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A model for continuous monitoring of patients with major depression in short and long term periods

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Abstract

Background and objective: Major depressive disorder causes more human suffering than any other disease affecting humankind. It has a high prevalence and it is predicted that it will be among the three leading causes of disease burden by 2030. The prevalence of depression, all of its social and personal costs, and its recurrent characteristics, put heavy constraints on the ability of the public healthcare system to provide sufficient support for patients with depression. In this research, a model for continuous monitoring and tracking of depression in both short-term and long-term periods is presented. This model is based on a new qualitative reasoning approach.

Method: This paper describes the patient assessment unit of a major depression monitoring system that has three modules: a patient progress module, based on a qualitative reasoning model; an analysis module, based on expert knowledge and a rules-based system; and the communication module. These modules base their reasoning mainly on data of the patient's mood and life events that are obtained from the patient's responses to specific questionnaires (PHQ-9, M.I.N.I. and Brugha). The patient assessment unit provides synthetic and useful information for both patients and physicians, keeps them informed of the progress of patients, and alerts them in the case of necessity.

Results: A set of hypothetical patients has been defined based on clinically possible cases in order to perform a complete scenario evaluation. The results that have been verified by psychiatrists suggest the utility of the platform.

Conclusion: The proposed major depression monitoring system takes advantage of current technologies and facilitates more frequent follow-up of the progress of patients during their home stay after being diagnosed with depression by a psychiatrist.

Keywords: Major depressive disorder, Remote monitoring system, Rule-base system, Qualitative reasoning

1. Introduction

Major depression is one of the most common psychiatric disorders present in the general population, with a lifetime prevalence of 12.8%, and 12-month prevalence range between 3.6% and 9.1% in Europe. The Global burden of disease study has identified depression as one of the leading causes of Years Lived with Disability (YLD) and Disability Adjusted Life Years (DALYs), emphasizing the importance of non-fatal health outcomes in the quantification of disease burden [1].

The cost of depression presents a growing economic burden on European society. It has become a major concern for European economic welfare that has consequences for healthcare providers and policy makers. In 2004, the total annual cost of depression in Europe was estimated at 118 billion Euros, making it the most costly brain disorder in Europe [2]. The cost of depression in Asia is also a huge economic burden. The mean annual total cost per depressed patient in 2008 was 7638 US dollars in Singapore, a developed country in Asia [3].

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Depression is treatable. The current response rate to antidepressants is between 62% to 67% [4], and patients show improvement in depressive symptoms by the end of the first week of use [5]. However 60% of people with depressive disorder do not receive any kind of healthcare for this condition [6], and most of those who manifest a need for care are treated by a general practitioner (GP) [7, 8]. According to most of the clinical practice guidelines, the monitoring of patients should be close, at least during the first 4 weeks, then monthly or every 2 months. Many GPs work under extreme pressure and limited time for patients has been identified in the literature as a barrier to good assessments and treatment [9-11].

Half of people experiencing a first episode of depression will develop chronic or recurrent depressive disorder and will spend more than 20% of their life in the depressive condition [12]. Most patients will eventually experience either a relapse (another depressive episode within 6 months after response) or recurrence (another depressive episode 6 months or more after recovery), if followed over a long enough period without sustained treatment. If followed over a 15-year period, almost 90% of patients could be expected to become depressed again after experiencing an acute depressive episode [13].

As stated above, depression is the most prevalent mental disorder. It has a high tendency for relapse and recurrence, is one of the leading causes of YLD, and creates a growing economic burden on healthcare systems. For all this, depression has become a global public health concern and strategic efforts are needed to manage this challenge and provide the best care to meet the needs of patients suffering from depression.

Advances in communication and information technologies have raised expectations for healthcare. As stated by Zhang and Ho, Electronic health (E-health) is an efficient way to deliver healthcare services which allow interaction with patients via internet, smartphone and text message technology [14].

Beating the Blues, in the UK [15], and MoodGym, in Australia [16], are two examples of evidence-based treatment programs already in place for mild to moderate depression. As far as we know, there is no tool currently being used to track the changes of short-term and long-term progress in patients with depression, even though the widespread use of mobile phones and computers make continuous remote follow-up of the patient completely feasible.

The goal of this paper is to present a model for continuous monitoring and tracking of depression in patients, throughout the short-term and long-term treatment process. The proposed major depression monitoring system facilitates a more frequent follow-up of patient progress during their home stay after being diagnosed with depression by a psychiatrist. It is important to make clear that this model does not intend to substitute the physician or the psychiatrist, but rather it gives extended information about the changes suffered in patients, which doctors do not usually have access to due to the infrequency of visits they are able to make with each patient in relation to clinical assistance pressure that Public Health Systems often suffer.

2. Computer Methods and Major Depression

Different computer methods are applied to different types of depression problems with diverse goals. In this section we try to summarize some of these studies focusing mainly on major depression.

The first group of studies is mostly concerned with the problem of diagnosis of depression type and severity, trying to provide different automatic diagnosis tools or classification techniques for these diagnoses [17-22]. There are also some studies in this group focused on evaluating and improving the diagnostic and therapeutic reasoning of primary care physicians [23]. The second group of studies tries to solve the problem of monitoring treatment efficiency in different treatment types, such as pharmacological or Cognitive Behavioral Therapy (CBT) and individualized therapy [24-26]. The third and smaller group of studies focuses on the recurrent nature of depression, either predicting relapse or providing support to prevent relapse and recurrence of depression symptoms.

Aziz et al. designed and developed an ambient agent system to support relapse prevention and early alerting of recurrence of unipolar depression based on the collected data from sensors and questionnaires [27]. The domain model is based on several personal characteristics and a

representation of events (i.e., life events or daily hassles). The proposed model has been tested by several simulation experiments, but there is still a lack of experimentation in real world conditions.

Empath is a comprehensive real-time home depression monitoring system that aimed to provide caregivers with more accurate and thorough information about the client's current functioning, thus helping in their diagnostic assessment and therapeutic treatment planning [28]. It also helps patients in the management and tracking of their symptoms. Empath incorporates factors such as speech, sleep, weight, and movement and is designed for home monitoring of people who live alone. It has been tested by way of a case study, but further investigations are needed.

A project related to depression monitoring and similar to Empath was set up by MIT and Mass General Hospital using their LiveNet system [29]. LiveNet is able to collect similar behavioral features as Empath, however it requires costly mobile physiologic sensing technology and is not designed for daily home monitoring since it monitors patient response to electroconvulsive therapy in a hospital setting. Optimisim App is another application that is designed for bipolar patients but is customizable for other mental disorders as well [30]. Optimisim's main goal is to actively involve patients in their treatment by providing an environment for self-reporting many factors as well as follow-up charts and reports.

However, it does not provide reasoning or diagnosis based on the collected information; instead it mainly focuses on representation of collected information in synthetic and interpretable form.

ICT4 Depression is a European project that has already been completed in which a mobile solution for the treatment of depression, called Moodbuster, has been developed [31]. The research done in this project is closely related to our work. Moodbuster integrates different data from mobile phone apps, physiological sensors, the adherence monitor which is accelerated every time a patient opens and closes the drug container, and a website with different tools and self-management modules that have been shown to be effective in face-to-face and internet-based treatments. It has a reasoning module that translates sensor information and patient provided information together into therapy information. However, the cost would not be negligible if the proposed approach is to be available to and used by a large number of patients, that is any patient who suffers major depression.

In summary, despite the recognized magnitude of the problem of recurrence and relapse in depression patients, little attention has been focused on applying low cost technologies to find patterns in patients' progress in order to provide the necessary support in the early stages and prevent further development of depressive symptoms. Accordingly, one major possible effort towards reducing the disabling effects of depression could be a shift toward preventing the recurrence of it, especially in patients with a high risk of recurrence.

3. Methods

As mentioned before, little work exists on the development of monitoring systems that goes beyond the compilation of data streaming from sensors, questionnaires, and clinical registers, and that give basic medical feedback to patients and doctors based on the collected data. Our research is centered on the design and development of a major depression remote monitoring system that performs an automatic assessment on the progress of the patient on a short-term. The architecture of the proposed approach is presented in Figure 1. It is composed of the Patient Assessment Unit (PAU) and the Communication Module (CM).

The goal of the PAU is to follow the progress of the patient in the short-term, during their recovery, in order to understand their behavior and give advice to patients, psychiatrists, and primary care physicians. The Communication Module (CM), communicates between the monitoring system and the actors involved by means of mobile phones, computers, and/or tablets.

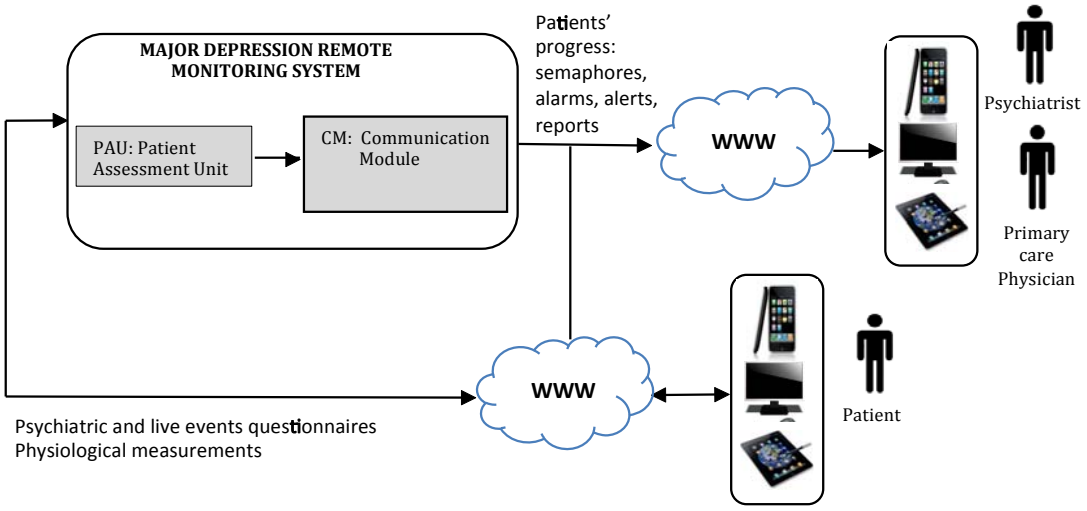

Fig. 1 Architecture of the major depression monitoring system

This paper is focused mainly on the PAU, which is a key element of the major depression monitoring system and that is based on a new qualitative reasoning approach. The qualitative reasoning process proposed in this research can be applied to other systems, not necessarily in the field of medicine, which have similar behaviour characteristics to the system discussed in this article. Before going through the description of the PAU it is necessary to briefly describe major depression characteristics. It is now generally recognized that depression is a multifactor disorder characterized by phenotypic heterogeneity and having complex genetic, experiential, and developmental causes [32].

