

Using Patient Reported Outcomes
(PROs) to improve recognition of
common mental disorders in
primary care

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Abstract

Access to care and treatment for common mental disorders begins with an adequate diagnosis. Unfortunately, the detection of common mental disorders in non-specialized healthcare settings is sometimes of questionable adequacy. Yet, the exact magnitude of this problem is not fully known. Solutions that respond better to the current reality of the clinical practice are needed to facilitate access to care. The main objective of this thesis was to generate evidence on the recognition of common mental disorders (mood and anxiety disorders) in non-specialized healthcare settings and to explore solutions for its improvement.

We systematically reviewed the worldwide recognition of anxiety disorders by general practitioners over a period of 34 years. The data we used to investigate ways to improve the detection levels of common mental disorders in this setting came from the Inventory of Depression and Anxiety Symptoms (INSAyD) project. This is a prospective study conducted in a convenience sample of patients consulting several health care settings for mental health complaints in Barcelona, Spain in 2011-2013. The objective of this project was to develop shorter, easier to use and yet more informative instruments on the diagnosis and severity assessment of common mental disorders.

Our systematic review found that general practitioners were approximately two times better at ruling out negative cases of anxiety disorders (Specificity 90.8%) than at identifying positive cases (44.5%). But, if they used instruments to assist their diagnostic decisions, their recognition levels increased with almost 50%. The Patient Reported Outcomes (PRO) measures developed as part of the INSAyD project had very good psychometric properties. They were short and very easy to use. Their reliability was higher than 0.90 and they were very responsive to short-term clinical change (Standardized response mean > 0.8). They had very good diagnostic accuracy (Area Under the Curve >0.9) and measured adequately symptom severity. PRO measures of functional disability had good psychometric properties, being better at predicting patients' status during the long-term course than at estimating it cross-sectionally.

This thesis showed common mental disorders are substantially under-diagnosed in non-specialized healthcare settings. It also indicated that the use of PROs measures can improve the ability of practitioners to diagnose common mental disorders in non-specialized healthcare settings, being a feasible and valid solution to the under-diagnosis of common mental disorders in this setting.

Resumen

En los trastornos mentales más comunes, un diagnóstico correcto es imprescindible para acceder a servicios sanitarios y para un manejo adecuado del paciente. Desafortunadamente, la detección de los trastornos mentales comunes en entornos no-especializados es problemática y no obstante se desconoce aún su magnitud exacta. Hoy en día, una mejora en el acceso a servicios de salud requiere soluciones que respondan mejor a la realidad clínica del día a día. El objetivo de esta tesis fue aportar evidencia acerca de la detección de los trastornos mentales más comunes en entornos no-especializados y de investigar soluciones para su mejora.

Se realizó una búsqueda sistemática de la literatura sobre la precisión diagnóstica de trastornos de ansiedad en atención primaria a nivel mundial que cubrió el periodo 1980 – 2014. El proyecto El Inventario de Síntomas de Ansiedad y Depresión (INSAyD) proporciono los datos que se usaron para determinar formas de mejora para la detección de trastornos mentales comunes en niveles de atención no-especializados. El proyecto INSAyD es un estudio prospectivo con pacientes que acudieron por síntomas de depresión y ansiedad a distintos niveles de atención en Barcelona en 2011-2013. El objetivo de este proyecto fue desarrollar instrumentos más cortos, más informativos y más fáciles de usar que diagnostique y evalúe la gravedad de los trastornos mentales comunes.

En nuestra revisión, hemos encontrado que los profesionales de atención primaria tienen una capacidad dos veces mayor para excluir correctamente y no cometer falsos positivos (Especificidad=90.8%) que para identificar casos positivos (Sensibilidad=44.5%). Pero, si se usa un instrumento para realizar el diagnóstico, la sensibilidad diagnóstica aumenta

aproximadamente en un 50%. Las medidas de resultados reportados por el paciente (PROs) desarrolladas como parte del proyecto INSAyD mostraron muy buenas propiedades psicométricas. Son instrumentos cortos, fáciles de usar y con una alta fiabilidad (>0.90) y muy sensibles al cambio a corto plazo (respuesta media estandarizada >0.8). Tienen una capacidad diagnóstica excelente (área bajo la curva >0.9) y captan adecuadamente la severidad de los síntomas. Las medidas PRO de discapacidad mostraron buenas propiedades psicométricas y aportaron más a la predicción del pronóstico del paciente que a la predicción de su estado actual.

Esta tesis doctoral demostró que los trastornos mentales comunes están infradiagnosticados en entornos no-especializados. Además, demostró que el uso de medidas PRO mejora la capacidad diagnóstica de los profesionales de salud en entornos no-especializados, siendo una solución altamente válida y viable al frecuente infradiagnóstico de los trastornos mentales comunes en estos niveles asistenciales.

Preface

Given their high prevalence, mood and anxiety disorders receive the denomination of common mental disorders. A recent systematic review estimated a pooled lifetime prevalence of common mental disorders of 29.2% in the general population [1]. Higher prevalence rates were observed in clinical settings: 53.6% of primary care patients were found to suffer from any psychiatric disorder in a nationwide, cross-sectional study in Spain [2]. In non-specialized healthcare settings affective and anxiety disorders are the most prevalent mental disorders [3].

The severity of common mental disorders is as important as their high prevalence rates. Mood and anxiety disorders are associated with substantial functional decline, diminished quality of life, increased burden and service utilization, and higher risk of hospitalization and mortality [4, 5]. Despite the disabling nature of these disorders, many individuals are often under and misdiagnosed by physicians especially in non-specialized healthcare settings [6–9]. Low detection of true cases leads to higher rates of patients with chronic disorders and poorer quality of life. It also generates an additional burden due to increases in self-medication, substance abuse, use of medical services and also due to inappropriate treatment, social isolation, and educational and occupational impairment [10, 11].

The recent economic crisis has led to increased budgetary constraints and to health system reforms in many countries with universal healthcare coverage [12]. In this context, the delivery of mental health services has been increasingly transferred from specialized to non-specialized healthcare levels. The feasibility and effectiveness of this model of service delivery is currently supported by recent research evidence [13]. This shift in mental health service delivery as well as the important individual, societal and economic consequences of under- and misdiagnosis emphasize acutely the need to improve detection rates of common mental disorders. One way of improving detection levels is through the provision of better tools that non-specialized healthcare professionals could use to diagnose more adequately common mental disorders.

The aim of this thesis was to generate evidence on the level of recognition of common mental disorders in non-specialized healthcare settings and to explore solutions for its improvement through the use of Patient Reported Outcomes (PRO) measures. We systematically reviewed the evidence available on detection levels of anxiety disorders in primary care and we proposed solutions for its improvement based on data from a one-year prospective study with patients seeking assistance for common mental disorders.

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1 INTRODUCTION

1.1 Burden of common mental disorders

Physical and mental health are closely intertwined, with mental health playing a key role in one's ability to maintain a good physical health. More precisely, mental health is as essential as physical health to achieve a complete state of wellness [14]. As of late, mental health revolves around two major concepts: mental well-being and mental illness. Mental well-being goes beyond the absence of psychopathology and focuses on positive aspects of mental health. It has a major impact on health and social outcomes [15], being inversely correlated with mental and physical disorders and disability. It is also a strong predictor of mental illness [16].

