Suppes, T., Luckenbaugh, D. A., Leverich, G. S., ... & Post, R. M. (2007). Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder 1. Bipolar disorders, 9(5), 531-535.

[11] Hirschfeld, R. M. (2004). Bipolar depression: the real challenge. European Neuropsychopharmacology, 14, 83-88.

[12] Centers for Disease Control and Prevention, National Center for Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS): https://www.cdc.gov/ncipc/wisqars

[13] Stewart, T. (2022). Overview of Motor Vehicle Crashes in 2020 (No. DOT HS 813 266).

[14] Novick, D. M., Swartz, H. A., & Frank, E. (2010). Suicide attempts in bipolar I and bipolar II disorder: a reviewand meta-analysis of the evidence. Bipolar disorders, 12(1), 1-9.

[15] Baldessarini, R. J., Pompili M., Tondo L. Suicide in Bipolar Disorder: Risks and Management. CNS Spectrums. 2006, 11(6), 465-471. ISSN 1092-8529. doi:10.1017/S1092852900014681

[16] Gonda X, Pompili M, Serafini G, Montebovi F, Campi S, Dome P, et al. Suicidal behavior in bipolar disorder: epidemiology, characteristics and major risk factors. J Affect Disord. 2012;143:16–26

[17] Hawton K, Sutton L, Haw C, Sinclair J, Harriss L. Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. J Clin Psychiatry. 2005;66:693–704

[18] da Costa LS, Alencar ÁP, PJN N, et al. Risk factors for suicide in bipolar disorder: a systematic review. J Affect Disord. 2015;170: 237–54. A useful review of risk factors for suicide in bipolar disorder

[19] Williams MD, Shah ND, Wagie AE, Wood DL, Frye MA. (2011) Direct costs of bipolar disorder versus other chronic conditions: an employer-based health plan analysis. Psychiatric Services, 62 (9):1073–1078.

[20] Cloutier, M., Greene, M., Guerin, A., Touya, M., & Wu, E. (2018). The economic burden of bipolar I disorder in the United States in 2015. Journal of affective disorders, 226, 45-51.

[21] Bessonova, L., Ogden, K., Doane, M. J., O'Sullivan, A. K., & Tohen, M. (2020). The economic burden of bipolar disorder in the United States: a systematic literature review. ClinicoEconomics and outcomes research: CEOR, 12, 481.

[22] Walker, W. H., Walton, J. C., DeVries, A. C., & Nelson, R. J. (2020). Circadian rhythm disruption and mental health. Translational Psychiatry, 10(1), 28. https://doi.org/10.1038/s41398-020-0694-0

[23] Schneider, J., Bakštein, E., Kolenič, M., Vostatek, P., Correll, C. U., Novák, D., & Španiel, F. (2020). Motor activity patterns can distinguish between interepisode bipolar disorder patients and healthy controls. CNS spectrums, 1-11.

[24] Bauer, M. S., McBride, L., Williford, W. O., Glick, H., Kinosian, B., Altshuler, L., ... & Sajatovic, M. (2006). Collaborative care for bipolar disorder: part I. Intervention and implementation in a randomized effectiveness trial. Psychiatric services, 57(7), 927-936.

[25] Merikangas, K. R. et al. (2019) 'Real-time Mobile Monitoring of the Dynamic Associations among Motor Activity, Energy, Mood, and Sleep in Adults with Bipolar Disorder', JAMA Psychiatry, 76(2), pp. 190–198. doi: 10.1001/jamapsychiatry.2018.3546.

[26] Hirschfeld, R. M., Bowden, C. L., Gitlin, M. J., Keck, P. E., Perlis, R. H., Suppes, T., ... & Wagner, K. D. (2003). Practice guideline for the treatment of patients with bipolar disorder (revision). Focus, 1(1), 64-110.

[27] Novák D, Albert F, Španiel F. Analysis of actigraph parameters for relapse prediction in bipolar disorder: a feasibility study. Annu Int Conf IEEE Eng Med Biol Soc. 2014;2014:4972-5. doi: 10.1109/EMBC.2014.6944740. PMID: 25571108.

[28] Schneider,J.(2021).DlouhodobýAktigrafickýZáznamuBipolárníAfektivníPoruchy:Zpracování,AnalýzaaVyužitívDiagnostice(Doctoral dissertation, Czech Technical University).

[29] Anýž, J., Bakštein, E., Dally, A., Kolenič, M., Hlinka, J., Hartmannová, T., Urbanová, K., Correll, C. U., Novák, D., & Španiel, F. (2021). Validity of the Aktibipo Self-rating Questionnaire for the Digital Self-assessment of Mood and Relapse Detection in Patients With Bipolar Disorder: Instrument Validation Study. JMIR Mental Health, 8(8), e26348. https://doi.org/10.2196/26348

[30] Cuesta-Frau, D., Schneider, J., Bakštein, E., Vostatek, P., Spaniel, F., & Novák, D. (2020). Classification of Actigraphy Records from Bipolar Disorder Patients Using Slope Entropy: A Feasibility Study. Entropy, 22(11), 1243. https://doi.org/10.3390/e22111243