A telemedicine platform to improve clinical parameters in paranoid schizophrenia patients: Results of a one-year randomized study

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A B S T R A C T

Objective: The study objective was to test a smartphone-based MONEO platform designed to improve the clinical condition of paranoid schizophrenia patients. Telemedicine treatment is considered to be as effective as traditional treatment in outpatient clinics.
Method: A total of 290 patients with paranoid schizophrenia in the symptomatic remission state were recruited to this 12-month multicenter, open-label randomized trial. A study group (n = 191) received a smartphone with the MONEO platform installed. Patients conducted cognitive training twice a week. Patients' mental state was assessed every month via teleconference. A placebo group (n = 99) received a platform with functionality limited to monthly teleconsultation and performing cognitive training every 6 months. The clinical status was measured using the Positive and Negative Syndrome Scale (PANSS), Calgary, and Clinical Global Impression-Severity (CGI-S) clinical scales.
Results: After 12 months, a significant reduction of symptoms was observed in the study group, as assessed using the Calgary (36%, $P < 0.01$) and PANSS (8.6%, $P < 0.05$) scales. Symptom reduction of 23.6% was also observed in the placebo group ($P < 0.05$, Calgary scale). In the study group, depression, positive symptoms, excitement, general psychopathology and disorganization subscales decreased significantly, while in the placebo group, only the depression subscale decreased. The greatest improvement of 11.2% (study group, $P < 0.05$), vs 16.2% (placebo group, $P < 0.05$), was observed for the depression subscale.
Conclusion: The MONEO platform was demonstrated to positively influence the clinical condition of individuals with paranoid schizophrenia. A lack of negative consequences associated with usage of the device was also reported.

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1. Introduction

Schizophrenia is a chronic mental disorder which affects approximately 1% of the general population (Perälä et al., 2007). Individuals with schizophrenia have a 2.6-fold increased risk of death, mainly due to suicide and cardiovascular disease (McGrath et al., 2008). Schizophrenia impairs several aspects of everyday life such as interpersonal relationships or professional activity, often limiting patient independence (Harvey, 2014). Treatment involves both pharmacologic and psychosocial interventions, however their efficacy is only moderate (Jaaskelainen et al., 2013). Poor medication adherence (including treatment discontinuation) (Kane et al., 2013) and limited access to psychosocial care (Tandon et al., 2010) can contribute significantly to a low recovery rate and high risk of relapse.

Considering the rapid progress in telecommunication technology in recent years, telemedicine has become a promising approach to improve the management of schizophrenia (Kasckow et al., 2014). Telepsychiatry can provide patients with convenient and immediate home-based access to medical consultations. This can be applied to the management of patients with schizophrenia, enabling better control of treatment adherence and increasing chances to receive proper psychosocial intervention. Both telephone-based platforms (Stentzel et al., 2015) and electronic medication dispensers (Frangou et al., 2005) have been proposed to be used to improve treatment compliance of patients with schizophrenia. According to the results of a 6-month evaluation of schizophrenic patients, a smartphone-based system significantly enhanced medication compliance in individuals with low treatment adherence (Krzystanek et al., 2015). However, in a 12-month observation, no such improvement was achieved (Krzystanek et al., 2017). Telephone-based psychotherapy on the other hand, was proven to be effective in treating anxiety disorder (Brenes et al., 2015), depression (O'Neil et al., 2015; Preschl et al., 2011), and posttraumatic stress disorder (Morland et al., 2014).

So far, the application of telehealth technology in schizophrenia has focused on three modalities: telephone- and Internet-based

interventions and videoconferencing (Kasckow et al., 2014). Among telephone-based interventions, the availability of smartphone-based applications dedicated to individuals with schizophrenia increases (Firth and Torous, 2015). The results of the above-mentioned studies indicate that telemedicine, and in particular telephone- or smartphone-based interventions, might act as a promising and affordable tool for the care of patients with schizophrenia. A study of Ben-Zeev et al., who compared two recovery-oriented self-management techniques: a smartphone-based intervention (FOCUS) and a widely-used clinic-based intervention (Wellness Recovery Action Plan), showed that, as well as similar improvements in clinical outcomes observed for both technologies, mHealth technology was beneficial to standard therapy in terms of patient engagement (Ben-Zeev et al., 2018). Telemedicine was shown to improve both medication adherence and clinical status, as well as to decrease rates of hospitalization and emergency visits (Frangou et al., 2005; Spaniel et al., 2008). The telemonitoring platform @HOME employing electronic medicine dispensers was shown to significantly increase medical adherence of patients with schizophrenia from 75.3% observed for the control group to as much as 92.3% for telemedicine platform users (Frangou et al., 2005). At the same time, patients using the @HOME platform had greater improvements in clinical outcome (measured with the PANSS and CGI scales) than the control groups at the end of the study (Frangou et al., 2005). A significant decrease (60%) in the number of hospitalizations was achieved with the ITAREPS mobile phone platform for weekly patient monitoring, providing evidence that telemedicine might be beneficial in preventing psychotic relapse (Spaniel et al., 2008). The telehealth monitoring system reduced the hospitalization rate in veterans with schizophrenia from 32% to 5% when added to intensive case monitoring program (Flaherty et al., 2017). However, given the small sample size of the aforementioned analyses, there remains a need for further testing.