Mental illnesses have traditionally been grouped into two big categories: serious mental illness and common mental illness. Serious mental disorders, such as schizophrenia, schizoaffective disorders or bipolar disorder, are highly disabling. They interfere significantly with every day aspects of life and are perceived as chronic, non-curable, deteriorating disorders [17, 18]. They are less common, with lifetime prevalence levels between 0.5% and 1% in case of schizophrenia for example [19]. In spite of their lower prevalence, they incur great costs not only at individual level but also at society level. Unlike serious mental disorders, common mental disorders, such as mood and anxiety disorders, are highly prevalent, but less disabling with a more episodic course. Nevertheless, they can have an unfavourable evolution with important negative consequences. In the general world population, the lifetime prevalence of any anxiety disorder was estimated at approximately 16% and the 12-month prevalence at approximately 11% across surveys [20]. In community epidemiological surveys, mood disorders had a lifetime prevalence of around 12% and a 12-month prevalence of around 6% [20].

According to the European Study of Epidemiology of Mental Disorders (ESEMeD), a cross-sectional epidemiological study on mental disorders conducted in the general

population from 2001 to 2003 in six European countries, the lifetime prevalence of any mood disorder in Spain was 11.5% and of any anxiety disorder 9.4% [21]. In Spain, common mental disorders are somewhat less prevalent than in other countries (e.g., France, the Netherlands or Belgium), but a high prevalence has been described in clinical settings: approximately one out of two patients presenting to primary care has one or more psychiatric disorders according to a large cross-sectional epidemiologic study [2]. The most common mental disorders are affective (35.8%), anxiety (25.6%), and somatoform (28.8%) disorders [2]. Hence, clear pathways to care are needed to ensure prompt and adequate care for patients suffering from these disorders.

Common mental disorders are not only highly prevalent but they also have multiple consequences at health, social and economic level. Mood and anxiety disorders are associated with considerable impairments in quality of life and functioning [22], being as disabling as chronic medical conditions [23]. In Spain, mood and anxiety disorders accounted for 2,634 and 805 QALY losses annually per 100,000 primary care patients [24]. Additionally, the early onset of depressive and anxiety disorders has been associated with chronic physical conditions like heart disease, asthma, arthritis, back/neck pain or headache [25]. They also have a considerable impact on day-to-day role functioning, with depression being a major contributor to the number of days totally out of role¹ in the population [26].

The social impact of common mental disorders is far-reaching and worrisome as it extends across the entire course of life. Satisfactory educational attainment is influenced by the presence of mental disorders at each of the educational levels: primary, secondary and higher (college entry and termination). For example, mood disorders are significantly associated with termination of secondary education in upper-middle-income and high-income countries [27]. Additionally, people with common mental disorders have fewer job opportunities, with employment rates being as low as 35% in case of a recent diagnosis of mood or anxiety disorders [28]. Hence, they have limited income generating opportunities. This leads to poverty and prevents them from building solid social networks and from achieving a status within the community [29].

¹ Days out of role – number of days during which one is completely unable to work or carry out normal activities because of health problems

People with mental disorders are at higher risk of poverty than other people. The economic impact of common mental disorders is not only limited to poverty, but it also includes serious effects on economic development. These effects are mainly caused by the high indirect costs associated with this type of morbidity. Their highly disabling nature implies functioning limitations in many domains of life that subsequently lead to productivity losses. Absenteeism, poor performance within the workplace and premature retirement [30–32] are the main drivers of the great economic burden caused by mental disorders. Overall, it is estimated that by 2030 mental disorders will account for an aggregate GDP loss of US\$ 16.3 trillion [33].

All in all, common mental disorders are associated with a great overall burden. Hence, providing adequate care to people with common mental disorders is fundamental and ensuring appropriate pathways to care should be a priority in order to reduce this burden.

1.2 Common mental disorders: pathways to care

Undoubtedly, common mental disorders are impairing and disabling conditions that generate great burdens at individual and society level. Hence, early access to care, adequate detection and assessment combined with timely interventions are essential. Unfortunately, accessing mental health care is not always an easy and straightforward process. According to Goldberg and Huxley [34] people with common mental disorders must pass five levels of care and four filters to access mental health care (see Figure 1). This hierarchical access to mental health care reflects the decreasing proportions of the initial population who actually access higher levels of care. Also, it underlines that access to mental health care depends on the behaviour of the individual and on that of the health care professional.

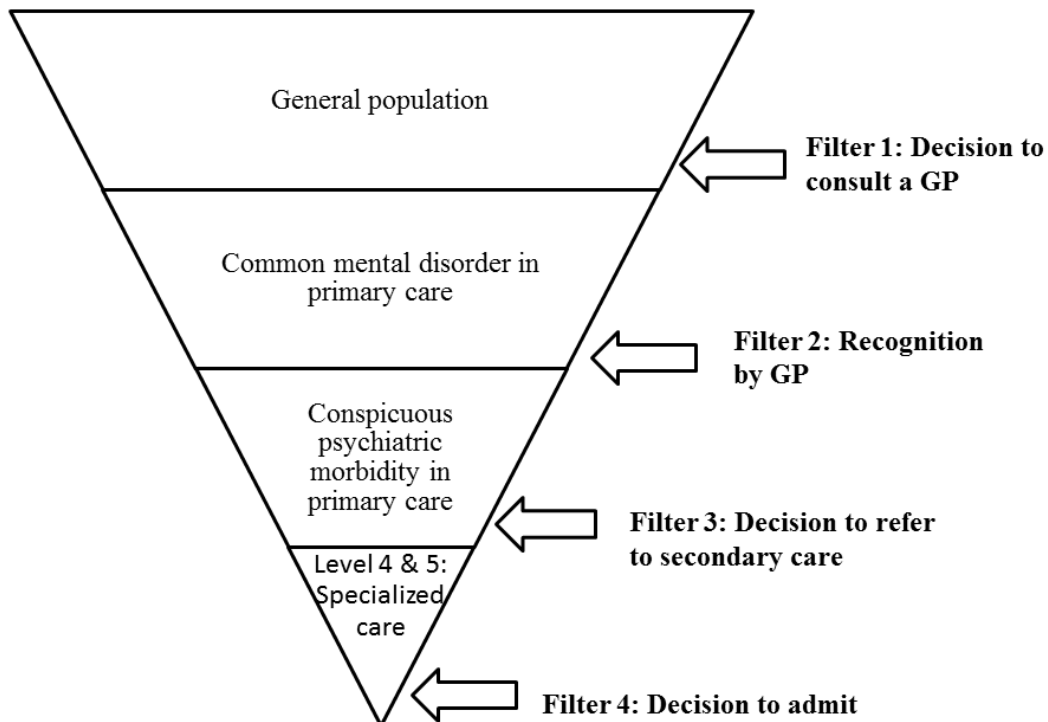


Figure 1 – Pathways to mental health care (adapted from Goldberg & Huxley 1992)

As mentioned above, access to mental health care can be restricted by a wide range of factors which depend on supply (healthcare professional) and also on demand (patient). They include: gaps in coverage, scope of health basket, cost-sharing, geographical barriers, organisational barriers, supply-side responsiveness, health literacy and user attitudes. Some of the most important and relevant barriers to Spanish mental health services are listed below [35]:

- a) Organisational barriers
- b) Geographical barriers
- c) Stigma and discrimination
- d) Insufficient knowledge about mental illness

Organisational barriers

Organisational barriers have a powerful and direct impact on access to health care with limiting effects on demand. This is why they can be a very effective mechanism of restricting healthcare expenditures. Waiting times or lists reflect perfectly this dual

characteristic of organisational barriers. In Spain for example, waiting lists are the major cause of people's dissatisfaction with the healthcare system. In 2014 the average wait time for a visit in specialized care was 53 calendar days and about 30.5% of the cases had to wait for more than 60 days between the date the referral was made and the appointment [36]. Moreover, 36.3% of the Spanish citizens think that health authorities do not take any action to improve the waiting list situation: almost half of the respondents (45.1%) believe that the problem remains the same and 18.2% consider that the problem has worsened in the last 12 months [37]. Additionally, Spaniards think that waiting times before entering the doctor's office have increased in the last year for both primary and specialized care and that they also face more difficulties for accessing an appointment with the doctor [38].