Major depressive disorder is a medical condition characterised by depressed mood and/or loss of pleasure in most activities [33]. Five of the nine following symptoms have to be experienced by the patient in order to be diagnosed as MDD: significant weight change (5%) or change in appetite, change in sleep patterns (insomnia or hypersomnia), change in activity (psychomotor agitation or retardation), fatigue or loss of energy, cognition abnormalities (such as inappropriate guilt and feelings of worthlessness), diminished ability to think or concentrate, more indecisiveness, and/or suicide thoughts or plans. Symptoms must persist throughout most of the day, be present nearly every day for at least two consecutive weeks, and produce a significant impairment to the patient's daily life. To count toward a major depressive disorder, symptoms must be newly present or must have clearly worsened compared with the patient's pre-episode status.

As described in Figure 2, PAU receives the following information (input data): the clinical data of the patient (personal information and clinical history); the patient's mood and life events that are obtained from the patient's responses to specific questionnaires (PHQ-9, M.I.N.I. and Brugha); and physiological data obtained from weight, sleep, and movement changes. The CM is responsible for scheduling patients' measurements and transmitting the results of PAU to the actors involved.

The PHQ-9 is a depression assessment measure, which scores each of the 9 diagnosis criteria of this mental disorder. The questionnaire is designed to assess the patient's mood over the last 2 weeks [34]. It has been suggested that scores between 0 and 4 reveal minimal depressive symptoms; scores between 5 and 9 reveal mild symptoms; scores between 10 and 14 reveal moderate symptoms; scores between 15 and 19 reveal moderately severe symptoms; and scores between 20 and 27 reveal severe depressive symptoms. Several studies support its validity, feasibility, and its capacity to detect changes of depressive symptoms over time [35-36]. It has also been proven that reliable results can be obtained even when this questionnaire is conducted over the telephone [37].

The Brugha questionnaire is a self-reporting questionnaire that examines the incidence of 12 categories of negative life events over the last 6 months [38]. The questionnaire assesses life

stressors which pose medium or long-term threats such as illness or injury, the death of a close friend or relative, unemployment, financial loss, and loss of important relationships. The use of this questionnaire in our system is to help understand certain variations in patient progress that would be inexplicable without such information.

The Mini-International Neuropsychiatric Interview (M.I.N.I.) is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe. The M.I.N.I. has two goals: first, to meet the need for a short but accurate structured psychiatric interview for multi-center clinical trials and epidemiology studies, and second, as a first step in outcome tracking in non-research clinical settings [39]. In this research we only use the M.I.N.I. suicide risk questionnaire in order to detect suicidal intentions when a patient gives the highest value to question 9 of PHQ-9 (i.e., thoughts that you would be better off dead or of hurting yourself in some way).

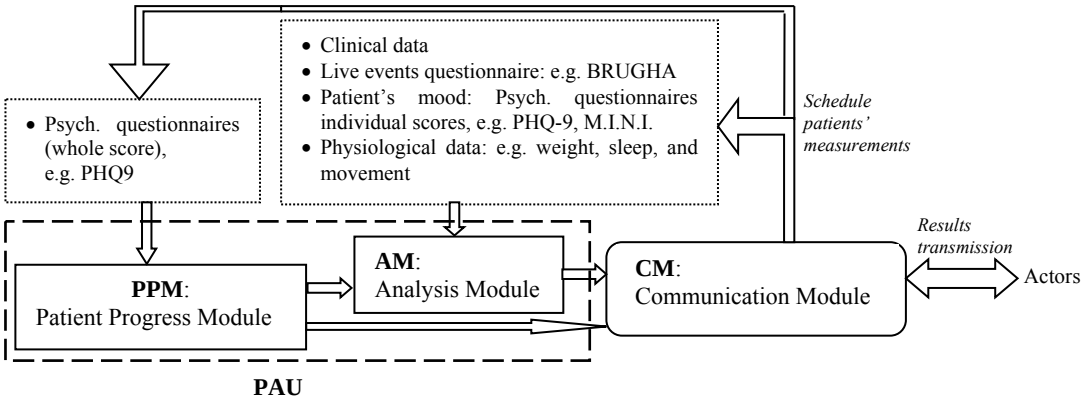

Fig. 2 Patient assessment unit (PAU), composed of the Patient Progress Module (PPM) and the Analysis Module (AM). The Communication Module (CM) is also included to show the transmission of the information from the PAU to the actors involved and vice versa

It is important to note that this research strictly follows the established mental health guidelines of the Institute for Clinical System Improvement (ICIS) [40] and tries to follow the standardized interface terminology, the Omaha system, developed for these guidelines [41].

PAU processes these inputs by using two modules: the Patient Progress Module (PPM), based on a qualitative reasoning model and the Analysis Module (AM), based on expert knowledge and a rules-based system. Outside the PAU, the Communication Module (CM) provides the required information to patients, primary care physicians, and psychiatrists, as shown in Figure 2.

PPM allows for tracking the progress of patients during a short-term basis (15 days) in order to characterize their reestablishment to the mental health pattern. PPM is centered on the overall rate of the PHQ-9 questionnaire. AM defines a framework for assessing both the process of healing and the patient's risk/hazard level for each stage of treatment, starting from the input data described before and the short-term patient progress status, which is the output of PPM (see Figure 2). The use of the word "risk" here refers to the possibility of the patients to get worse clinically, and has nothing to do with the risk of not taking the medication. CM has two responsibilities. The first responsibility is to schedule the registration of the patient's data every 2 weeks and make it available to the rest of the PAU modules; second it is responsible for sorting the risk data derived from AM and providing adequate information to the different actors involved in the treatment process, which are the patient, primary care physicians, and psychiatrists.

PAU's dynamic works as follows, every 2 weeks the PHQ-9 is administrated to the patient and he/she is asked about possible negative life events that have occurred during this time period. If needed, patients are assessed using the Brugha and/or the M.I.N.I. questionnaires to obtain extra information related to life events and the risk of suicide, as explained before. Then

the patient responds few questions related to weight, sleep, and movement general changes; with respect to the last time the patient was questioned.

The PHQ-9 data are given to the PPM, which produces information of the patient's progress as an output. This information, together with the rest of the data gathered from the patient, is used by the AM to perform the reasoning and give feedback to the actors involved in the healing process. The details of the PPM, AM, and CM are given below.

3.1. Patient Progress Module

The challenge of developing a model that would be capable of capturing all of the possible patient's progress patterns is of major concern. PPM is based solely on the overall rate of the PHQ-9 questionnaire. A PPM model based on each individual question of the PHQ-9 does not make sense at this point, because only the PHQ-9 as a whole is an instrument for clinically measuring the depression level. This statement is based on the guidelines established for depression management by the Macarthur Foundation Initiative on Depression and Primary Care [42].

In order to have as much information as possible, patients should be asked to answer the questionnaire every 2 weeks. A set of three PHQ-9 measures is used, corresponding to a period of 1 month, in order to omit normal mood fluctuations. The qualitative model is designed in a way that omitting these normal fluctuations does not lead to a loss of important information in providing alarms. This idea is shown in Figure 3.

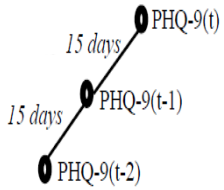

Fig. 3 Period used by the PPM to evaluate short-term progress of the patient. Three PHQ-9 measures: at present time (t), 15 days ago (t-1), and 1 month ago (t-2), are taken into account in the model.

There are two situations where it is mandatory to use only two measures. The first one corresponds to the initial period, when the patient has answered the questionnaire only two times since the follow-up began. In this case, the PPM gives feedback to the actors involved in the treatment process using the information registered during these two weeks. The second situation occurs when the patient does not answer the questionnaire at the time required. Under these circumstances, the time period between one measure and the next, that is when the patient answers the questionnaire again, might be very long. In this case, the measures are not symmetric from the time point of view and the ante-penultimate measure loses its relevance. Therefore, the best strategy is to use only the last two measures and take into account the time elapsed between them.

To characterize patients' dynamic responses to treatment, three main variables are used to define each state of change in status. These three variables are direction, velocity, and quality of change. The direction describes the tendency of the patient's changes in the PHQ-9 measures and it is discretized into three classes: worsening, improvement, and without changes (stuck). The velocity describes the speed of the patient's PHQ-9 changes and is also discretized into three classes: quick, slow, and normal. Finally, the quality of change describes the shape and has three possible representations: maintained, intuited, and oscillated. Figure 4 describes the meaning of the three classes of both direction and quality of change variables.

As is shown in Figure 4: *maintained* means the direction (without changes, worsening, or improvement) is continuous during the period analyzed, that is the direction is the same in consecutive PHQ-9 measurements pairs; *intuited* means there is an overall worsening or improvement but the direction is not kept in consecutive measurements pairs; and *oscillated* means that the direction of the first measurement pair is the opposite of the direction of the second pair.

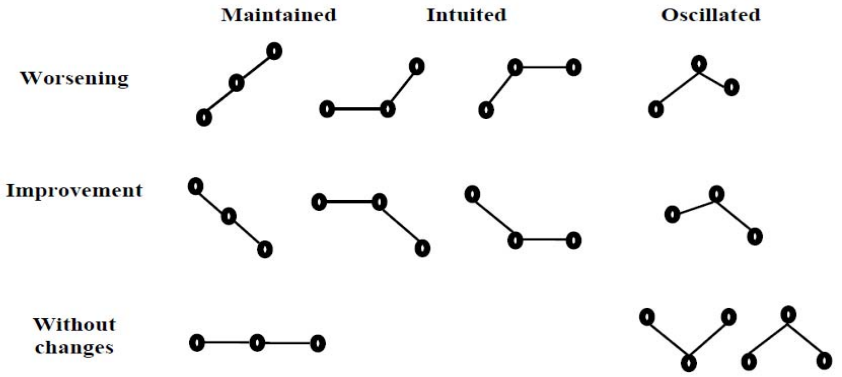

Fig. 4 Possible patient progress patterns for direction and quality of change variables.