The possibility to collect and analyze a large amount of data regarding the patient's daily routine in the real-time triggered the development of smartphone applications oriented toward early identification of psychotic relapse. A smartphone-based data collection system, CrossCheck, captures data regarding the user's behavior, such as physical activity or speech frequency, and smartphone usage (Ben-Zeev et al., 2017). This input, together with information from the patient's self-reports is intended to be used for predicting the onset of relapse. However, the observed significant heterogeneity in the digital traces of the psychotic relapses underlines the need for further analyses, which, hopefully, will recognize behavioral patterns of symptomatic decline.

Videoconferencing has proven to be well-accepted and tolerated among patients with schizophrenia, and the clinical assessment obtained was shown to be equivalent to an in-person examination (Sharp et al., 2011). This demonstrates the possibility of remotely conducting reliable psychiatric assessment of psychotic patients, further increasing the feasibility of telepsychiatry not only to improve treatment efficacy, but also to provide an early diagnosis and remotely manage the condition of psychotic patients.

In this study, we described the potential of a new smartphone-based MONEO platform to improve the clinical condition of paranoid schizophrenia patients. As secondary objectives, we investigated whether use of the MONEO platform influenced the stability of the patients' clinical condition, rates of hospitalization, and visits to an outpatient clinic.

2. Methods

2.1. Study design, participants, and randomization

The study was a multicenter, open-label, randomized trial. A total of 290 patients with paranoid schizophrenia were enrolled from 27 centers in Poland; 199 constituted the study group, and 91, the placebo group. All patients were Caucasian, aged between 18 and 45 years, with paranoid schizophrenia diagnosed within the past 10 years. All enrolled patients were in the state of symptomatic remission (the severity

of symptoms was not greater than mild and did not affect daily functioning and behavior) and their schizophrenic symptoms were stable at a mild level (enabling daily functioning) for at least 6 months prior to study enrollment. All study participants confirmed constant access to a high-speed Internet connection (3G). Exclusion criteria were as follows: a co-existing psychiatric condition (particularly schizophrenic-like syndromes or organic psychotic disorders); an unstable mental (acute episodes in the past 6 months) or physical state (serious or chronic somatic disease); participation in another clinical trial in the past 6 months; lack of ability to use an electronic device with a touch screen; pregnancy or lactation; any other reason that, according to the investigator, prevented the individual from participating in a clinical study.

Randomization was performed by the MONEO system after patient registration. Patients were randomized either to the study group (who received a full version of the MONEO application) or to the placebo group (who received an inactive version of the application with limited functionality). All enrolled patients gave written informed consent to participate in the study. Recruitment took place from January to July 2014. Follow-up ended in November 2015. The study was registered by the Polish Office for Registration of Medicinal Products, Medical Devices, and Biocides under the ID number UR.DNB.4501.0024.2013.

2.2. Intervention and implementation

After enrollment, each patient received a smartphone with the MONEO telemedicine platform installed (for detailed description, see Supplementary Data).

The software in the study group reminded the patient of the need to take medication 1 h before and after the scheduled time. Medical adherence was monitored based on feedback messages sent by the patient. The software enabled the patient to conduct cognitive training twice a week. The patient received the reminder about scheduled training one day before the training and completed it of his/her own will. Software also contained a library of videos and audiobooks accessible to the patients at will. Patients were able to report the need for a televisit, with the investigator providing an answer immediately, or, if not available, as soon as possible. The investigator assessed the mental state of the patient using psychometric scales every month during a 12-month study via teleconference. Visits to an outpatient clinic were arranged at least once every 3 months.

The placebo group was provided with an inactive version of the software, which only allowed for: a monthly examination by an investigator (using a clinical scale, as previously defined) during a videoconference; performance of cognitive training at the beginning of the trial, then after 6 and 12 months of the trial; and registration for an outpatient visit.

During the study, patients were treated with any necessary psychiatric medications to maintain their health. The study made no changes to current pharmacological treatment unless the investigator deemed this necessary during a televisit. All adverse events associated with the use of the platform or medications taken were noted by the investigator.

2.3. Outcomes and measures

The level of improvement in the clinical status of patients associated with the use of the MONEO platform was measured by the percentage change in the total score obtained from the clinical assessment scales (see below) after 6 and 12 months, compared with that at the beginning of the study. The difference in the mean severity level of clinical symptoms was measured by the global score in the clinical scales listed below at the beginning and after 6 and 12 months of the study, within and between the study and placebo groups.