Another relevant organisational barrier is the training level of health care professionals in mental health. The training level of the practitioner can influence recognition rates of mental illness [39]. A study conducted in primary care in Castilla-La Mancha revealed that 92.5% of the general practitioners considered that they needed additional training in mental health [40]. Another study conducted in seven primary care centres from the Girona Health Region also showed that general practitioners needed a better training in mental health and that collaboration and support from mental health centres was essential [41]. This thesis tackles with recognition rates of common mental disorders as the main system barrier to the use of health care services and more details on this aspect will be presented in the next section.

Geographical barriers

Access to mental health services depends on several geographical factors such as distance, rural-urban inequalities and the availability, safety and costs of transport to health care centres. Longer territorial and temporal distances between the place of residence and the location of mental health services have been shown to decrease the usage rate [42]. In Spain, primary care centres are highly accessible with most of the centres being reachable in less than 15 minutes from any place of residence [37]. Unfortunately, the case is quite different for specialized care especially for patients living outside major cities. For example, lower levels of access to acute care, day and intermediate mental health services was reported for rural areas of Andalusia, with most

of the users receiving only outpatient care in mental health community centres [43]. Additionally, 3.21% of the Andalusians live within 30 to 60 minutes distance from the nearest outpatient mental health centre [44]. This limits considerably their access to mental health care [44]. These rural-urban inequalities are also supported by the results of the 2006 Eurobarometer survey that revealed that 46.1% of the Spanish citizens believed that there were differences in access between rural and urban areas [45].

Stigma and discrimination

Stigma and discrimination act as a barrier to access to care through their negative behavioural consequences, such as not seeking help when it is needed [46]. They also have a negative influence on service use and they are frequently associated with non-adherence to treatment [46, 47]. Not only public stigma toward mental illness, but also self-perceived stigma has negative consequences. For example, in individuals with common mental disorders self-perceived stigma has been associated with a poorer health-related quality of life and more work/role limitation [48].

Stigma against mental illness is also common among health care professionals across all countries from the Western world [49]. Things do not seem different in Spain: stigma and discrimination against older people with mental disorders is a reality in the health sector and among the public at large according to a WHO study [50]. Nevertheless, other studies have shown more promising results at least in primary care: Spanish primary health care professionals do not have a negative attitude towards mental health patients, but they do acknowledge their lack of training on mental health and psychiatry issues [51]. Also, most of the Spanish GPs consider that mental illness suffering is comparable with physical illness [52]. Still, 47% of them believe that primary care teams are not motivated enough to manage patients with mental disorders [52]. A recent study on Spanish medical students' attitudes and views towards mental health and psychiatry suggested that Spanish medical students do not have a negative attitude towards mental illness [53]. Moreover, they have a good perception of psychiatry. These attitudes could favour an adequate and appropriate management of patients with mental disorders in the future, as doctors with positive views towards mental health are known to have better recognition rates [54].

A study on how the Spanish media address mental health issues revealed that the press depicts mental disorders in a way that favours stigmatization [55]. According to that study, in the year 2010, 362 news items strictly related to psychiatric illnesses were published in the Spanish media. Most of them did associate mental disorders with danger either through violent crime (35.9%) or danger to others (34.8%) [55]. Hence, as in many parts of the world, the general public in Spain has stigmatised attitudes towards mental disorders, with stigma being more robustly associated with depression and anxiety, than with chronic physical disorders [56].

Insufficient knowledge about mental illness

Mental health literacy is defined as the knowledge and beliefs that the general public has about mental disorders that can aid their recognition, management or prevention [57]. In case of many chronic disorders, a low health literacy level has been linked with many negative health outcomes. For example, inadequate health literacy has been associated with increased risk of hospital admission [58], poorer prevention practices (e.g. glycaemic control) in people with diabetes [59] or with lower adherence to antiretroviral therapies in HIV patients [60]. Mental health literacy has been less extensively researched in spite of it being an important determinant of help-seeking behaviour [61]. Higher mental health literacy is related to a better recognition of mental disorders, thus influencing a person's attitude and behaviour towards those with mental disorders [62]. Interventions to increase mental health literacy have been shown to be effective and to have significant impact on improving opinions about mental illness and on improving attitudes toward seeking help from professional mental health services [63].

A study on stigma and knowledge on mental illness conducted in the general population of the autonomous community of Madrid revealed that the level of knowledge held by the general public about mental illness was average [64]. A high percentage of the respondents (80-90%) had a correct knowledge on treatment and knew that people suffering from mental illness could still work [64]. Lower levels of knowledge were reported for causes of mental illnesses and the levels of awareness of mentally ill people about their illness. Additionally, mental retardation was often confused with mental illness by an overwhelming 56.4% of the respondents. Nevertheless, more studies are

needed in order to fully understand the levels of mental health literacy in Spain so that actions can be planned towards its improvement.

a Pathways to care

The complexity of the concept “access to care” is only partially revealed by the description of the previously presented barriers. Multidimensional terms, such as potential access, realized access and (in)equitable access, are needed in order to comprehensively define and measure it [65].

Potential access

Potential access is defined as the presence of enabling resources [65]. In Spain, mental health care is integrated in the public health system. Nevertheless, due to health reforms some services, such as psychiatric care for people with intellectual disabilities, drug addiction or people in need of psychogeriatric care, have been transferred outside the health system. They are currently provided by the social care sector [66]. Throughout the years the Spanish mental health system has evolved from an institution-based psychiatric system to a more modern model based on community services. This led to considerable efforts being put into creating mental health centres, increasing the number of psychiatric day units and into providing more care to acute cases in general hospitals than in psychiatric hospitals. The current model of health care places mental health services under the jurisdiction of specialized care. In spite of this, several legislative actions, such as the update of the mental health service package in 2006 (Royal Decree 1030/2006) and the 2007 ‘Strategy to Tackle Mental Health’ issued by the Ministry of Health, have been taken in order to emphasize the role of primary care in identifying mental health problems [67]. Thus, new clinical guidelines for general practitioners and specialists were issued on the identification and prevention of mental health problems underlining the importance of a community-care led system for mental health problems.

However, Spain’s overall index of mental health care provision, an index calculated based on the number of GPs, psychiatrists, clinical psychologists and psychiatric beds, was estimated at only 45.1% [68]. The community-based network of mental health care had in 2007 a total number of 466 mental health centres/units for adults, 155 units for

children/adolescents and 175 psychosocial rehabilitation centres nationwide [38]. In 2007, the distribution of hospital-based mental health care resources was the following: the total number of beds for adults and children and adolescents was 272 and 137 respectively in case of short-term/acute hospitalization, the rate of day care places per 100,000 inhabitants was 22.8 in case of day hospitals and the rates of beds per 100,000 inhabitants in hospital rehabilitation and long-term hospital care was 41.3 and 52.0 respectively [38]. In terms of human resource availability for mental health services, Spain has a rate of 8.6 psychiatrists per 100,000 inhabitants [69], 6.6 nurses working in the mental health sector per 100,000 inhabitants [69], 1.9 clinical psychologists per 100,000 inhabitants [70] and 60.0 general practitioners per 100,000 inhabitants [71]. These rates are lower than those for other Western European countries like France, Belgium or Italy.