The velocity is defined by means of five constants (k_1 to k_5), that represent the change of PHQ-9 values between times (t) and (t-2) (see Figure 3), which are quantified based on expert knowledge from psychiatrists. The minimal change value considered clinically significant in terms of PHQ-9 is k_1. A patient responding the questionnaire twice in the same day could have a slightly different overall rate of PHQ-9 each time. These small variations in PHQ-9 answers are filtered by k_1. Constants k_2 and k_3 represent an improvement in the depression level and correspond to a normal and fast improvement from a psychiatric perspective, respectively. Constants k_4 and k_5 represent a worsening in the depression level and correspond to a normal and fast worsening, respectively. If we define Δ= PHQ-9(t-2) - PHQ-9(t), then the slow class is characterized by the equations $k_1 < |\Delta| \leq k_2$ for improvement and $k_1 < |\Delta| \leq k_4$ for worsening; the normal class by $k_2 < |\Delta| \leq k_3$ for improvement and $k_4 < |\Delta| \leq k_5$ for worsening; and the quick class by $|\Delta| > k_3$ for improvement and $|\Delta| > k_5$ for worsening. These constants represent monthly rates. In cases, as mentioned earlier, where only two measures are taken into account, these constants are proportionally adjusted.

The different progress patterns shown in Figure 4, combined with the velocity variable, form the short term PPM composed of 20 rules. Table 1 presents an example of 2 of these rules that conform to the PPM. The terms $\Delta 1$ and $\Delta 2$ are defined as $\Delta 1$= PHQ-9(t-1) - PHQ-9(t) and $\Delta 2$= PHQ-9(t-2) - PHQ-9(t-1).

TABLE 1 AN EXAMPLE OF TWO RULES THAT COMPOSE THE PPM

IF ($\Delta > k_1$) **AND** ($\|\Delta\| > k_3$) **AND** ($\Delta_1 \cdot \Delta_2 < 0$) **THEN** patient's progress is: *improving quickly in an oscillation manner*
IF ($-k_1 \leq \Delta \leq k_1$) **AND** ($\Delta_1.\Delta_2 > 0 \vee (\|\Delta_1\| \leq k_1 \wedge \|\Delta_2\| \leq k_1)$) **THEN** patient's progress is: *no changes in a maintained form*

Therefore, the output of the PPM is a description of the patient's progress in terms of the values of each previous variable: direction, velocity, and quality of change. An important feature of this module is its ability to dynamically self-adjust the interpretation of the patient's progress depending on the different stages of treatment.

According to medical literature related to MDD's response to medication [43], there are four treatment stages: *initial*, *partial response*, *response*, and *remission*, which are defined by the patient's progress behavior. The *initial* stage is the period of time in which there is no evidence that the treatment is acting. In the *partial response* stage the antidepressant starts functioning, but a reduction of 50% of the severity of symptoms' on the depression scale (i.e. PHQ-9) is not yet reached. The *response* stage is reached when there is a reduction of 50%, suggesting that there is a response to medication. Finally, the *remission* phase starts when the patient is asymptomatic (i.e. no longer meets syndromal criteria for MDD and has no more than minimal symptoms). When reaching this phase the patients should continue taking the antidepressant for 6 months to 1 year. In this study, in order to capture patients' progress behaviors more precisely, we have extended the number of treatment stages to eight, in such a way that the new stages are

based on the original four. The eight stages used in this research are called: IN for *INitial*, PR for *Partial Response*, CR for *Consolidated Response*, RC for *Remission Continuation*, RP for *RelaPse*, RM for *Remission Maintenance*, and RV for *RecoVery*.

IN corresponds to the original *initial* stage, PR to the *partial response* stage, CR to the *response* stage, and RC and RM to the *remission* stage. RP represents the stage when the patient gets significantly worse after the *response* stage. This might indicate the initiation of a relapse. Therefore, the stage will not change until the patient starts improving. Finally, RV stage is reached when, over more than 43 weeks, a patient's PHQ-9 overall rate is less than k_n (k_n is a constant, set by experts, that defines the normal range of PHQ-9).

PPM is able to characterize these stages using the patient progress rules described before and interpreting the rules appropriately in each phase. For example, the second rule described in Table 1 has two different interpretations in the IN (initial) and CR (consolidated response) stages. If the patient is in the IN stage a *"no changes in a maintained form"* behavior might be reasonable since it might take some time for the treatment to start functioning. Therefore, a green light is set. However, *"no changes in a maintained form"* is not a desirable behavior when the patient is in the CR stage. In this case, a yellow light is chosen to alert primary care physicians and psychiatrists of this fact. Each rule used by the PPM has been discussed and evaluated with the psychiatrists of Parc Sanitari Sant Joan de Déu and each constant value has been defined following their advice.

3.2. Analysis Module

The AM is a rule-based model that processes a set of heterogeneous information related to the patient with the goal of monitoring and assessing the process of the patient's healing. It should present the information to the actors involved in an intuitive way that does not require too much interpretation time. To meet these requirements, the output of the AM is designed to provide synthesized visual information, and relevant and detailed information of the reasoning or analysis process. Such information will not only be very helpful for both doctor and patient, it will also be essential to facilitate the psychiatrist's decision making. The set of heterogeneous information that the AM requires during the reasoning process is the following:

- Progress of the patient state (i.e. the inferred rules obtained by PPM),
- Incidence of new major stressful life events (i.e. Brugha questionnaire),
- Significant variations in the physiological data (i.e. sleep, weight, and movement sensors),
- Preexistence of alarms in the past weeks,
- Number of weeks passed from the beginning of the medication,
- Clinical history of patients regarding to prior suicide attempt or prior recurrence or relapse,
- Continuous high risk response to persistent suicidal thoughts (i.e. question 9 of PHQ-9 questionnaire and MINI's suicide section).

The AM's rules system processes this set of inputs in order to establish the effectiveness of the patient's treatment. AM produces two levels of conclusions: first it provides a classification that, in a very synthetic way, warns if the treatment progresses successfully, if the progress is non-satisfactory, or if the treatment is failing or has a high risk of failure; second it stores information about the rules that have been shot in the reasoning process and that allow an explanation of the above classification. This information allows the CM to provide feedback to stakeholders.

Table 2 shows examples of three rules used in the AM reasoning's processes based on a combination of the heterogeneous information sources available. The concepts of Semaphore, AM_Assessment, and Message that appear in the consequent rules are explained in the CM section in detail.

TABLE 2 AN EXAMPLE OF THREE RULES THAT COMPOSE THE AM

IF (PPM is *no changes in a maintained form*) **AND** (PHASE is *initial*) **AND** (MEDICATION_WEEK < 4) **AND not** (Brugha_change) **AND** (suicide_thaught is *low*) **AND not** (physiological_data_variation) **AND not** (prior_recurrence) **AND not** (prior_relapse) **THEN** Semaphore is *green* **AND** AM_Assessment is *alert* **AND** Message is *waiting for medication to be effective*
IF (PPM is *no changes in a maintained form*) **AND** (PHASE is *initial*) **AND** (MEDICATION_WEEK > 4) **AND not** (Brugha_change) **AND** (suicide_thaught is *low*) **AND not** (physiological_data_variation) **AND not** (prior_recurrence) **AND not** (prior_relapse) **THEN** Semaphore is *yellow* **AND** AM_Assessment is *alert* **AND** Message is *medication most probably is not effective*
IF (PPM is *no changes in a maintained form*) **AND** (PHASE is *response*) **AND** (MEDICATION_WEEK < 54) **AND not** (Brugha_change) **AND** (suicide_thaught is *low*) **AND not** (physiological_data_variation) **AND not** (prior_recurrence) **AND not** (prior_relapse) **THEN** Semaphore is *green* **AND** AM_Assessment is *alert* **AND** Message is *no change*

Every 2 weeks patient's information is updated (scheduled by the CM) and a short-term analysis of the patient's state is performed by the PPM and AM. The results of the analysis are sent to the CM (communication module) which prepares and sends the appropriate messages and alarms to the involved actors (see Figure 2). The system is robust in order to deal with those situations where no data are registered on time, such as the patient not answering the questionnaires when required or the system being unable to save the data that were generated, etc. In these cases, the PPM is able to perform a 2-point reasoning as described before, and the AM sends an alarm to the physicians indicating that the patient is not being assessed by the major depression monitoring system.

3.3. Communication Module

The CM is responsible for scheduling the registration of patient's data every 2 weeks, making the data available to the rest of the PAU modules, and transmitting the results of the monitoring process to those actors who are involved in the healing process, that is physicians, psychiatrists, and patients. As shown in Figure 5, this module provides four hierarchies of communication: semaphore, alerts, reports, and alarms. The highest level of the hierarchy, the semaphore, is visible for all actors involved in the system. A green light means that the patient is progressing adequately, indicating to the physicians that no further action is needed. A yellow light means that the patient is doing well but there is the possibility in the near future that the progress of the patient suffers a recess. In this case the primary care physician should closely observe the patient. An example of a yellow light could be when the PPM gives as output that the patient is improving quickly but a terrible life event, captured by the Brugha questionnaire, occurred recently. In this case the AM concludes that a yellow light is the adequate alert level and sends this information, plus the reasoning performed by the model, to the CM. A red light represents an alarm meaning that the patient is not doing well and that physicians need to take actions, such as to have a personal interview with the patient to asses him/her more deeply, change the patient's medication, increase the dosage of a medication, etc.

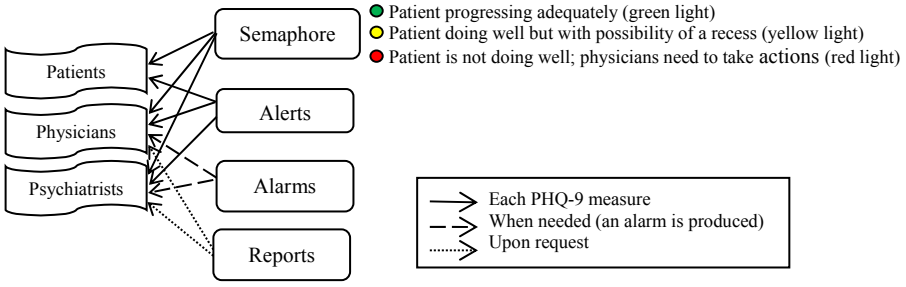

Fig. 5 Diagram of the CM: communication between the PAU and the actors involved in the healing process

The format of the hierarchical levels, alerts, reports, and alarms, are presented as a set of text messages that explain the reasoning process carried out by the AM but with different language, priority, and detail depending on the level and type of the actor to whom the information is sent. The different messages to a particular actor can be inhibited or activated depending on the system requirements specified by psychiatrists and primary care physicians.