The assessment of the stability of the clinical status of patients in the study and placebo groups was expressed as the time elapsed to deterioration in clinical scale scores by at least 20%, compared with values recorded at the beginning of the study, within and between groups.

The following clinical scales were used to assess the clinical condition of the patients:

a. *the PANSS scale* for positive and negative schizophrenic symptoms (each of 30 items is rated from 1 to 7 according to increasing levels of psychopathology, where: 1 - absent, 7 - extreme).
b. *the Calgary scale* for affective symptoms (each of 9 items is rated from 0 to 3, where: 0 - absent, 3 - severe).
c. *the Clinical Global Impression – Severity* (*CGI-S*) *scale* for global clinical impression (1 item, rated from 1 to 7, where: 1 - normal, 7 - among the most extremely ill patients).

Analysis of clinical symptom dimensions of the PANSS scale, conducted both within and between the study and placebo groups, was based on the total number of points in each of the following subscales of the PANSS scale: positive symptoms (sum of P1-P7 items); negative symptoms (sum of N1-N7 items); symptoms of hostility/excitement (sum of P4, P7, O4, O8, and O14 items); symptoms of anxiety/depression (sum of O1-O3, O6, and O15 items); symptoms of disorganization (sum of P2, N5, O5, O10, O11, O13, and O15 items); and cognitive symptoms (sum of N5, O10, P2, P6, and N7 items).

The number of hospitalizations and visits to outpatient clinics was gathered directly from the MONEO platform. The total number of such incidents after 12 months of the trial was compared between the study and placebo groups.

The safety of the study protocol was assessed by the incidence of adverse effects associated with the use of the MONEO platform and was compared both within and between the study and placebo groups. The occurrence of adverse effects was determined by the investigators during televisits with the patients.

2.4. Statistical analysis

Final analysis was performed for all patients who completed the scheduled procedures throughout the study. Missing data were omitted without imputation. All statistical analyses were conducted using STATISTICA 10 (StatSoft) software. Continuous variables were described with the number of non-missing observations, arithmetic mean, standard deviation, median, quartiles, and range. Categorical variables were expressed with the number of non-missing observations and percentages. Univariate and multivariate statistical tests with repeated measurement for dependent groups were applied (Student's *t*-test, Wilcoxon test, ANOVA). For multivariate analysis measurements, post-hoc tests were applied (Tukey test, LSD test, Scheffe test, Games-Howell test). To counteract the problem of multiple comparisons, the Bonferroni correction was used (Dunn, 1961). All data were controlled for equality of variances and normal distribution. If these assumptions were not met, the Welch-type adjustments were used. To assess clinical stability, the number of hospitalizations and visits to outpatient clinics were compared between the study and placebo groups with McNemar's test and Cochran's Q ANOVA applied. A two-tailed *P* value ≤ 0.05 was considered statistically significant.

3. Results

3.1. Baseline patient characteristics

Initially, 300 patients were enrolled in the study. Due to lack of signed informed consent (n = 9) or signed consent for personal data processing (n = 1), 10 patients were excluded, giving a total n = 290 (study group = 199 and placebo group = 91). Fig. 1 shows the flow of patients throughout the study, and Table 1 shows baseline demographic and clinical characteristics of enrolled patients. All participants were Caucasian, the majority (60%) were male and the mean age was 32.1 years (standard deviation = 6.2, min = 19, max = 46).

3.2. Clinical outcomes

Changes in the clinical status of the patients within the study and placebo groups are listed in Table 2. After 12 months of the study, patients using the active version of the MONEO platform reported a significant reduction in both affective symptoms (by 36%, $P < 0.01$) and in the symptoms assessed with the PANSS scale (by 8.6%, $P < 0.05$), whereas the improvement of the clinical status (CGI-S scale) was not significant (3.4%, $P > 0.05$). Within the placebo group, the decrease in the symptoms was assessed as significant only when using the Calgary scale (23.6%, $P < 0.05$), and insignificant using the PANSS (10.8%, $P > 0.05$) and CGI-S (8.5%, $P > 0.05$) scales. The interactional effects between the study and placebo groups were significant only for the PANSS scale ($P < 0.05$).

To assess the stability of the patients, we compared their clinical symptoms measured every month throughout the study. Changes in clinical symptoms during the study (in both study and placebo groups) did not reach a critical 20% level on the CGI-S and PANSS scales, indicating the stability of the clinical condition of patients. Considering the study group, the initial results of the PANSS total score were significantly different from those obtained after the fifth, eleventh, and twelfth month of the study ($P < 0.05$). No significant differences between the study and the placebo group within all subsequent study periods were observed.