Realized access

Realized access is the actual use of mental health care services. In Spain the use of health services (mental health specialty services and general medical services) was estimated at 56% in case of individuals with any 12-month mood disorder and at 31.3% in case of individuals with any 12-month anxiety disorder [72]. Overall, individuals with any 12-month mental disorder consulted more frequently general medical services than mental healthcare services or non-healthcare services (24% versus 20.9% and 1.9% respectively) [72]. Spanish individuals with anxiety disorders would rather visit a general medical professional than a mental health specialist (24.9% versus 14.5%) for their mental health problems. In case of mood disorders, similar rates of consultation to general medical professionals and mental health specialists were observed (37.5% versus 35.8%).

The use of health services is influenced by multiple factors that vary from personal health practices to environmental factors and population characteristics [65]. Out of these, age, gender and socioeconomic status play the most significant roles. A study on gender differences in the use of health services for mental disorders across the European Union [68] revealed that women were significantly more likely to use any mental health care service than men. For example, in Spain women had higher odds of using any mental healthcare service for mental health problems than men while adjusting for age, income level, employment status, education and marital status [68]. Additionally, they

had a higher probability of consulting either a general practitioner or a psychiatrist for mental health problems than men (use of services: 14.2% versus 6.7% and 9.7% versus 5.7% respectively). Nevertheless, gender differences in use of services tended to disappear when the overall severity of mental health problems was taken into account [68].

The use of health care services is also conditioned by a great number of potential barriers [73]. Problems in arriving at the correct diagnosis are probably the most important system barrier [74] and of relevance for this thesis. Case-identification and recognition rates play a fundamental part in the correct use of health care services in case of common mental disorders. This is so due to the fact that an appropriate management of patients is highly dependent on the outcome of the consultation. Moreover, treatment success is highly dependent on the early identification of a case. Therefore, such an important barrier should not be overlooked and will be presented in more detail in section 1.3.

(In)equitable access

Unmet healthcare needs can be used to assess equity of access to medical care across population subgroups [75]. At European level a 3.1% (95% CI 2.7–3.6) unmet need for mental healthcare was reported in the adult general population [76]. Higher percentages (48.3%) were reported in those with mental healthcare need [76]. The risk of unmet need for mental health care was higher in younger age groups (18 – 24 years) compared with older age groups. Additionally, homemakers and retired people had higher risk of unmet need than those in paid employment. The same study revealed that the Spanish population had a lower risk of not using mental healthcare services when there was a need for care when compared with other countries like The Netherlands, Germany or France [76].

1.3 Case identification

Recognition of common mental disorders is essential to ensure an adequate disease management and case management for patients who have contacted health care services due to mental health symptomatology. It is also one of the main system-dependent

barriers that controls the access to mental health care. Given that it precedes and determines treatment initiation, recognition of common mental disorders is an area that deserves further investigation. This is especially true in case of primary care where an appropriate patient management requires a high level of precision. This high level of precision is mainly conferred by an adequate diagnosis rather than a simple procedure of screening.

a Recognition of depression

Depression is one of the most common mood disorders, strongly associated with an increased toll of suffering and morbidity. It is projected to become the second global cause of disability by the year 2030 [77]. The high prevalence levels of depression as well as its predicted upsurge as a cause of impairment underline the need for its adequate recognition at all health care levels. However, recognition rates of depression by non-psychiatric physicians are low [78]. A systematic review with meta-analysis [78] revealed that non-psychiatric physicians had a sensitivity of 36.4% (95% CI: 27.9–44.8) and a specificity of 83.7% (95% CI: 77.5–90.0) when diagnosing depression. This means that less than half of the patients suffering from depression are recognized by their physicians. This leads to under-treatment and subsequently to unnecessary suffering with a negative impact on the overall health of undetected patients. Another systematic review that assessed the accuracy of unassisted diagnoses of depression in primary care showed similar results [79]. General practitioners are better at ruling out depression cases (Specificity=81.3%; 95% CI: 74.5% to 87.3%) than at identifying true cases (Sensitivity=47.3%; 95% CI: 41.7% to 53.0%). Still, if we are to extrapolate these results to an urban primary care centre, over-detection (misidentification) is probably more common than under-detection (missed cases) in the case of routine unassisted diagnoses of depression made by GPs.

More research is available on identification rates of depression in primary care than on recognition of depression by professionals that have a medical specialty other than mental health. Nevertheless, several studies have shown that the accuracy of depression diagnoses made by other non-specialized health care professionals is also low. For example, general hospital physicians recognized as depressed only 32.5% of their

patients [80]. Neurologists also had a low diagnostic accuracy for depression of only 35% [81]. Depression is often missed by emergency physicians as well: only 13% (95% CI, 4% to 31%) of depressed patients were referred for further mental health evaluation in an urban, university-affiliated public hospital [82].

When comparing the diagnostic accuracy rates for depression in non-specialized health care settings with the rates registered in specialized mental health care, results are more promising, but yet quite far from being perfect. Sensitivity for the diagnosis of depression is higher for mental health specialists: 0.75 versus 0.49 while specificity levels are quite similar (higher than 0.75) for both levels of care [83]. In other words, the likelihood of detecting a case of depression is three times higher in mental health specialized care than in primary care (OR=3.19, 95% CI: 1.47–6.90) [83]. When adjusted for sociodemographic characteristics and clinical variables, a patient presenting to specialized care is 17.34 times more likely to receive a valid diagnosis of depression than a patient presenting to primary care (OR=17.34, EE=0.66; 95CI: 4.73–63.61).

b Recognition of anxiety disorders

In contrast to other mental disorders, anxiety disorders have been less extensively researched. Less data on management and diagnosis of anxiety disorders in non-specialized health care settings is available than that for depression. Throughout the years, anxiety disorders have consistently been an overlooked topic of systematic research. This is quite remarkable given that about a quarter of the general population is or has been affected at some point in their lives by an anxiety disorder [84]. Additionally, most of the anxiety disorders have a very early onset [85, 86] and a tendency toward chronicity [87] with high comorbidity rates [88] and low treatment rates [89].

Most of the research done so far on recognition of anxiety disorders has focused mainly on panic and on generalized anxiety disorder. This research revealed somewhat worse recognition rates than that for depression. Additionally, several studies have reported very low recognition rates in primary care [90–92] with only one third of anxiety cases being correctly diagnosed [93]. Misdiagnosis rates can be as high as 97.8% for social

anxiety disorder, 85.8% for panic disorder and 71.0% for generalized anxiety disorder [94]. An epidemiological survey conducted in 77 primary care centres representative of Catalonia revealed similar worrying figures: GPs registered a diagnosis of panic disorder in three patients who, according to the SCID-I – the gold standard, did not meet the criteria for this condition [95]. Additionally, they had a sensitivity of only 0.03 in detecting generalized anxiety disorders. Overall, their sensitivity for detecting any anxiety disorder was estimated at 0.28, while their specificity was almost three times higher (0.90) [95].