Alerts are activated each time the patient is responding to the questionnaires. In accordance with the light's color, the alert shows important information needed to interpret the light properly, and is specific to each actor. In order to satisfy efficiency of information delivery, alerts are produced dynamically through a defined structure to prepare the most suitable sentences that are rich in content without being repetitive. Reports explain in an extensive and detailed way the inference performed by the rule-based system defined in the AM, adapting the set of messages to each recipient. The reports are available upon request. Alarms inform psychiatrists and physicians about critical states that require taking specific actions and are transmitted rapidly by means of SMS, e-mail, etc.

4. Results and discussion

In this section, six hypothetical and clinically approved patient scenarios are described and the results of the PAU model for these cases are presented. All of these scenarios are inspired by experiences of psychiatrists collaborating in this study. This set of hypothetical patients has been defined in order to perform a rich and complete scenario evaluation. Each of these patients is monitored with the PAU and the four hierarchical levels that the CM offers, meaning that semaphore, alerts, reports, and alarms have been analyzed by the psychiatrists of Parc Sanitari Sant Joan de Déu. Based on this test, they have agreed that the proposed major depression remote monitoring system model promises to be a useful tool for monitoring patients and following their healing process.

5.1 Scenario #1: A patient who responds to medication in the first weeks.

Antidepressant therapy as a treatment has different effects on different people. Usually, if patients respond to a specific type of antidepressant, which means showing a reduction of 5 points in their overall rate of the PHQ-9, it would occur between weeks 4 and 8 from the time they started treatment. Although some factors might influence the duration of this period, in the best-case scenario the patient responds to the prescribed antidepressant sooner. Case #1 is considered a best-case scenario patient that heals continuously, except for a worsening in week 14. The semaphores provided by the monitoring system every 2 weeks are shown in Figure 6, representing the progress path of the patient during the 48 weeks of treatment.

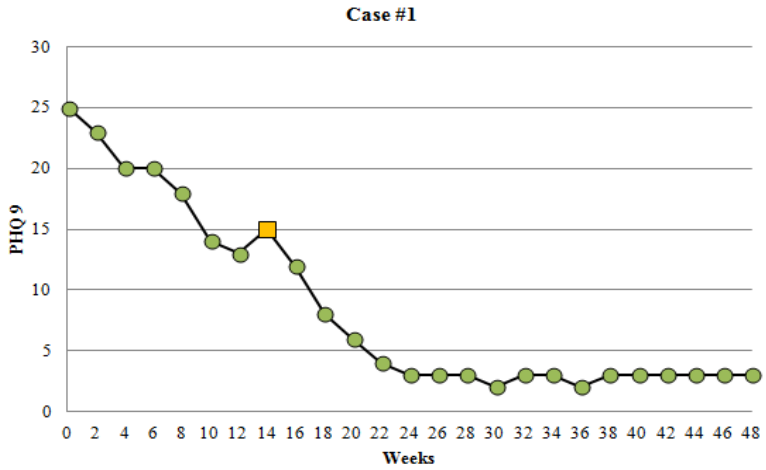

Fig. 6 Visual progress of Patient #1 during treatment at home. The patient responds well to the prescribed medication. The symbols represent the different lights of the semaphore: round = green; square = yellow; triangle =

red. The abscissa corresponds to the accumulated weeks of treatment and the ordinate stands for the overall rate of the PHQ-9

Table 3 presents the set of messages associated to the progress of patient #1. The first column shows the number of weeks from the start of treatment and follow-up. The second column lists the overall rate of the PHQ-9. The third column describes the treatment stages the patient goes through. The last two columns show the outputs of the monitoring system, first the semaphore light, and second the messages to the patient. In this scenario only the messages to the patient are shown in order to keep the table to a manageable size. In the rest of the scenarios proposed, messages for psychiatrists will also be displayed. In this case, the messages for the patient are messages of encouragement. The patient is taking the medication adequately and the treatment is working well. Therefore, no red lights show up and no alarms are sent to the psychiatric unit.

TABLE 3 SET OF MESSAGES ASSOCIATED TO THE PROGRESS OF PATIENT #1. THE PHASE COLUMN REPRESENTS THE STAGE ASSOCIATED TO THE PROGRESS OF THE PATIENT. THE MEANING IS: IN: INITIAL; PR: PARTIAL RESPONSE; CR: CONSOLIDATED RESPONSE; RC: REMISSION CONTINUATION; RP: RELAPSE; RM: REMISSION MAINTENANCE; RV: RECOVERY

Week	PHQ9	Phase	Semaphore	Message to Patient Alert
0	25			Welcome to the major depression remote monitoring system. Thank you for completing your first assessment. Please complete your next assessment in 2 weeks.
2	23	IN	G	Good news, your treatment is proving effective! Please continue with your treatment as advised.
4	20	PR	G	Very good, you are doing well and taking all necessary steps to ensure your improvement. Your treatment is proving effective. Please remember that compliance is important.
6	20	PR	G	Good, you are continuing to improve. Please continue with your treatment as advised.
8	18	PR	G	Very good, you are doing well and taking all necessary steps to ensure your improvement. Remember it is important that you continue with your treatment as advised. We look forward to your newly completed assessment in 2 weeks.
10	14	PR	G	Very good, you are continuing to improve. Even though you may feel better, it is important that you continue your treatment as advised.
12	13	PR	G	Very good, you are continuing to improve. Please continue with your treatment as advised. We look forward to your newly completed assessment in 2 weeks.
14	15	PR	Y	Your assessment results are not showing any changes during the last weeks. Do not worry, as this is normal. Be sure to continue with your treatment as advised by your physician. We look forward to receiving your newly completed assessment in 2 weeks.
16	12	CR	Y	Your assessment results are not still showing any changes during the last weeks. Please contact your physician to discuss your progress.
18	8	CR	G	Excellent! It seems you are improving rapidly. Please remember it is important to continue with your treatment as advised.
20	6	CR	G	Very good, you are continuing to improve. Make sure to continue taking your prescriptions as advised. We look forward to receiving your newly completed assessment in 2 weeks.
22	4	RC	G	Very good, you improvement is going great. Congratulations, you have defeated depression! Please remember that even though you feel fine, it is very important that you continue your treatment as advised.
24	3	RC	G	Great, you are doing well. Please remember that even though you feel fine, it is very important that you continue your treatment as advised to avoid any relapses.
26	3	RC	G	Excellent, everything is going great. As you know, it is very important that you continue your treatment even though you feel fine. We look forward to receiving your newly completed assessment in 2 weeks.
28	3	RC	G	Great, you are doing well. Please remember that even though you feel fine, it is very important that you continue your treatment as advised to avoid any relapses.
30	2	RC	G	Excellent, everything is going great. As you know, it is very important that you continue your treatment even though you feel fine.
32	3	RC	G	Great, you are doing well. Please remember that even though you feel fine, it is very important that you continue your treatment as advised to avoid any relapses. We look forward to receiving your newly completed assessment in 2 weeks.
34	3	RC	G	Excellent, everything is going great. As you know, it is very important that you continue your treatment even though you feel fine.

36	2	RC	G	Great, you are doing well. Please remember that even though you feel fine, it is very important that you continue your treatment as advised to avoid any relapses.
38	3	RC	G	Excellent, everything is going great. As you know, it is very important that you continue your treatment even though you feel fine. We look forward to receiving your newly completed assessment in 2 weeks.
40	3	RC	G	Great, you are doing well. Please remember that even though you feel fine, it is very important that you continue your treatment as advised to avoid any relapses.
42	3	RC	G	Excellent, everything is going great. As you know, it is very important that you continue your treatment even though you feel fine.
44	3	RC	G	Great, you are doing well. Please remember that even though you feel fine, it is very important that you continue your treatment as advised to avoid any relapses. We look forward to receiving your newly completed assessment in 2 weeks.
46	3	RV	G	Excellent, everything is going great. As you know, it is very important that you continue your treatment even though you feel fine.
48	3	RV	G	Congratulations! You have completely recovered from your depression. Monitoring ends here. Please continue following the instructions of your physician. Good-bye.

5.2 Scenario #2: A patient who does not respond to medication in the first weeks

This scenario shows a patient that does not respond to the antidepressant medication prescribed by his/her physician during the first 8-week period. This scenario represents a typical case of a woman in her post-menopause stage of life. According to clinical literature, menopausal status and old age are predictors of a poor response to antidepressant treatments [44]. Psychiatrists take action by changing the type of antidepressant and immediately the patient shows a positive response to the new medication. Figure 7 shows the progress of the patient through the visualization of the semaphore lights involved in the healing process.

Table 4 presents the set of messages associated to the progress of patient #2. The organization of the table is exactly the same as Table 3 (patient #1). The messages shown are intended for the patient. As in the previous patient, the messages offer continuing encouragement, however, in this case at week 8 a warning message is sent to the patient asking that the doctor be contacted. Although it is not shown here, due to space limitations, the physicians receive an alarm through SMS or e-mail indicating the updated status of the patient. The doctor decides to change the medication and use a different antidepressant for this patient after receiving the results from the 8-week assessment. The new medication works well and the depression is overcome at week 22.