3.3. Clinical symptom dimensions

To further investigate the changes in the clinical status of patients during the study, we assessed the dimensions of the clinical symptoms given on the subscales of the PANSS score (Table 3). In the study group, the decrease in the symptoms was significant for positive symptoms, general psychopathology, excitement, depression, and disorganization subscales, while insignificant for negative and cognitive symptoms subscales. In the placebo group, only symptoms on the depression subscale declined significantly. The greatest improvement was observed in the depression subscale: symptoms of anxiety and depression were reduced by 11.2% after 12 months in the study group ($P < 0.05$) and by 16.2% in the placebo group ($P < 0.05$).

3.4. Frequency of hospitalizations and visits to outpatient clinics

Both the number of hospitalized patients and the length of hospitalization were similar between the study and placebo groups ($P > 0.05$). However, the number of analyzed cases was low (n = 20 and 8, for the study and placebo groups, respectively). No cases of hospitalization were related to the use of the MONEO platform. Similarly, the number of visits to outpatient clinics did not differ between the study and placebo groups (mean number of visits = 7.8 and 6.8 for the study and placebo groups, respectively [$P > 0.05$]).

3.5. Adherence to MONEO platform usage

The adherence to MONEO platform usage was defined as the number of patients who underwent visits by video call (the physician calls the patient) or as the number of the patients' visits to the outpatient clinic at the particular timepoints of the study. According to the schedule, the patients should undergo one obligatory video call visit every month and one obligatory visit to the outpatient clinic every three months. The data regarding patients' adherence for both study and placebo groups is shown in Table 4.

3.6. Safety data

During the study, a total of 63 adverse events were reported, of which 12 (19%) were related to pharmacotherapy. These events
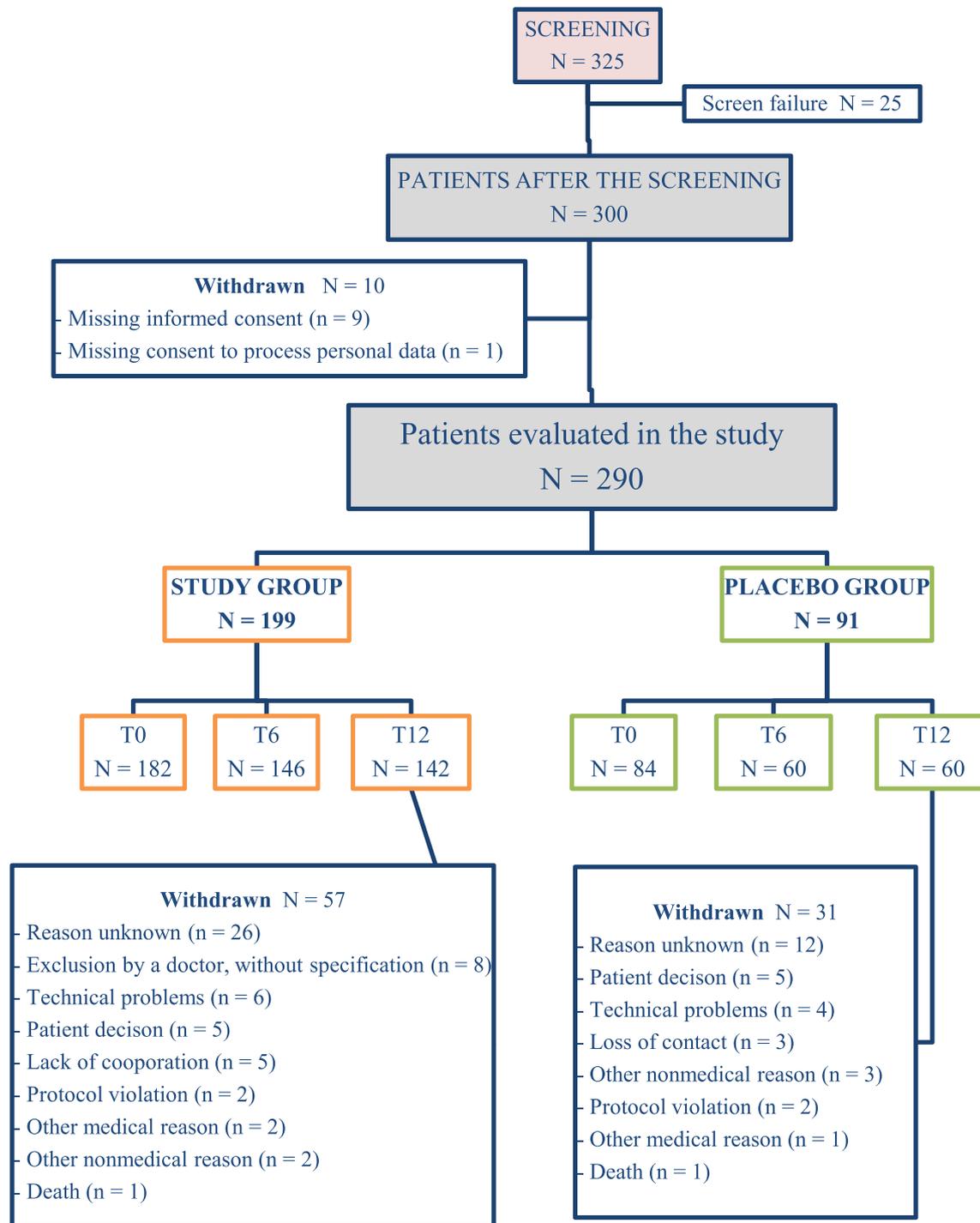
Fig. 1. Participant flow throughout the study. Changes in the analyzed population during 12 months of the study are illustrated, based on the number of patients who underwent visits to the doctor's office at baseline (T0), after 6 months (T6), and at the end of the study (after 12 months, T12).