Recognition of anxiety disorders by other non-specialized health care professionals is also low. Neurologists for example had a diagnostic accuracy of 42% for anxiety disorders [81], while emergency department physicians recognized only 7.4% of panic cases in patients presenting to the emergency department with complaints of chest pain [96]. Similar identification rates (10.8%) were observed in case of anxiety assessments made by non-psychiatric residents (medical and surgical residents) in patients admitted to a general hospital [97]. Higher recognition rates were registered in inpatient cardiac units when approximately 50% of the patients admitted with acute myocardial infarction were identified by medical residents and nurse practitioners [98].

Identification levels across health care levels are similarly low in the case of anxiety disorders. In a study conducted in Spain, general practitioners had a sensitivity of 63% for any anxiety disorder while mental health professionals had a sensitivity of only 59% [83]. In specialized care, a tendency of mental health professionals being better at detecting pure anxiety disorders (sensitivity=0.90) than at detecting comorbid disorders (0.50) was also observed [83].

c Factors that influence the recognition of common mental disorders

Recognition of common mental disorders can be affected by multiple factors, such as patient characteristics, health care professional's characteristics, and system-related factors [99]. Patients' sociodemographic characteristics play a key role in depression recognition: women, patients with higher education levels or with more severe

symptoms have a higher likelihood of being diagnosed [100]. Additionally, recognition rates seem to improve when patients present with psychiatric comorbidities or they report having an inability to work [101]. Given that stigma is associated with mental illness, patients might be reluctant to disclose symptoms of common mental disorders thus hindering recognition. Also, they might be more willing to report somatic complaints rather than mental complaints, given that somatic complaints are perceived as cultural idioms of distress in many ethnocultural groups [102]. Finally, patients may delay making an initial contact with health care providers after the first onset of a mental disorder. A US survey [103] revealed that only 37.4% of the people suffering from major depressive episode made treatment contact in the year of the first onset of the disorder. Delays in making treatment contact in those that eventually make contact are of approximately 8 years in case of major depressive episode [103]. Delays in case of anxiety disorders are even longer: between 9 and 23 years can pass since first onset of disorder before patients make a first treatment contact [103]. Nevertheless, patients with GAD or panic disorder make treatment contact in the very year of disorder onset in higher percentages than patients with specific phobia or separation anxiety disorder for example (approximately 33% versus 1.6% and 1% respectively) [103].

Physicians' attitudes toward mental illness define their manner of conducting patients' assessment. For example, physicians who consider common mental disorders not to be "real disorders" might not even enquire about mental distress or might not think of including common mental disorders as a possible cause for the patient's ailments when making a differential diagnosis. Practitioners with such attitudes or who blame their patients for exaggerating or prolonging their mental illness make fewer accurate diagnoses [54]. Besides attitudes, physicians' interviewing skills are also crucial. Practitioners who are more sensitive to non-verbal cues or who make more empathic or supportive comments that encourage psychosocial disclosure diagnose more cases [54]. Unfortunately, during their professional education physicians most probably acquire better interviewing skills for conducting physical targeted assessments. This is likely due to the prevailing biomedical approach to medical training. Hence, not only patients, but physicians themselves might feel more comfortable discussing aspects related to their patients' physical health rather than their emotional status when conducting a clinical interview [104]. Other barriers to adequate recognition or treatment include

physicians' inadequate knowledge on either diagnostic criteria, procedures or on the mental disorder itself [105].

System barriers include limited accessibility and availability of mental health professionals at practice level [106], as well as inadequate continuity of care or disruptions in the physician/patient relationship [107]. The limited appointment times that give little time for patient education and counselling [105], as well as productivity pressures or lack of a systematic method for managing patients with common mental disorders [108] have also been identified as potential barriers. In addition, the appropriateness of clinical guidelines for non-specialized health care settings has often been questioned [104]. Current guidelines are based on diagnostic criteria developed mainly in psychiatric settings. Hence, they are sometimes impractical for routine use and have uncertain impact on clinician behaviour [109, 110].

Even though all these potential barriers to recognition have been identified, the exact cause of the low recognition rates is still unclear and deserves further research. Until then, the immediate impact of inadequate recognition translates into delays in access to care and treatment. For example, the duration of untreated illness (time from age at onset and age at first treatment) in patients with major depressive disorder was estimated at 39.1 months (SD= ± 97.6) [111]. In case of anxiety disorders, it was longer and varied from 44.4 months (panic disorder) to 90.6 months (obsessive-compulsive disorder) [111]. Longer duration of untreated illness has been associated with worse clinical outcomes and a more negative impact on professional, familiar and occupational impairment [111, 112]. In the case of anxiety disorders, negative treatment response [113], lower levels of functioning [114] and negative course of the disorder [115] were reported. Also, the longer the disorder was left untreated the higher the probability of chronicity [116] and of comorbidity [117].

As discussed, recognition of common mental disorders is problematic in primary care and non-specialized healthcare settings. The evidence available for depression is more conclusive than that for anxiety disorders, but there are still some limitations to consider. For instance, few studies were adequately designed to account for the fact that the practitioner, when in doubt, might revise his/her opinion with subsequent patient visits. In contrast with the systematic research available for depression, no systematic

reviews reporting on the accuracy levels of GPs' diagnoses of anxiety disorders are available yet. This is so in spite of the low recognition levels of anxiety disorders and of the growing evidence that shows that they can be more frequently chronic and more impairing than mood disorders [118]. A systematic evaluation of the recognition levels of anxiety disorders would have the potential of easing health policy decisions and economic evaluations in this area of health care services. It would also contribute substantially to a better acknowledgement of detection problems of anxiety disorders in primary care and other non-specialized health care settings, thus providing an invaluable estimation of misdiagnosis rates at this healthcare level. Hence, the impact and future implications of such an endeavour would be considerable given the high prevalence and high costs of anxiety disorders, particularly when left undetected. It would also lead to an improved understanding of diagnostic issues of anxiety disorders in non-specialized healthcare settings. Thus, improved access to care and treatment might be achieved for patients with anxiety disorders.

d Assessment

Worldwide, the evaluation of common mental disorders is based on two major categorical diagnostic systems that are recognized as international standards: the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) for mental and behavioural disorders. Irrespective of the reference used, the assessment of common mental disorders does not facilitate their recognition especially in non-specialized healthcare settings [109, 110]. Actually, it has been shown to be one of the main system-related factors contributing to the low recognition rates of depression and anxiety described at the beginning of this chapter.

The clinical interview is the most widely used assessment method to diagnose mental disorders in clinical practice. This is so because it ensures a comprehensive understanding of the patient's problems. Clinical interviews can be unstructured, semi-structured and structured. Unstructured clinical interviews are completely flexible favouring the development of a very close rapport between patients and healthcare professionals. They require the interviewer to have a high level of expertise and training and have often been criticized for their reduced reliability and validity. Semi-structured

interviews are more directed but with a flexible and fluid format, while structured methods are more restrictive and goal-oriented.

In non-specialized healthcare settings the semi-structured interview is the recommended method to diagnose mood and anxiety disorders. Healthcare professionals usually begin by trying to find out the reason for the consultation. Then they slowly guide the conversation towards a more exploratory phase. In case of depression, several guidelines, like those issued by the UK National Institute for Clinical Excellence (NICE) [119] recommend the use of case finding questions especially in patients with a past history of depression or a chronic physical health problem with associated functional impairment. Hence, if the doctor suspects a patient suffers from depression, he/she should explore the presence of the two compulsory DSM symptoms for depression by asking the following two questions:

- *During the last month, have you often been bothered by feeling down, depressed or hopeless?*
- *During the last month, have you often been bothered by having little interest or pleasure in doing things?*

If the answer to either of the two questions is affirmative, then the health care professional should proceed to a more detailed assessment exploring for the presence of symptoms, their duration, severity, and associated functional disability. Symptoms are to be explored based on DSM criteria (currently in its 5th version) [120] and they should be severe, disabling and persistent for nearly every day for more than 2 weeks to be considered diagnostic criteria. According to DSM criteria, arguably the gold standard when it comes to diagnostic classification, there are 9 symptoms for depression divided in 2 core symptoms (also used for screening) and 7 secondary symptoms (see table 1).