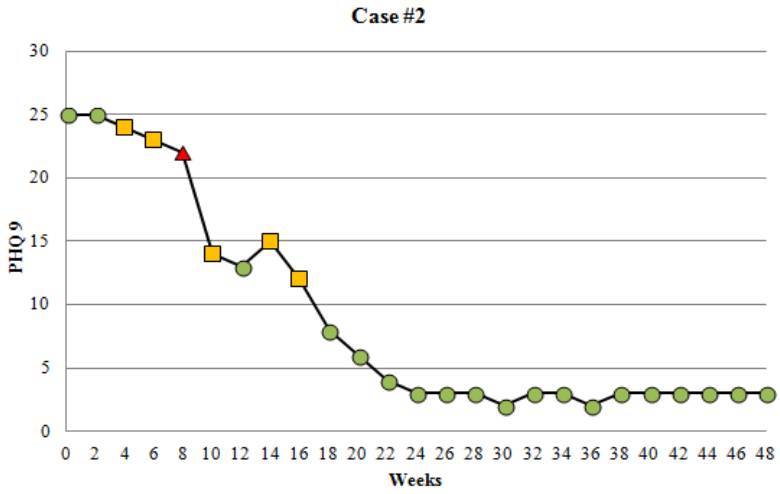

Fig. 7 Visual progress of Patient #2 during treatment at home. The patient does not respond to the first prescribed medication, but does respond when the medication is changed. The symbols represent the different lights of the semaphore,round = green; square = yellow; triangle = red. The abscissa corresponds to the accumulated weeks of treatment and the ordinate stands for the overall rate of the PHQ-9

TABLE 4 SET OF MESSAGES ASSOCIATED TO THE PROGRESS OF PATIENT #2. THE PHASE COLUMN REPRESENTS THE STAGE ASSOCIATED TO THE PROGRESS OF THE PATIENT. THE MEANING IS: IN: INITIAL; PR: PARTIAL RESPONSE; CR: CONSOLIDATED RESPONSE; RC: REMISSION CONTINUATION; RP: RELAPSE; RM: REMISSION MAINTENANCE; RV: RECOVERY

Week	PHQ9	Phase	Semaphore	Messages to Patient
				Alert
0	25			Welcome to the major depression remote monitoring system. Thank you for completing your first assessment. Please complete your next assessment in 2 weeks.
2	25	IN	G	Your assessment results are not showing any changes during the last weeks. Do not worry; the treatment takes time to be effective. Please be patient and continue with your treatment as advised by your physician.
4	24	IN	Y	Your assessment results are not still showing any changes during the last weeks. Treatment takes time to be effective, please continue to be patient and continue with your treatment as advised.
6	23	IN	Y	Your assessment results are not still showing any changes during the last weeks. Please contact your physician to discuss your progress.
8	22	IN	R	Your depression is not responding to your medication yet. Please contact your physician as soon as possible for a possible adjustment to your treatment.
10	14	PR	Y	Good, your treatment is now proving effective. Please continue with your treatment as advised.
12	13	PR	G	Excellent! It seems you are improving rapidly. Please remember it is important to continue with your treatment as advised. We look forward to receiving your newly completed assessment in 2 weeks.
14	15	PR	Y	Your assessment results are not showing any changes during the last weeks. Please make sure you continue taking your medication as advised.
16	12	CR	Y	Your assessment results are not still showing any changes during the last weeks. Please contact your physician to discuss your progress.
18	8	CR	G	Excellent! It seems you are improving again rapidly. Please remember it is important to continue with your treatment as advised.
20	6	CR	G	Very good, you are continuing to improve. Please continue with your treatment as advised. We look forward to your newly completed assessment in 2 weeks.
22	4	RC	G	Very good, you improvement is going great. Congratulations, you have defeated depression! Please remember that even though you feel fine, it is very important that you continue your treatment as advised.
24	3	RC	G	Great, you are doing well. Please remember that even though you feel fine, it is very important that you continue your treatment as advised to avoid any relapses.
26	3	RC	G	Excellent, everything is going great. As you know, it is very important that you continue your treatment even though you feel fine. We look forward to receiving your newly completed assessment in 2 weeks.
28	3	RC	G	Great, you are doing well. Please remember that even though you feel fine, it is very important that you continue your treatment as advised to avoid any relapses.
30	2	RC	G	Excellent, everything is going great. As you know, it is very important that you continue your treatment even though you feel fine.
32	3	RC	G	Great, you are doing well. Please remember that even though you feel fine, it is very important that you continue your treatment as advised to avoid any relapses. We look forward to receiving your newly completed assessment in 2 weeks.
34	3	RC	G	Excellent, everything is going great. As you know, it is very important that you continue your treatment even though you feel fine.
36	2	RC	G	Great, you are doing well. Please remember that even though you feel fine, it is very important that you continue your treatment as advised to avoid any relapses.
38	3	RC	G	Excellent, everything is going great. As you know, it is very important that you continue your treatment even though you feel fine. We look forward to receiving your newly completed assessment in 2 weeks.
40	3	RC	G	Great, you are doing well. Please remember that even though you feel fine, it is very important that you continue your treatment as advised to avoid any relapses.
42	3	RC	G	Excellent, everything is going great. As you know, it is very important that you continue your treatment even though you feel fine.
44	3	RC	G	Great, you are doing well. Please remember that even though you feel fine, it is very important that you continue your treatment as advised to avoid any relapses. We look forward to receiving your newly completed assessment in 2 weeks.
46	3	RV	G	Excellent, everything is going great. As you know, it is very important that you continue your treatment even though you feel fine.

48	3	RV	G	Congratulations! You have completely recovered from your depression. Monitoring ends here. Please continue following the instructions of your physician. Good-bye.

5.3 Scenario #3: A patient with one overcome relapse risk

This scenario represents a patient who is initially responding to antidepressant treatment, but suddenly stops taking medications; the sudden stop could be for any number of reasons. As a result, the patient faces a relapse condition. Due to the close monitoring provided, GPs and/or psychiatrists would be able to quickly detect the change and make an informed decision about the medication, for example should they prescribe a different antidepressant that does not have the same side-effect profile as the first medication. Figure 8 shows the visual progress of the patient's healing process through the semaphore lights.

Table 5 presents the set of messages associated with the progress of patient #3. The structure of the table is the same as those of the previous patients'. In this case, the messages shown are those established for psychiatrists. The alerts are continuously indicating to the psychiatrists the situation of the patient, such as improving adequately, improving rapidly, worsening rapidly, risk of relapse, etc. This information is given to the doctors every 2 weeks. From week 22 to week 32 the monitoring system sends alarms to the doctors that warn them of the possibility and risk of a relapse. Psychologists take action and decide to change the antidepressant. The new treatment is effective and from week 28 the patient starts improving. However, as can be seen in Figure 8, in week 30 the semaphore is still red although the patient is improving. The red semaphore is due to the fact that although the patient had an improvement in week 30 compared to week 28, when that improvement is compared to week 26 there is very little overall improvement. Therefore, the situation is still not stable. The yellow light in week 32 is due to the past week's red alerts. This information is crucial to the physician's ability to make the appropriate decision at the appropriate time.

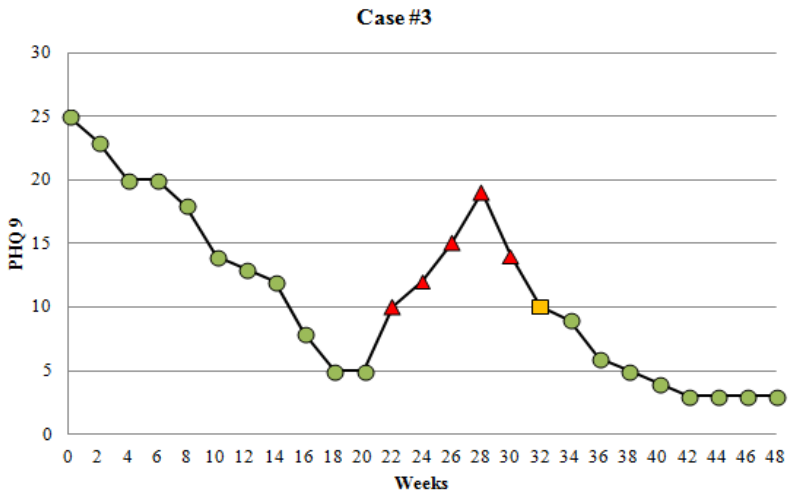

Fig. 8 Visual progress of Patient #3 during treatment at home. The patient leaves the medication and faces a relapse that he/she is able to overcome. The symbols represent the different lights of the semaphore, round = green; square = yellow; triangle = red. The abscissa corresponds to the accumulated weeks of treatment and the ordinate stands for the overall rate of the PHQ-9

TABLE 5 SET OF MESSAGES ASSOCIATED TO THE PROGRESS OF PATIENT #3. THE PHASE COLUMN REPRESENTS THE STAGE ASSOCIATED TO THE PROGRESS OF THE PATIENT. THE MEANING IS: IN: INITIAL; PR: PARTIAL RESPONSE; CR: CONSOLIDATED RESPONSE; RC: REMISSION CONTINUATION; RP: RELAPSE; RM: REMISSION MAINTENANCE; RV: RECOVERY

Week	PHQ9	Phase	Semaphore	Messages to the Psychiatric Unit

				Alert	Alarm
0	25			The major depression remote monitoring starts.	
2	23	IN	G	The patient is improving adequately.	
4	20	PR	G	The patient is improving adequately. Responding to medication.	
6	20	PR	G	The patient is improving adequately.	
8	18	PR	G	The patient is improving adequately.	
10	14	PR	G	The patient is improving adequately.	
12	13	PR	G	The patient is improving adequately.	
14	12	CR	G	The patient is improving adequately.	
16	8	CR	G	The patient is improving adequately.	
18	5	RM	G	The patient is improving adequately.	
20	5	RM	G	The patient is improving adequately.	
22	10	RP	R	The patient is worsening rapidly. Risk of relapse.	Relapse might have started.
24	12	RP	R	The patient is worsening rapidly. Risk of relapse for 2 weeks.	Relapse continues.
26	15	RP	R	The patient is worsening rapidly. Risk of relapse for 4 weeks.	Relapse continues.
28	19	RP	R	The patient is worsening rapidly. Risk of relapse for 8 weeks.	Relapse continues.
30	14	RP	R	Risk of relapse reduces.	Relapse stops.
32	10	CR	Y	The patient is improving rapidly.	Previous red alarm.
34	9	CR	G	The patient is improving adequately.	
36	6	CR	G	The patient is improving adequately.	
38	5	RM	G	The patient is improving.	
40	4	RM	G	The patient is improving.	
42	3	RM	G	The patient is improving.	
44	3	RM	G	The patient is recovered.	
46	3	RM	G	The patient is recovered.	
48	3	RV	G	The patient is recovered. Monitoring ends here.	

5.4 Scenario #4: A patient with residual depressive symptoms

This scenario shows a patient who is improving until week 20, then, due to a serious life-threatening event in week 12, the loss of a loved-one, the patient is not cured completely and ends up with residual depressive symptoms after 48 weeks despite continued use of medication. In this scenario, the patient experiences a serious relapse from week 22 as an effect of the recent loss of a loved-one. Since the patient's PHQ-9 level is still in the range of consolidated response (CR) to medication and the patient does not get worse, the semaphores are yellow. In spite of the fact that the physician augments the doses of the antidepressant and prescribes psychotherapy treatment as a complementary method, the patient remains in a state of depression with residual symptoms until the end of the monitoring. Figure 9 describes visually the progress of the patient using the semaphore lights that are the output of the monitoring system.