occurred in 34 patients (11.7% of all patients). The study and placebo groups did not differ significantly with regard to the seriousness of the reported adverse cases or relationship of the cases to the smartphone device ($P > 0.05$). A total of seven cases were related to the device, of which four (2%) were observed in the study group and three (3.3%) in the placebo group (Table 5). The majority of device-related cases (5 of 7) were due to device failure. All adverse events related to the device are listed in Table 6. Reported adverse events coded in System Organ Class and in Preferred Term are listed in Table S1.

4. Discussion

The rapid increase in the availability of mobile phones, together with the growing popularity of telemedical services, presents an opportunity to develop a new, promising approach to treat schizophrenia patients using smartphone-based platforms. Regular monitoring of patients using a smartphone device might be beneficial not only for preventing relapse, but such monitoring allows for the possibility of conducting remote interventions which can improve patients' clinical outcomes, particularly when face-to-face access to a psychiatrist is restricted.

Table 1
Baseline demographic and clinical characteristics of the patients.

Characteristic	Study group (n = 199)	Placebo group (n = 91)	P
Mean age (years)	32.0 (5.92)	32.2 (6.94)	0.8
Sex - male	114 (57.3%)	60 (65.9%)	0.16
Race - Caucasian	199 (100%)	91 (100%)	1
Clinical status			
Total PANSS score	58.0 (20.3)	59.8 (23.7)	0.51
Calgary scale	4.0 (4.2)	3.4 (4.1)	0.26
CGI-S scale	2.7 (1.0)	2.7 (1.1)	1.0
PANSS subscales			
PANSS positive symptoms	12.8 (5.4)	12.3 (5.3)	0.46
PANSS negative symptoms	16.4 (7.8)	16.5 (6.6)	0.92
PANSS general psychopathology	30.6 (12.4)	30.2 (10.6)	0.79
PANSS excitement	8.8 (3.5)	8.9 (3.6)	0.82
PANSS depression	9.6 (4.2)	9.5 (3.9)	0.85
PANSS disorganization	14.0 (6.1)	13.2 (4.9)	0.27
PANSS cognitive symptoms	10.4 (4.7)	9.8 (3.9)	0.29

Data in parentheses show the percentage of patients, unless otherwise indicated. Age and clinical scale scores are presented as mean values with the standard deviation shown in parenthesis, alpha = 0.05.

The use of digital devices among 457 individuals with schizophrenia was recently assessed with a web-based survey by Gay et al. (2016). A great majority of respondents (411/457, 90%) declared access to at least two digital items such as computers, mobile phones, landline phones, or tablets. The devices were frequently used: as much as 89% of survey participants spent 1 h or more each day on a personal computer, and 85% on mobile phones. Respondents used the technology to deal with schizophrenia in several ways: to manage auditory hallucinations with audio files (42%), to seek information about mental health (38%), to be reminded about appointments (37%), to manage their treatment schedule (28%), to develop relationships with others living with schizophrenia (26%), to monitor symptoms (25%), and to identify coping strategies (24%). The MONEO platform, described in this study, addresses most of the aforementioned needs. In particular, it enables one to explore information about mental health and find coping strategies by providing access to the library of audiobooks and videos, it reminds patients about appointments and the necessity of taking medications, and it helps to control symptoms in a regular manner by facilitating medical televisits. Two-thirds of the respondents declared that digital technology will play a central role in their recovery in the near future, underlining the demand for the development of

telemedical tools dedicated to the management of schizophrenia (Gay et al., 2016).