Table 1 – DSM-5 criteria for major depressive episode

Criteria for Major Depressive Episode: DSM - 5
<p>A. Five (or more) of the following symptoms have been present during the same 2 - week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.</p> <p>Note: Do not include symptoms that are clearly due to a general medical condition, or mood - incongruent delusions or hallucinations.</p> <ul style="list-style-type: none">• Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.• Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).• Significant weight loss when not dieting or weight gain (e.g., a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.• Insomnia or hypersomnia nearly every day.• Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).• Fatigue or loss of energy nearly every day.• Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).• Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).• Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
<p>B. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.</p>
<p>C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).</p>

Source: DSM -V, American Psychiatric Association

In order to meet the requirements of a diagnosis, the patient must have five or more out of nine symptoms with at least one from the first two core symptoms (depressed mood and loss of interest). Hence, the diagnosis of depression is dependent on a simultaneous

decision made on the presence of individual symptoms, duration and disability. Afterwards, the health care professional should conduct a differential diagnosis in order to exclude general medical conditions or a history of substance abuse or a recent bereavement or other mental disorders as possible causes for the presence of symptoms. Besides symptoms, duration and disability, clinicians are advised to consider other risk factors that might affect severity and course of the disorder, such as past history of mental or physical disorders, living conditions, etc. Finally, it is important to conduct a suicide risk assessment as part of the symptom exploration given that depression is associated with a 4-fold higher risk of suicide than the general population [121].

Clinical assessment in case of anxiety disorders follows the same principles as in depression, but the complexity and great variety of different subtypes of anxiety disorders make the assessment even more complicated. Symptoms are again assessed based on DSM criteria (see table 2) and must be associated with functional disability and have a certain duration.

Table 2 - DSM-5 criteria for generalized anxiety disorder

Criteria for Generalized Anxiety Disorder: DSM - 5	
A.	Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B.	The individual finds it difficult to control the worry.
C.	The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):
Note: Only one item is required in children.	
a)	Restlessness or feeling keyed up or on edge.
b)	Being easily fatigued.
c)	Difficulty concentrating or mind going blank.
d)	Irritability.
e)	Muscle tension.
f)	Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).
D.	The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E.	The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).
F.	The disturbance is not better explained by another mental disorder.

Source: DSM -V, American Psychiatric Association

Next, the healthcare professional must make sure that the presence of symptoms is really due to anxiety and not to other factors like a medical condition, a different psychiatric disorder or even substance or medication induced. Given the high rate of comorbidity among patients with anxiety disorders [122, 123] the presence of another psychiatric or medical condition should also be investigated. Risk factors, such as family history of anxiety, female gender or having a chronic medical condition, among others should also be explored given that they might help the clinician recognize a case quicker. Finally, a specific type of anxiety disorder must be identified and the clinician must choose out of almost 12 different types of anxiety disorders [124]. Suicide risk is

not very high for anxiety disorders, but self-harm is quite common and according to different guidelines should be a criteria for referral to specialized care [125]. Hence, the myriad possibilities available in the DSM system for anxiety disorders make it difficult to develop simple but robust case identification and assessment strategies in this area [119].

The assessment, as presented above, is the one recommended by the current clinical guidelines. However, the reality of the clinical practice combined with complexity of the DSM system for both depression and anxiety disorders transforms most often the semi-structured clinical interview into an unstructured interview based on unstructured anamnesis.

e Detection in primary care and non-specialized health care settings

Designed by psychiatrists for psychiatric use, the assessment process as recommended by the DSM can sometimes be difficult to navigate through without guiding tools. Considerable efforts have already been put into simplifying and adapting the manual to the needs and characteristics of non-specialized health care settings. However, as seen in the previous subchapter 1.3.e, the DSM diagnostic system is still rather lengthy and complex. In addition, the characteristics of the non-specialized settings make the process even more difficult. First of all, the majority of patients attending this level of care often present with mixed, atypical or transient syndromes that do not fully match the DSM criteria. Additionally, their demands are seldom expressed as mental health complaints due to stigma or other reasons. Secondly, as the manual was initially meant for psychiatric uses only, the current assessment process requires a level of training and expertise in mental health that most of the non-specialized healthcare professionals do not have. Finally, non-specialized healthcare settings are subject to considerable time pressures due to the high number of patients that they attend every day. For example, general practitioners in some countries can attend up to 60 patients per day [84] often presenting with highly variable expressions of mood and anxiety disorders. Hence, even though the diagnostic process has been greatly facilitated by the development of relatively short and valid instruments to identify mood and anxiety disorders, these

instruments might be of little use if the practitioner has less than 10 minutes with his patients [126].

In an attempt to facilitate diagnostic decisions several clinical guidelines [119, 124, 125] recommend the use of formal rating scales. However, these scales are meant to guide the assessment and not to replace the clinical interview. A list of the most widely used questionnaires to guide the assessment of depression and anxiety disorders in non-specialized health care settings is presented in table 3. As shown in the table, most of the scales for both depressive and anxiety disorders have very good diagnostic accuracy levels, but at the same time some have certain characteristics that make them rather impractical at this level of care. For example, some clinician rated scales require specialized training and previous experience to administer and interpret the results. Additionally, some are very time-consuming to administer and others, that are shorter, might not differentiate very well between the different types of mental disorders.

Table 3 – Most frequently used questionnaires to assess depression and anxiety disorders in non-specialized health care settings

Depression			
Name	Type of instrument	Advantages	Disadvantages
Hamilton Rating Scale of Depression (HRSD) [127]	<ul style="list-style-type: none"> Severity measure 	<ul style="list-style-type: none"> Good psychometric properties Standard measure of depression severity in clinical trials Clinician-rated 	<ul style="list-style-type: none"> Requires training and previous experience Uneven weight attributed to different symptom domains Presence of items measuring different constructs Failure to include all symptom domains of major depressive disorder (e.g. reverse neurovegetative symptoms) Lengthy time of administration (30-40 min)
PHQ-9 [128, 129]	<ul style="list-style-type: none"> Diagnostic and severity measure 	<ul style="list-style-type: none"> Quick self-administered questionnaire for depression (3 min) Captures both symptoms and severity Good discriminative ability when compared with clinical interviews and HDRS 	<ul style="list-style-type: none"> Uses only diagnostic criteria from DSM-IV It doesn't measure anxiety in conjunction with depression Final scores are subject to each person's interpretability and perceptions
Beck Depression Inventory (BDI) [127]	<ul style="list-style-type: none"> Screening measure 	<ul style="list-style-type: none"> Easy administration (5-10 min); self-reported Good psychometric properties Good sensitivity to treatment changes 	<ul style="list-style-type: none"> Apparent instability of scores over time Covers a broad spectrum of somatic symptoms Problems discriminating depression from anxiety
The Center for Epidemiologic Studies Depression Scale (CES-D) [127]	<ul style="list-style-type: none"> Screening measure 	<ul style="list-style-type: none"> Short administration times (7-12 min); self-reported Good psychometric properties 	<ul style="list-style-type: none"> Low test-retest reliability for individual items Problems differentiating depression from GAD
Zung Self-Rating Depression Scale (ZSDS) [127]	<ul style="list-style-type: none"> Screening measure 	<ul style="list-style-type: none"> Adequate internal consistency Adequate validity Adequate to establish presence of symptoms Quick administration (10-15 min); self-reported 	<ul style="list-style-type: none"> Not sensitive to treatment effects Assesses frequency of symptoms rather than severity