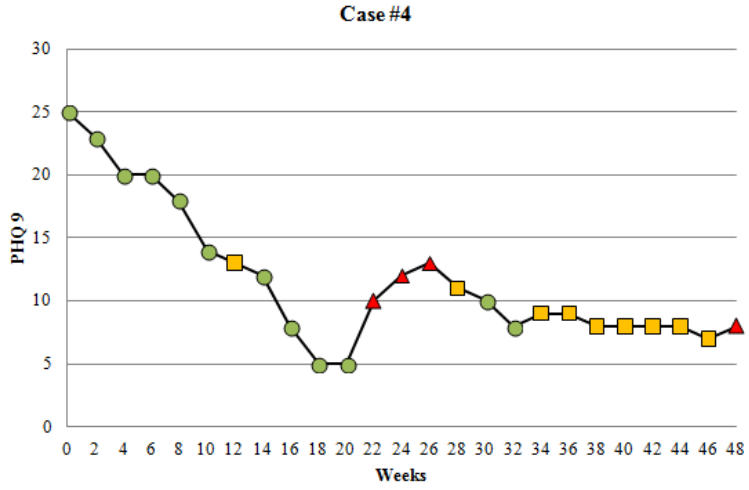

Fig. 9 Visual progress of Patient #4 during treatment at home. The patient remains in a state of depression with residual symptoms. The symbols represent the different lights of the semaphore, round = green; square = yellow; triangle = red. The abscissa corresponds to the accumulated weeks of treatment and the ordinate stands for the overall rate of the PHQ-9

Table 6 presents the messages to the patient related to his/her situation indicating that in the last months there is no change while the patient is in the possible relapse state.

TABLE 6 SET OF MESSAGES ASSOCIATED TO THE PROGRESS OF PATIENT #4. THE PHASE COLUMN REPRESENTS THE STAGE ASSOCIATED TO THE PROGRESS OF THE PATIENT. THE MEANING IS: IN: INITIAL; PR: PARTIAL RESPONSE; CR: CONSOLIDATED RESPONSE; RC: REMISSION CONTINUATION; RP: RELAPSE; RM: REMISSION MAINTENANCE; RV: RECOVERY

Week	PHQ9	Phase	Semaphore	Messages to Patient
				Alert
0	25			Welcome to the major depression remote monitoring system. Thank you for completing your first assessment. Please complete your next assessment in 2 weeks.
2	23	IN	G	Good news, your treatment is proving effective! Please continue with your treatment as advised.
4	20	PR	G	Very good, you are doing well and taking all necessary steps to ensure your improvement. Your treatment is proving effective. Please remember that compliance is important.
6	20	PR	G	Good, you are continuing to improve. Please continue with your treatment as advised.
8	18	PR	G	Very good, you are doing well and taking all necessary steps to ensure your improvement. Remember it is important that you continue with your treatment as advised. We look forward to your newly completed assessment in 2 weeks.
10	14	PR	G	Very good, you are continuing to improve. Even though you may feel better, it is important that you continue your treatment as advised.
12	13	PR	Y	It seems you've been through a very difficult situation recently. It is very important to continue with your treatment, and you should contact your physician. We look forward to your newly completed assessment in 2 weeks.
14	12	CR	G	Good, it seems you are improving. Please remember it is important to continue with your treatment as advised. We look forward to receiving your newly completed assessment in 2 weeks.
16	8	CR	G	Very good, you are continuing to improve. Make sure to continue taking your prescriptions as advised.
18	5	RM	G	Excellent, you improvement is going great! Congratulations, you have defeated depression! Please remember that even though you feel fine, it is very important that you continue your treatment as advised.
20	5	RM	G	Great, you are doing well. Please remember that even though you feel fine, it is very important that you continue your treatment as advised to avoid any relapses.
22	10	CR	R	Caution! You are worsening rapidly. You are facing a risk of relapse. You should contact your physician as soon as possible to discuss your progress.
24	12	CR	R	Caution! You are worsening rapidly. You have a high risk of relapse. If you have not already done so you should contact your physician as soon as possible to discuss your progress.
26	13	CR	R	Caution! You are still worsening. You have a high risk of relapse. If you have not already done so you should contact your physician immediately. Make sure to continue taking your treatment as advised.
28	11	CR	Y	Caution! You are still not showing any change. Please seek help from your physician if you need to do so.
30	10	CR	G	Very good, you are doing well. Make sure to continue taking your treatment as advised. Please remember compliance is important. We look forward to receiving your newly completed assessment in 2 weeks.
32	8	CR	G	Very good, you are continuing to do well. Make sure to continue taking your treatment as advised. Please remember compliance is important.
34	9	CR	Y	Caution! Your assessment results are not showing any changes during the last weeks. Please be sure to continue with your treatment as advised by your physician.
36	9	CR	Y	Caution! Your assessment results are not showing any changes during the last weeks. Please be sure to continue with your treatment as advised.
38	8	CR	Y	Caution! Your assessment results are not showing any changes during the last weeks. Please be sure to continue with your treatment as advised. Remember, compliance is important. We look forward to receiving your newly completed assessment in 2 weeks.
40	8	CR	Y	Caution! Your assessment results are not showing any changes during the last weeks. Please be sure to continue with your treatment as advised.

42	8	CR	Y	Caution! Your assessment results are not showing any changes during the last weeks. Please be sure to continue with your treatment as advised. Remember, compliance is important. We look forward to receiving your newly completed assessment in 2 weeks.
44	8	CR	Y	Caution! Your assessment results are not showing any changes during the last weeks. Please be sure to continue with your treatment as advised. Please seek help from your physician if you need to do so.
46	7	CR	Y	Caution! Your assessment results are not showing any changes during the last weeks. Please remember it is important to continue with your treatment as advised. We look forward to receiving your newly completed assessment in 2 weeks.
48	8	CR	G	Caution! Your assessment results are still not showing any changes during the last weeks. You are facing a risk of relapse. You should contact your physician immediately. Monitoring ends here. As you can't be considered fully recovered from depression, please continue following the instructions of your physician.

5.5 Scenario #5: A patient that has several changes in the different phases

This scenario represents a patient who sometimes responds to medication and improves, and sometimes worsens and reverts to previous stages. The first worsening had no specific reason and since it did not continue it had no effect on the procedure other than alerting the physicians to be cautious concerning the patient. It was more of a mood change and does not have any major importance. The second worsening lasted longer than the first and grabbed the attention of the physicians. A change in the medication dosage was made and the patient began to improve again. After improving for few weeks, around weeks 34 and 36 the patient stops taking the medication and as a consequence experiences a relapse. The treatment period ends without patient recovery. Figure 10 offers a visual representation of the semaphore lights that described the progress of the patient #5. Table 7 presents the messages to the patient related to his/her situation indicating that it is very important that he/she continues taking the medication and when it is important that he/she gets in touch with the physicians.

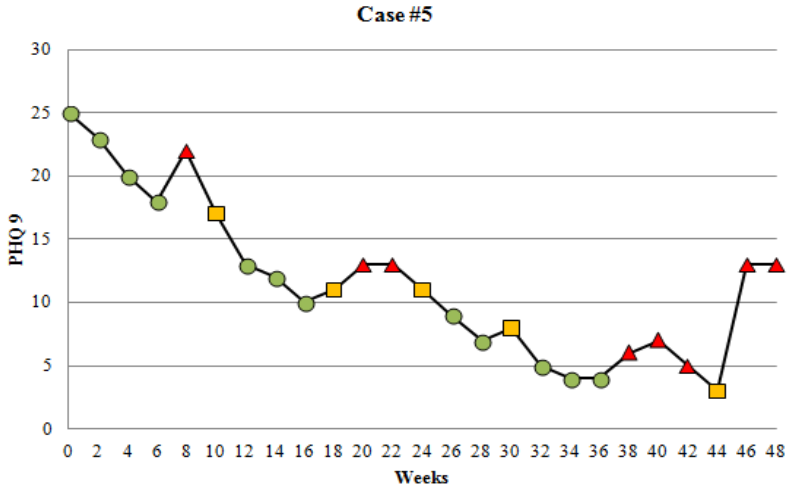

Fig. 10 Visual progress of Patient #5 during treatment at home. The patient has several changes in different phases. The symbols represent the different lights of the semaphore, round = green; square = yellow; triangle = red. The abscissa corresponds to the accumulated weeks of treatment and the ordinate stands for the overall rate of the PHQ-9

TABLE 7 SET OF MESSAGES ASSOCIATED TO THE PROGRESS OF PATIENT #5. THE PHASE COLUMN REPRESENTS THE STAGE ASSOCIATED TO THE PROGRESS OF THE PATIENT. THE MEANING IS: IN: INITIAL; PR: PARTIAL RESPONSE; CR: CONSOLIDATED RESPONSE; RC: REMISSION CONTINUATION; RP: RELAPSE; RM: REMISSION MAINTENANCE; RV: RECOVERY

Week	PHQ9	Phase	Semaphore	Messages to Patient
				Alert
0	25	IN		Welcome to the major depression remote monitoring system. Thank you for completing your first assessment. Please complete your next assessment in 2 weeks.