Similarly to the general population, the ownership of mobile phones among people with schizophrenia is constantly increasing, and exceeded 80% in 2015 (Firth et al., 2016). More importantly, a large study of 1592 patients with severe mental illnesses revealed that 81% of those who owned a mobile phone expressed an interest in receiving mHealth support (Ben-Zeev et al., 2013). Smartphone technologies can provide convenient tools for self-monitoring, training, and facilitating patient's self-management of the disease (Luxton et al., 2011). Although availability of smartphones increases and their application in improving outcomes of patients with schizophrenia is promising, their implementation in clinical practice is still poorly supported by empirical evidence (Firth and Torous, 2015). The use of telemedicine devices (in particular videoconferences) in psychiatry has raised serious concerns, including a possible low acceptance rate of such virtual contact, among psychotic patients. However, recent studies showed that videoconferences are not only well-tolerated and accepted by patients (without deterioration of their psychotic symptoms) (Sharp et al., 2011), but also, in some cases, can be more beneficial than in-person consultations. The increased distance between patient and medical professional obtained via a videoconference was demonstrated to be less anxiety-provoking and minimized the risk of overstimulation (Magaletta et al., 2000).

Currently, research into telehealth technologies in patients with schizophrenia has focused mostly on interventions based on telephones, particularly smartphones, whereas studies considering Internet- and video-based approaches have largely been centered around the development of these platforms and the assessment of their feasibility, rather than the clinical management of patients themselves (Kasckow et al., 2014). The MONEO platform described in this study combines the advantages of all three modalities. Being a smartphone-based system, it enables one to hold videoconferences to remotely assess patient condition, and, similarly to Internet-based systems, it allows the patient to conduct cognitive training and self-educate using a library of available audiobooks and videos.

A wide range of possibilities offered by smartphones are being successfully utilized for management of schizophrenia. The ClinTouch application, described in 2012, serves as a platform to obtain self-assessment of psychiatric symptoms by PANSS and Calgary scales up to six times a day. The results delivered with the application were clinically meaningful and correlated with those obtained during face-to-face interviews (Palmier-Claus et al., 2012). The

Table 2
Change in the overall clinical status for all clinical scales considered (study and placebo groups).

Group	Clinical scale	Time	N	Mean (SD)	Difference (T0–T12)	Median (IQR)	Min-max	P (T0–T12)
Study	CGI-S	T0	165	2.7 (1.0)	−3.4%	3.0 (1.0)	1.0–5.0	0.38
		T6	166	2.5 (1.0)		2.0 (1.0)	1.0–6.0	
		T12	121	2.6 (0.9)		3.0 (1.0)	1.0–5.0	
	CALGARY	T0	174	4.0 (4.2)	−36.1%	3.0 (6.0)	0.0–20.0	**0.003**
		T6	170	2.6 (3.6)		1.0 (4.0)	0.0–20.0	
		T12	122	2.6 (3.4)		1.0 (4.0)	0.0–13.0	
	PANSS	T0	168	58.0 (20.3)	−8.6%	53.0 (32.5)	30.0–115.0	**0.035**
		T6	169	54.9 (20.9)		50.0 (32.0)	30.0–113.0	
		T12	122	53.0 (19.3)		49.0 (26.0)	30.0–122.0	
Placebo	CGI-S	T0	76	2.7 (1.1)	−8.5%	3.0 (1.0)	1.0–5.0	0.332
		T6	64	2.7 (1.2)		3.0 (2.0)	1.0–5.0	
		T12	46	2.5 (1.0)		2.0 (1.0)	1.0–5.0	
	CALGARY	T0	81	3.4 (4.1)	−23.6%	2.0 (5.0)	0.0–18.0	**0.048**
		T6	66	2.6 (3.2)		1.0 (4.0)	0.0–12.0	
		T12	46	2.6 (4.1)		0.0 (4.0)	0.0–14.0	
	PANSS	T0	79	59.8 (23.7)	−10.8%	55.0 (33.0)	30.0–129.0	0.123
		T6	65	57.5 (21.9)		54.0 (39.0)	30.0–106.0	
		T12	46	53.3 (20.6)		48.5 (36.0)	30.0–107.0	

N, number of observations; SD, standard deviation; IQR, interquartile range; T0, baseline; T6, after 6 months; T12, end of the study (after 12 months). Significant P values between T0–T12 are marked in bold, alpha = 0.05.

Table 3
Analysis of clinical symptoms using the PANSS subscales (study and placebo groups).