Table 3 – Most frequently used questionnaires to assess depression and anxiety disorders in non-specialized health care settings

Anxiety			
Name	Type of instrument	Advantages	Disadvantages
Hamilton Rating Scale of Anxiety [127]	<ul style="list-style-type: none"> • Severity measure 	<ul style="list-style-type: none"> • It measures both physical and psychological symptoms of anxiety • Clinician –rated scale of anxiety severity 	<ul style="list-style-type: none"> • Poor ability to discriminate between anxiolytic and antidepressant effects • Unsuitable for differential diagnosis • Lengthy time of administration (20 min)
The Clinical Anxiety Scale [130]	<ul style="list-style-type: none"> • Severity measure 	<ul style="list-style-type: none"> • Clinician-rated scale • Very sensitive to change • Good psychometric properties 	<ul style="list-style-type: none"> • Does not capture objective signs of somatic anxiety
Physician Questionnaire [131]	<ul style="list-style-type: none"> • Severity measure 	<ul style="list-style-type: none"> • Good psychometric properties • Focus on mixed anxiety and depressive symptoms 	<ul style="list-style-type: none"> • Lower sensitivity to change

Both depression and anxiety			
Name	Type of instrument	Advantages	Disadvantages
The Goldberg Anxiety and Depression Scale (GADS) [132]	<ul style="list-style-type: none"> • Severity measure 	<ul style="list-style-type: none"> • Good psychometric properties 	<ul style="list-style-type: none"> • Questionable utility in elderly
The Hospital Anxiety and Depression Scale (HADS) [129]	<ul style="list-style-type: none"> • Screening measure 	<ul style="list-style-type: none"> • Very short administration times (2-5 min) • Discriminates well between anxiety & depression • Good reliability • Not confounded by physical illness 	<ul style="list-style-type: none"> • Does not allow making a diagnosis of major depression • Does not detect a specific subtype anxiety disorder

According to the current diagnostic criteria [120] and clinical guidelines [119], a diagnosis of either depression or anxiety disorder is dependent on the assessment of several aspects: symptoms, severity, functional disability and duration. They are all required criteria for making a diagnosis. But, not all of them seem equally justified. For example, little is known about the contribution of functional disability criteria to the diagnostic process. In addition, the relevance of assessing all these aspects is not limited to diagnostic purposes only. It can also benefit other steps of the healthcare process. For example, the assessment of severity has been linked with improved clinical management, higher quality of care and a more appropriate choice of interventions for

both anxiety disorders [133] and depression [134]. Additionally, it plays an important part in the referral decision-making process as different studies show that higher severity is associated with higher prescription rates of antidepressants and increased referral to secondary care [135]. The assessment of functional impairment is useful for treatment planning [19] and for tracking clinical progress [136], facilitating decision-making processes [137].

Even though progress towards the improvement of the assessment of depression and anxiety disorders in non-specialized healthcare settings has been made, there is still a need for further enhancements. One way of improving detection rates of common mental disorders in non-specialized healthcare levels might be the development of new tools. These new tools should have greater diagnostic accuracy for common mental disorders than screening instruments and should be specifically designed to address the particular characteristics of this setting. Hence, they should adapt perfectly to consultation times that are 3-4 times shorter than in specialized care. Undoubtedly, there is a growing need for practitioners to have at hand more holistic instruments that inform at the same time on diagnosis, severity or change over time. Short, easy to use instruments that rely more on the patient's perspective and that maximize the information on criteria whose exploration might be more feasible in non-specialized healthcare settings (e.g., functional disability criteria) might also be a solution.

1.4 Care implications and costs for common mental disorders

A correct diagnosis is the first step in the process of ensuring adequate care to patients with mood and anxiety disorders. Its importance is undisputable given that it guides and informs in high percentage treatment decisions. In clinical practice, treatment choices are routinely made based on the physician's clinical judgement and on the patient's preference. Treatment options vary from a wide range of pharmacological drugs to psychological interventions or a combination of both. Their effectiveness depends on diagnosis but also on the person's characteristics [138]. In order to facilitate the process of care, therapy algorithms for the treatment and management of common mental disorders have been developed and included in clinical guidelines. These algorithms are

tailored to the characteristics of each disorder subtype, thus reflecting once again the importance of an accurate diagnosis. They all include follow up visits and recommend assessing response to treatment with the purpose of determining whether symptoms have remitted and whether functioning levels have been restored to premorbid levels.

Common mental disorders are mainly treated in non-specialized healthcare settings rather than in the mental health care system [104, 139]. This is in line with one of the key WHO recommendations [140]. Still, not all patients undergo treatment even though the disorder is correctly recognized by the practitioner. Reasons for not accepting treatment are varied and range from the belief that pharmacological treatments are harmful [141] to the erroneous association of pre-treatment symptoms to drug-related symptoms after treatment initiation [142]. Another treatment barrier might be patients' non-adherence to medication: up to 42% of patients discontinue treatment with antidepressants after 12 weeks [143]. Finally, treatments prescribed might not always be adequate: treatment adequacy rates for anxiety disorders and major depressive episodes were estimated at 57.4% and 23% respectively by a cross-sectional study conducted in 6 European countries [144]. The recognition, assessment and management of common mental disorders are undoubtedly complex and challenging tasks. Additionally, and as seen previously, there is an impressive number of barriers that they must face at every step of the care process. Hence, common mental disorders have widespread implications that affect not only the individual but the society as a whole.

The extended web of consequences of common mental disorders affects life at multiple levels and generates great emotional and economic burden. The economic impact of common mental disorders spreads from costs of treatment and care to productivity and work costs. The low mortality rates combined with the early onset of most of the common mental disorders make costs due to lost or reduced productivity higher than other related costs. A study on the cost of disorders of the brain in Europe [145] estimated the total cost of mood disorders at € 3,406 billion and of anxiety disorders at €74.4 billion (currencies converted using Purchasing Power Parity 2010) [146]. The average cost per patient was approximately three times higher for mood disorders than for anxiety disorders: €3,406 vs €1,076. Indirect costs constituted the majority of costs in case of mood disorders (63.5%), whereas direct medical costs made up the bulk of costs in the case of anxiety disorders (62.2%) [145]. These differences in cost patterns

are due to the different behavioural patterns that people adopt when suffering from these disorders: patients with anxiety disorders are known to be frequent users of healthcare services [147] whereas the debilitating nature of depression expresses itself more in losses of productivity. In Spain in 2010, the total costs of mood disorders were very similar to those of anxiety disorders: 10,763 € million and 10,365 € million respectively. Direct and indirect costs contributed in almost equal shares to the total costs of both disorders: 42.2% and 41.5% direct costs for mood and anxiety disorders respectively and 44.7% and 57.1% indirect costs.