2	23	IN	G	Good news, your treatment is proving effective! Please continue with your treatment as advised.
4	20	PR	G	Very good, you are doing well and taking all necessary steps to ensure your improvement. Your treatment is proving effective. Please remember that compliance is important.
6	18	PR	G	Good, you are continuing to improve. Please continue with your treatment as advised.
8	22	IN	R	It seems you are doing slightly worse. You should contact your physician as soon as possible to discuss your progress. Please remember to continue with your treatment as advised.
10	17	PR	Y	Your assessment results are not still showing any changes during the last weeks. Make sure to continue taking your prescriptions as advised. We look forward to receiving your newly completed assessment in 2 weeks.
12	13	PR	G	Very good, you are doing well and taking all necessary steps to ensure your improvement. Your treatment is proving effective. Please remember that compliance is important.
14	12	CR	G	Good, you are continuing to improve. Please continue with your treatment as advised.
16	10	CR	G	Very good, you are doing well and taking all necessary steps to ensure your improvement. Please continue with your treatment as advised. We look forward to receiving your newly completed assessment in 2 weeks.
18	11	CR	Y	Good, you are continuing to improve. Please continue with your treatment as advised.
20	13	RP	R	Caution! You are showing more symptoms than your last assessment. You are facing a slight risk of relapse. Please contact your physician to discuss your progress.
22	13	RP	R	Caution! Your condition is worsening. You have a high risk of relapse. If you have not already done so you should contact your physician as soon as possible to discuss your progress. Please remember to continue with your treatment as advised.
24	11	CR	Y	Very good, you are doing well and taking all necessary steps to ensure your improvement. Your treatment is proving effective. Please remember that compliance is important. We look forward to receiving your newly completed assessment in 2 weeks.
26	9	CR	G	Very good, you are continuing to improve. Please continue with your treatment as advised. We look forward to your newly completed assessment in 2 weeks.
28	7	CR	G	Very good, you are continuing to improve. Please continue with your treatment as advised.
30	8	CR	Y	Your assessment results are not showing any changes during the last weeks. Be sure to continue with your treatment as advised by your physician.
32	5	RM	G	Very good, you improvement is going great. Congratulations, you have defeated depression! Please remember that even though you feel fine, it is very important that you continue your treatment as advised.
34	4	RM	G	Very good, you are continuing to improve. Please continue with your treatment as advised. We look forward to your newly completed assessment in 2 weeks.
36	4	RM	G	Your assessment results are not showing any changes during the last weeks. Be sure to continue with your treatment as advised by your physician.
38	6	CR	R	Your assessment results are showing slightly more symptoms than 2 weeks ago. If it continues worsening, you should contact your physician.
40	7	CR	R	Caution! Your condition is worsening. You have a slight risk of relapse. If you have not already done so you should contact your physician as soon as possible to discuss your progress. Please remember to continue with your treatment as advised. We look forward to your newly completed assessment in 2 weeks.
42	5	RM	R	Your assessment results are not showing any changes during the last weeks. Be sure to continue with your treatment as advised by your physician.
44	3	RM	Y	Very good, you are continuing to improve. Please continue with your treatment as advised.
46	13	RP	R	Caution! Your condition is worsening rapidly. Your have a slight risk of relapse. You should contact your physician as soon as possible to discuss your progress.
48	13	RP	R	Caution! Your condition is worsening rapidly. Your have a slight risk of relapse. If you haven't already, you should contact your physician as soon as possible to discuss your progress. Monitoring ends here. As you can't be considered fully recovered from depression, please continue following the instructions of your physician.

5.6 Scenario #6: A patient with three consecutive relapses

This scenario represents a patient that experiences two relapses during his/her recovery process and eventually ends up not fully recovered and with medium symptoms. The first relapse is due to the occurrence of a life-threatening event in the patient's life, job loss. In a few more weeks the patient falls into another full-blown depression and the physician prescribes him/her a higher

dosage of antidepressant. After a few intakes the effectiveness of the medication becomes clear, but the patient has problems with the side effects of the treatment and quits taking the medication. This is the reason why in week 46, patient #6 has a worsening condition and a risk of relapse.

Figure 11 shows the output of the major depression monitoring system semaphore clarifying the progress of the patient during the entire treatment process.

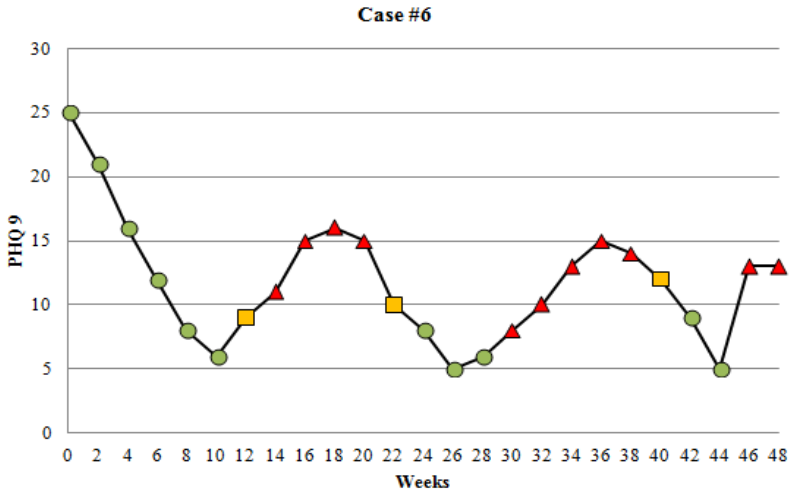

Fig. 11 Visual progress of Patient #6 during treatment at home. The patient has three consecutive relapses. The symbols represent the different lights of the semaphore, round = green; square = yellow; triangle = red. The abscissa corresponds to the accumulated weeks of treatment and the ordinate stands for the overall rate of the PHQ-9

Table 8 presents the messages that he monitoring system offers to the psychiatric unit in order to facilitate the monitoring of the patient's progress and to make decisions when necessary. In this case, the alerts inform the physicians when things are not going well, for example in week 12 when there is a yellow light, a message indicating that the patient is responding to medication but is showing stagnant progress will be sent to the physician. The monitoring system also sends alarm messages to psychiatrists for this patient because several red-light situations occur. The alarms can indicate when the relapses start, grow, or stop.

TABLE 8 SET OF MESSAGES ASSOCIATED TO THE PROGRESS OF PATIENT #6. THE PHASE COLUMN REPRESENTS THE STAGE ASSOCIATED TO THE PROGRESS OF THE PATIENT. THE MEANING IS: IN: INITIAL; PR: PARTIAL RESPONSE; CR: CONSOLIDATED RESPONSE; RC: REMISSION CONTINUATION; RP: RELAPSE; RM: REMISSION MAINTENANCE; RV: RECOVERY

Week	PHQ9	Phase	Semaphore	Messages to Psychiatric Unit	
				Alert	**Alarm**
0	25			Monitoring starts.	
2	21	IN	G	The patient improves adequately.	
4	16	PR	G	The patient is improving rapidly.	
6	12	CR	G	The patient is improving rapidly.	
8	8	CR	G	The patient is improving adequately.	
10	6	CR	G	The patient is improving adequately.	
12	9	CR	Y	The patient shows no change.	
14	11	RP	R	The patient is worsening rapidly. Risk of relapse.	Relapse starts
16	15	RP	R	The patient is worsening rapidly. Risk of relapse for 2 weeks.	Relapse continues
18	16	RP	R	The patient is worsening rapidly. Risk of relapse for 4 weeks.	Relapse continues
20	15	RP	R	The patient shows no change.	Relapse stops
22	10	CR	Y	The patient is improving adequately.	Previous red semaph.
24	8	CR	G	The patient is improving adequately.	
26	5	RM	G	The patient is improving adequately.	
28	6	CR	G	The patient is improving adequately.	
30	8	RP	R	The patient is worsening rapidly. Risk of relapse.	Relapse starts
32	10	RP	R	The patient is worsening rapidly. Risk of relapse for 2 weeks.	Relapse continues
34	13	RP	R	The patient is worsening rapidly. Risk of relapse for 4 weeks.	Relapse continues
36	15	RP	R	The patient is worsening rapidly. Risk of relapse for 6 weeks.	Relapse continues
38	14	RP	R	The patient shows no change.	Relapse stops
40	12	CR	Y	The patient is improving adequately.	Previous red semaph.
42	9	CR	G	The patient is improving adequately.	

44	5	RM	G	The patient is improving rapidly.	
46	13	RP	R	The patient is worsening rapidly. Risk of relapse.	Relapse starts
48	13	RP	R	The patient is worsening rapidly. Risk of relapse. Monitoring ends here. The patient is not recovered.	Relapse continues

The Patient Assessment Unit is implemented as prototype software with both web and mobile interfaces. PPM, AM, and CM, and the database of the system are all implemented using java, Mysql, RESTFUL, and Android technologies. The functionality of each prototype of each module has been separately tested and currently PAU is in its last stage of the integration process.

As commented before, we think that the PAU model could be of high usefulness when applied to Public Health Systems, reducing medical costs and enhancing the follow-up of the progress of patients. However, we also think that the proposed PAU model can be developed by clinicians using low-cost methodologies as the ones describe by Zhang et al. [45]. In this sense, a single doctor could develop a PAU app and use it to their own patients in an easy and effective way.

5.7 PAU Limitations

In this section the main limitations of the proposed Patient assessment unit (PAU) model are reviewed.

First, suicide is a major risk in patients suffering from depressive disorder. A single question from the PHQ-9, used in the Patient Progress Module (PPM), does not have adequate sensitivity and specificity. Although the Analysis Module (AM) uses as part of its reasoning the M.I.N.I. suicide risk questionnaire in order to detect suicidal intentions when a patient gives the highest value to question 9 of PHQ-9 (i.e., thoughts that you would be better off dead or of hurting yourself in some way), we think that it can be interesting that a future PPM includes a validated measure such as the six-item Suicidal Affect-Behavior-Cognition Scale (SABCS) to perform individual evaluation on affect, behavior and cognition related to suicide risk [46].

Second, the PPM lacks of therapeutic component. Therefore, it would be necessary that a future PPM should be able to incorporate the psychotherapeutic component. Evidence based psychotherapy such as cognitive behavior therapy can be delivered via internet for a long duration and such intervention is cost-effective [47].

5. Conclusions and Future work

Major depressive disorder is a very common mental disorder worldwide which can seriously affect a person's health, wellbeing, and life. Depression is a long-term condition and it is widely known for its recurrent characteristic. More systematic and frequent follow-up approaches in public healthcare systems could reduce the risk, or help in the early detection, of relapse and recurrence in major depressive patients, therefore, contributing to public well-being. A major depression monitoring system that takes advantage of current technologies, facilitates a more comprehensive follow-up of the progress of patients during their home stay after being diagnosed with major depressive disorder by a medical specialist. It is important to note that the monitoring system does not intend to substitute the physician or the psychiatrist, but rather it gives extended information about the changes suffered in patients, which doctors do not usually have access to due to the infrequency of visits they are able to make with each patient in relation to clinical assistance pressure that Public Health Systems often suffer.