GROUP	PANSS subscale	Time	N	Mean (SD)	Difference (T0–T12)	Median (IQR)	Min-max	P (T0–T12)
Study	Positive symptoms	T0	170	12.2 (5.2)	−8.8%	11.0 (7.0)	7.0–28.0	**0.043**
		T12	122	11.1 (5.2)		9.0 (5.5)	7.0–30.0	
	Negative symptoms	T0	170	16.2 (6.5)	−7.6%	15.0 (11.0)	7.0–32.0	**0.0102**
		T12	122	15.0 (5.7)		14.0 (9.0)	7.0–30.0	
	General psychopathology	T0	168	29.6 (10.4)	−9.0%	27.0 (17.0)	16.0–60.0	**0.035**
		T12	122	27.0 (10.2)		24.0 (14.0)	16.0–62.0	
	Excitement	T0	168	8.7 (3.5)	−9.9%	8.0 (5.0)	5.0–19.0	**0.0308**
		T12	122	7.8 (3.3)		7.0 (4.0)	5.0–19.0	
	Depression	T0	168	9.4 (3.8)	−11.2%	9.0 (6.0)	5.0–21.0	**0.0124**
		T12	122	8.3 (3.5)		7.0 (6.0)	5.0–18.0	
	Disorganization	T0	168	13.0 (4.8)	−7.3%	12.0 (7.5)	7.0–30.0	**0.0471**
		T12	122	12.1 (4.9)		11.0 (7.0)	7.0–31.0	
	Cognitive symptoms	T0	168	9.7 (3.8)	−7.1%	8.5 (6.0)	5.0–21.0	0.118
		T12	122	9.0 (3.7)		8.0 (5.0)	5.0–23.0	
Placebo	Positive symptoms	T0	79	12.8 (5.4)	−13.4%	11.0 (8.0)	7.0–27.0	0.069
		T12	46	11.1 (4.2)		9.5 (7.0)	7.0–21.0	
	Negative symptoms	T0	79	16.4 (7.8)	−10.2%	16.0 (13.0)	7.0–35.0	0.247
		T12	46	14.8 (6.7)		14.0 (9.0)	7.0–31.0	
	General psychopathology	T0	79	30.6 (12.4)	−10.0%	28.0 (16.0)	16.0–71.0	0.166
		T12	46	27.5 (11.3)		26.0 (16.0)	16.0–58.0	
	Excitement	T0	79	8.8 (3.5)	−7.0%	8.0 (5.0)	5.0–18.0	0.352
		T12	46	8.2 (3.4)		7.0 (6.0)	5.0–18.0	
	Depression	T0	79	9.6 (4.2)	−16.2%	8.0 (6.0)	5.0–24.0	**0.033**
		T12	46	8.0 (3.6)		6.5 (6.0)	5.0–18.0	
	Disorganization	T0	79	14.0 (6.1)	−11.1%	12.0 (10.0)	7.0–30.0	0.169
		T12	46	12.5 (5.4)		11.0 (10.0)	7.0–25.0	
	Cognitive symptoms	T0	79	10.4 (4.7)	−12.8%	9.0 (7.0)	5.0–22.0	0.116
		T12	46	9.1 (3.9)		8.5 (7.0)	5.0–19.0	

N, number of observations; SD, standard deviation; IQR, interquartile range; T0, baseline; T6, after 6 months; T12, end of the study (after 12 months). Significant *P* values between T0–T12 are marked in bold, alpha = 0.05.

feasibility of smartphone-based applications for individuals with schizophrenia, which were superior to those of conventional mobile phones, was demonstrated by Ainsworth et al.; participants completed application-based surveys faster and more often than surveys provided by text-message platform (Ainsworth et al., 2013). The FOCUS application, on the other hand, offers several tools that support the self-management of schizophrenia addressing medication adherence, social functioning, mood problems, auditory hallucinations, and sleep difficulties (Ben-Zeev et al., 2014). The application offers an individualized intervention based on results of the survey completed by the patient. Naslund et al. provided evidence that a smartphone-based, physical activity-tracking Fitbit application, designed for the general population, is both feasible and well-accepted by individuals with serious mental disorders, including schizophrenia (Naslund et al., 2015). Another smartphone application, WellWave, aims to promote physical well-being in adults with psychiatric disorders by encouraging mild physical exercise and offering the possibility of confidential text-messaging with program staff and access to a library of motivational ebooks and videos. It was proven to engage participants in physical activity and other activities that promote a healthy lifestyle, with a 73% mean response rate across all sent messages (Macias et al., 2015). Recently the Actissist application was proven to be feasible, acceptable, and safe in a randomized, controlled trial with early psychosis patients (Bucci et al., 2018). The application enables the patient to complete

a self-assessment set of questions, and, based on its results, it provides the patient with a range of activities such as mindfulness exercises, educational videos, fact sheets, and external links, designed to alleviate psychotic symptoms, as well as emergency contact resources. The graphical summary of weekly activities supports the patient in self-assessment of symptoms and may contribute to decision-making regarding treatment (Bucci et al., 2018).

The adherence to smartphone applications among patients with schizophrenia and other psychiatric disorders varied between 69% and 94% of all days or possible entries (Firth and Torous, 2015). This percentage, although obtained for short-term observations, is in agreement with the adherence data gathered for the 12-month study on the MONEO platform, which ranged from 61% to 85%.