The major depression monitoring system covers this necessity by taking advantage of its patient assessment unit that follows the progress of the patients in a short-term basis during their recovery in order to understand their common behaviors and provide advice to these patients, their psychiatrists, and their primary care physicians. In this paper, the Patient Assessment Unit (PAU) is presented and tested by means of a set of hypothetical patients that have been defined based on clinically possible cases in order to perform a complete scenario evaluation. The application of the PAU to this set of hypothetical patients suggests the utility of the platform that has been verified by the psychiatrists of Parc Sanitari Sant Joan de Déu involved in this

study. The next step is testing the model with real data collected from real patients. In this respect, PAU is now being implemented as a Mobile App and a website. This will allow the refinement of the PAU following the comments and suggestions of the patients, general practitioners, and psychiatrists.

References

[1] Hiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, Burstein R, Murray CJ, Vos T (2013) Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010, Lancet. 382(9904): 1575-86.

[2] Sobocki P, Jönsson B, Angst J, Rehnberg C (2006) Cost of depression in Europe, The Journal of Mental Health Policy and Economics 9:87-98.

[3] Ho RCM, Mak KM, Chua ANC, Ho CSH, Mak A (2013) The effect of severity of depressive disorder on economic burden in a university hospital in Singapore. Expert Rev. Pharmacoecon Outcomes Res. 13(4):549-59. PMID:23977979.

[4] Papakostas GI, Homberger CH, Fava M (2008) A meta-analysis of clinical trials comparing mirtazapine with selective serotonin reuptake inhibitors for the treatment of major depressive disorder, Journal of Psychopharmacology. 22(8):843-8. PMID: 18308801.

[5] Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z (2006) Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis, Achieve of General Psychiatry. 63(11):1217-23. PMID: 17088502

[3] Fernández A, Haro JM, Codony M (2006) Treatment adequacy of anxiety and depressive disorders: primary versus specialised care in Spain, J. Affect. Disord. 96: 9–20.

[4] Lecrubier Y (2007) Widespread underrecognition and undertreatment of anxiety and mood disorders: results from 3 European Studies, J Clin Psychiatry 68(2):36–41.

[8] Üstün TB, Sartorius N (1995) Mental Illness in General Health Care, Chichester: John Wiley.

[9] Oöpik P, Aluoja A, Kalda R, Maaroos HI (2006) Family doctors' problems and motivating factors in management of depression, BMC family practice 7: 64.

[10] Fernández A, Pinto-Meza A, Bellón JA, Roura-Poch P, Haro JM, Autonell J, Palao DJ, Peñarrubia MT, Fernández R, Blanco E, Luciano JV, Serrano-Blanco A (2010) Is major depression adequately diagnosed and treated by primary care physicians? Results from the DASMAP study**,** Gen. Hosp. Psychiat. 32-2:201–209.

[11] Pollock K, Grime J (2002) Patients' perceptions of entitlement to time in general practice consultations for depression: qualitative study, BMJ 325-687.

[12] Fava M (2003) Diagnosis and definition of treatment-resistant depression, Biological Psychiatry 53:649–659.

[13] Nierenberg AA, Petersen TJ, Alpert JE (2003) Prevention of Relapse and Recurrence in Depression: The Role of Long-Term Pharmacotherapy and Psychotherapy, Journal of Clinical Psychiatry 64:13-17.

[14] Zhang MWB, Ho RCM (2015) Enabling Psychiatrists to Explore the Full Potential of E-Health. Front Psychiatry. 15; 6:177. PMID: 26696912.

[15] http://www.beatingtheblues.co.uk/

[16] https://moodgym.anu.edu.au/welcome/new/splash.

[17] Chattopadhyay S, Kaur P, Rabhi F, Acharya UR (2011) Neural Network Approaches to Grade Adult Depression, Journal of Medical Systems 36:2803-15.

[18] Yu S, Lin Y (2008) Applications of Fuzzy Theory on Health Care: An Example of Depression Disorder Classification Based on FCM, WSEAS Transactions on Information Science and Applications 5:31-36.

[19] McBurnie K, Kwiatkowska M, Matthews L, D'Angiulli A (2007) A Multi-factor Model for the Assessment of Depression Associated with Obstructive Sleep Apnea: A Fuzzy Logic Approach, in Fuzzy Information Processing Society, NAFIPS '07. Annual Meeting of the North American, San Diego, 301-306.

[20] Kwiatkowskaa M, Kielan K (2013) Fuzzy logic and semiotic methods in modeling of medical concepts. Fuzzy sets and systems, Fuzzy Sets and Systems 214:35-50.
[21] Aamodt A, Gundersen OE, Loge JH, Wasteson E, Szczepanski T (2010) Case-Based Reasoning for Assessment and Diagnosis of Depression in Palliative Care, in IEEE 23rd International Symposium on Computer-Based Medical Systems (CBMS), Perth, 480-485.
[22] Zhang ZX, Tian XW, Lim JS (2011) New Algorithm for the Depression Diagnosis Using HRV: A Neuro-Fuzzy Approach, in International Symposium on Bioelectronics and Bioinformatics (ISBB), Suzhou, 283-286.
[23] Satter RM, Cohen T, Ortiz P, Kahol K, Mackenzie J, Olson C, Johnson M, Patel VL (2012) Avatar-based simulation in the evaluation of diagnosis and management of mental health disorders in primary care, Journal of Biomedical Informatics 45(6):1137-1150.
[24] Hu B, Hu B, Wan V, Dennis V, Chen H, Li L, Zhou Q (2010) Ontology-based ubiquitous monitoring and treatment against depression, Journal Wireless Communications & Mobile Computing - Pervasive Computing Technology and Its Applications 10:1303-1319.
[25] Zheng F, Hu B, Liu L, Zhu V, Li Y (2009) Fuzzy Logic in Exploring Data Effects: A Way to Unveil Uncertainty in EEG Feedback, in In proceeding of: Digital Human Modeling, Second International Conference, ICDHM , San Diego, 754-763.
[26] Serretti A, Olgiati P, Liebman MN, Hu H, Zhang Y, Zanardi I, Colombo C, Smeraldi E (2007) Clinical prediction of antidepressant response in mood disorders: Linear multivariate vs. neural network models, Psychiatry Research 152:223–231.
[27] Aziz AA, Klein MCA, Treur J (2009) An Ambient Intelligent Agent for Relapse and Recurrence Monitoring in Unipolar Depression, Lecture Notes in Artificial Intelligence 5651:186-190.
[28] Dickerson RF, Gorlin EI, Stankovic JA (2011) Empath: a Continuous Remote Emotional Health Monitoring System for Depressive Illness, in Wireless Health, October 10-13, San Diego, 5.
[29] Sung M, Marci C, Pentland A (2005) Objective Physiological and Behavioral Measures for Identifying and Tracking Depression State in Clinically Depressed Patients, MIT Technical Report 595:1-20.
[30] Optimisim Apps. http://www.findingoptimism.com/ [accessed: 15.Jan.2013].
[31] Warmedarm L, Riper H, Klein M, Van Den Ven P, Rocha A, Henriques MR, Tousset E, Silva H, Andersson G, Cuijpers P (2012) Innovative ICT solutions to improve treatment outcomes for depression:The ICT4Depression project, in *Studies in Health Technology and Informatics*, B.K. Wiederhold and G. Riva, Eds., 339-343.
[32] Stone EA, Lin Y, Quartemain Q (2008) A final common pathway for depression Progress toward a general conceptual framework, Neurosci. Biobehav. Rev. 32:508-24.
[33] American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, (2013) Fifth Edition. Arlington, VA, American Psychiatric Association
[34] Kroenke K, Spitzer RL, Williams JB (2001) The PHQ-9: validity of a brief depression severity measure, J. Gen. Intern. Med. 16 606–613.
[35] Wulsin L, Somoza E, Heck J (2002) The feasibility of using the Spanish PHQ-9 to screen for depression in primary care in Honduras, Prim. Care Companion J. Clin. Psychiatr. 4:191–5.
[36] Löwe B, Kroenke K, Herzog W, Gräfe K (2004) Measuring depression outcome with a brief self-report instrument: sensitivity to change of the Patient Health Questionnaire (PHQ-9), J. Affect, Disorders 81:61–6.
[37] Pinto-Meza A, Serrano-Blanco A, Peñarrubia MT, Blanco E, Haro JM (2005) Assessing depression in primary care with the PHQ-9: can it be carried out over the telephone?, J Gen Intern Med 20:738-42.
[38] Brugha T, Bebbington P, Tennant C, Hurry J (1985) The List of Threatening Experiences: a subset of 12 live event categories with considerable long-term contextual threat, Psychological Medicine 15:189–194.
[39] Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Janavs J, Weiller E, Bonora LI, Keskiner A, Schinka J, Knapp E, Sheehan MF, Dunbar GC (1997) Reliability and Validity of the MINI International, European Psychiatry 12:232-241.

[40] ICSI - Institute for Clinical Systems Improvement, http://www.icsi.org/ [accessed 21.04.2015]
[41] Monsen KA, Neely C, Oftedahl G, Kerr MJ, Pietruszewski P, Farri O (2012) Feasibility of encoding the Institute for Clinical Systems Improvement Depression Guideline using the Omaha System, Journal of Biomedical Informatics, 45:719-725.
[42] The Macarthur Initiative on Depression and Primary Care, http://www.depression-primarycare.org
[43] Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM (1991) Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence, Arch. Gen. Psychiatry, 48(9):851-5.
[44] Pae CU, Mandelli L, Kim TS, Han C, Masand PS, Marks DM, Patkar AA, Steffens DC, De Ronchi D, Serretti A (2009) Effectiveness of antidepressant treatments in pre-menopausal versus post-menopausal women: a pilot study on differential effects of sex hormones on antidepressant effects, Biomed Pharmacother 63:228-35.
[45] Zhang M, Cheow E, Ho CSh, Ng BY, Ho R, Cheok CC (2014) Application of low-cost methodologies for mobile phone app development. JMIR Mhealth Uhealth. 9;2(4):e55. PMID: 25491323.
[46] Harris KM, Syu JJ, Lello OD, Chew YLE, Willcox CH, Ho RHM (2015) The ABC's of Suicide Risk Assessment: Applying a Tripartite Approach to Individual Evaluations. PLoS One. 2015 Jun 1;10(6):e0127442. PMID: 26030590
[47] Zhang MWB, Ho RCM (2016) Moodle: The cost effective solution for internet cognitive behavioral therapy (I-CBT) interventions. Technol Health Care. 2016 Sep 20. [Epub ahead of print] PMID: 27689560).