In this study, we demonstrated that the clinical condition of 199 patients with schizophrenia using a smartphone-based MONEO platform was stable throughout a 1-year trial. Moreover, we showed that patients using the full version of the MONEO platform exhibited a pronounced reduction in the schizophrenic symptoms assessed using the Calgary

Table 4
Adherence to telemedical treatment with the MONEO platform throughout the study assessed as a number of completed video call visits.

Timepoint	Study group N = 199	Placebo group N = 91
T0	170 (85%)	79 (87%)
T6	169 (85%)	65 (71%)
T12	122 (61%)	46 (51%)

T0, baseline; T6, after 6 months; T12, end of the study (after 12 months).

Table 5
Characteristics of adverse events (excluding those related to pharmacotherapy) reported during the 12 months of the study.

	Study group (N = 199)	Placebo group (N = 91)	Overall (N = 290)
Seriousness			
Not serious	9 (4.5%)	3 (3.3%)	12 (4.1%)
Serious	33 (16.6%)	6 (6.6%)	39 (13.4%)
Relatedness to device			
Related	4 (2.0%)	3 (3.3%)	7 (2.4%)
Not related	39 (19.6%)	6 (6.6%)	45 (15.5%)
Subject outcome			
Recovered/resolved	38 (19.1%)	4 (4.4%)	42 (14.5%)
Not recovered/resolved	1 (0.5%)	0 (0%)	1 (0.3%)
On-going	0 (0%)	3 (3.3%)	3 (1.0%)
Death	1 (0.5%)	0 (0%)	1 (0.3%)
Unknown	22 (1.0%)	2 (2.2%)	4 (1.4%)

Table 6
Description of all cases of adverse events related to the smartphone device tested, reported during the 12 months of the study.

System organ class	Preferred term	Study group (N = 199)	Placebo group (N = 91)	Overall (N = 290)
General disorders and administration site conditions	*Device failure*	1.5% (n = 3)	2.2% (n = 2)	1.7% (n = 5)
Psychiatric disorders	*Irritability*	0.0% (n = 0)	1.1% (n = 1)	0.3% (n = 1)
NS	*NA*	0.5% (n = 1)	0.0% (n = 0)	0.3% (n = 1)
Expectedness according to protocol		2.0% (n = 4)	3.3% (n = 3)	2.4% (n = 7)

N, number of observations; NS, not specified; NA, not applicable.

and PANSS scales, whereas such improvement was weaker and statistically significant only when assessed using the Calgary scale, considering those individuals supplied with an inactive version of the software (placebo group). Analysis of symptom dimensions on the PANSS scale revealed that the study group improved significantly in 5 out of 7 subscales, while the reduction of symptoms within the placebo group reached statistical significance only for the depression subscale. Both study and placebo groups consisted of patients in the state of symptomatic remission. Therefore, observed slight however statistically significant improvement is indicative of a clinically pronounced reduction of symptoms toward further normalization of a psychic state and complete functional recovery.

Use of the MONEO platform did not influence the rate of hospitalization and visits to outpatient clinics. This may be because the population under study was young and only displayed mild symptoms of the illness. Additionally, the stability of the patients demonstrated here in the study suggests the potential of the MONEO platform in preventing considerable deterioration of symptoms. The MONEO platform was safe, with the frequency of adverse events in the study group being similar to that observed in the placebo group, as well as that detailed in other reports (Frangou et al., 2005; Salzer et al., 2004; Spaniel et al., 2008).

One of the concerns regarding telemedical platforms is their possible implementation in middle-aged or elderly patients with limited technical abilities. This issue seems to be particularly relevant for individuals with serious mental illnesses, who may additionally experience reduced cognitive functions. Therefore, our study was conducted on a group of young patients aged between 18 and 45 years. However, Whiteman et al. provided evidence that a smartphone-based platform could be successfully adapted to meet the needs of older patients (Whiteman et al., 2017).

The present study does, however, have certain limitations. Several centers recruited only 1 patient, which could result in bias regarding patient care. No data regarding the patients' pharmacotherapy were provided, which might have been useful when assessing symptom improvement. One of the secondary endpoints could not be fully analyzed as patients refused to disclose data regarding their hospitalizations in the 12 months prior to the commencement of the study. Finally, although the improvement in clinical status was generally higher in the study vs the placebo group, only one significant difference between the groups was shown.

5. Conclusions

The MONEO platform was demonstrated to positively influence the clinical condition of individuals with paranoid schizophrenia. The results obtained demonstrated both the stability of the patients and the lack of negative consequences associated with use of the smartphone device. As improvement was achieved in both the study and placebo groups, it might be hypothesized that possession of the device, irrespective of its functionality, provided the patients with a feeling of safety, contributing to the reduction of their symptoms. Therefore, to further examine the potential of the MONEO platform, it would be pertinent to compare patients using the device with those who do not have access to it at all.

Conflict of interest
All authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.08.016.

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