Costs of mood and anxiety disorders are even higher when left undetected and subsequently untreated. Physicians who recognize and record more mental health diagnoses have lower overall healthcare costs due to a reduction in the number of diagnostic tests ordered, referrals to specialists or avoided hospital admissions [148]. Additionally, untreated depression is associated with an increase in direct medical costs compared to adequately treated depression [149]. It also has a worse prognosis when left untreated [150]. On the other hand, undetected anxiety has been associated with an excessive use of healthcare resources [151]. Patients with unrecognized anxiety visit, on average, six times more general and specialty health providers than patients with detected anxiety [152]. Hence, costs of anxiety disorders are higher before diagnosis than after diagnosis, a difference reaching almost 94% in the case of panic disorder, for example [153].

All in all, the high prevalence of common mental disorders, their associated high morbidity and costs as well as the availability of effective treatments should encourage policy makers to improve the detection and management of common mental disorders. Actually, this should be a priority on their agendas. One strategy to improve detection rates might be through routinely assisting the diagnostic process with questionnaires. Like this, recognition rates might improve at a very low cost. Hence, evidence on the accuracy of the routine use of diagnostic tools for common mental disorders and on its cost-effectiveness might provide useful insights for policy makers. This might also enhance the quality of care for patients with common mental disorders.

1.5 Thesis rationale

Practitioners and scientists have long considered under-recognition of common mental disorders in non-specialized healthcare settings to be an important problem. Nevertheless, the available evidence supported this belief only for some specific mood disorders. Little was known in case of anxiety disorders, which traditionally have received less attention than other disorders.

In an ever more complex and time-constrained medical practice, evidence is fundamental to guide clinical decisions, strategies and the entire process of health care. In this context, general practitioners in non-specialized healthcare settings are expected to make valid diagnostic decisions in very short consultation times, following rather impractical and complex diagnostic processes. Hence, physicians are in need of better, shorter and more informative instruments to cover several aspects of this process at the same time (e.g., severity, duration, and diagnosis). Undoubtedly, there is also a need to explore the contribution of the guideline criteria for diagnosing common mental disorders and to uncover ways to make the process more efficient.

The INSAyD (Inventario de Síntomas de Ansiedad y Depresión) project was designed to address these exact issues by generating the evidence required to facilitate clinicians' choices and decisions in the assessment of common mental disorders. The INSAyD project is a prospective study conducted in a clinical sample that aimed to develop adequate tools of severity assessment based on the direct exploration of clinical symptomatology of mood and anxiety disorders, as informed by the patient. Patient reported outcomes (PROs) measures are the best tools available today to capture patients' perspectives on their health status. They are an invaluable source of information that should be at the core of any care improvement process. Even though they have clear benefits in other fields, such as cancer research [154], relatively less is known on the benefits of their use in certain areas of mental health care. It is for this reason that this thesis focused more on PROs measures as possible solutions to improve recognition of common mental disorders in non-specialized healthcare settings, a choice

that was also supported by the recent decision of the DSM to pass from clinician-rated measures of functional disability to self-reported ones.

Finally, this thesis was conceptualized around two major pillars of concern. The first part of this thesis deals with quantifying misdiagnosis rates of anxiety disorders in primary care. This was done in order to add the missing evidence to the one already existing for depression and hence to complete the knowledge on the detection of common mental disorders in primary care. The second part of the thesis provides evidence on rapid and thorough ways of detecting common mental disorders in this setting. This was done because, as indicated by the research available, case detection in non-specialized health care settings is problematic and far from being perfect with plenty of room for improvement.

1.6 Objectives and Hypotheses

The general aim of this Doctoral Thesis was to generate evidence on the recognition of common mental disorders in non-specialized healthcare settings and to explore solutions for its improvement.

Specific objectives:

1. To critically assess the evidence regarding the diagnostic accuracy of general practitioners' diagnoses of anxiety disorders.
2. To compare the accuracy of the diagnoses that general practitioners make when they use severity scales or instruments to detect anxiety disorders with the accuracy they have when they don't use such tools.
3. To study the psychometric properties of a continuous (dimensional) severity scoring system based on DSM-IV-TR symptom criteria for major depressive episode and generalized anxiety disorder.
4. To explore the contribution of functional disability measures to diagnose major depressive episode and generalized anxiety disorder.

Secondary objective:

1. To determine the ability of early changes in functional disability measures to predict the course of major depressive episode.

Hypotheses

1. General Practitioners have a low sensitivity to detect cases of anxiety disorders and a higher ability to identify non-cases.
2. General practitioners' accuracy is higher when they make diagnoses with the help of severity scales or other diagnostic instruments (assisted diagnoses) than when they make diagnoses without such tools (unassisted diagnoses).
3. The severity scoring system based on DSM-IV-TR symptom criteria for major depressive episode and generalized anxiety disorder will have high diagnostic ability, validity and responsiveness.
4. The assessment of functional disability will improve the accuracy of symptoms for diagnosing major depressive episode and generalized anxiety disorder.

Secondary hypothesis:

1. Functional disability trajectories can predict patients' mental health status after one year.

1.7 General Methodology

Specific objectives 1 and 2 were addressed by means of a systematic review of the literature. Specific objectives 3, 4 and the secondary objective of the thesis were addressed by analysing data from the INSAyD (Inventario de Síntomas de Ansiedad y Depresión) project.

We conducted a literature search in seven databases in order to identify studies that reported on rates of detection of anxiety disorders in primary care. All databases were searched from January 1980 to June 2014. The search strategy included “anxiety disorder”, “diagnosis” and “primary care”, as controlled vocabulary and as free text.

The INSAyD project consisted of two consecutive studies. In the first study, we calibrated a multidimensional item-response theory (IRT) model to score DSM

symptoms for major depressive episode and generalized anxiety disorder in the general population [155]. The model was calibrated on the European Study of Mental Disorders surveys' (ESEMED) sample (N = 21,425 general population respondents). The model was fitted using an unweighted least squares estimator with mean and variance corrections (ULSMV) in order to obtain robust standard errors and p values; parameters were estimated using unstandardized theta metric to achieve IRT slope/difficulty scaling metric [156]. The scores were obtained using an IRT scoring algorithm, calibrated with a 2-parameter normal ogive model [157]. Then, the INSAyD scoring model was validated in a prospective study (baseline, 1-month, 3-months and 1-year assessments) with a convenience sample of patients who actively sought professional help for symptoms of mood and anxiety disorders. The data from the clinical study of the INSAyD project were used to address specific objectives 3 and 4 and the secondary objective of the thesis.

a INSAyD project – clinical study sample

The study was conducted at three different healthcare levels: primary care, outpatient mental health centres and acute psychiatric inpatient facilities/hospitals.

Patients visiting a healthcare professional and presenting with active symptoms of mood or anxiety disorders or mixed anxiety-depressive disorders were invited to participate in the study from October 2011 to January 2013. Healthcare professionals from collaborating centres referred visiting patients for inclusion in the study according to specific criteria. Inclusion criteria were: adults older than 18 years old with active affective symptomatology, willing to participate in the study. Patients were excluded if they presented psychotic symptoms, syndromes attributable to organic or substance origin, or significant cognitive impairment.

All referred patients underwent a personal interview where they were informed again about the scope and aim of the study. When the patient met all the inclusion criteria and agreed to participate, he/she signed the informed consent and the assessment was performed with the help of a computer interviewing application. Following the clinical interview, patients were asked to fill-in the self-reported questionnaires. All interviews were conducted by certified clinical psychologists.

b INSAyD project – measures and instruments

Mental disorders were assessed using Mini International Neuropsychiatric Interview 5.0 (MINI). MINI 5.0 is a structured diagnostic interview for DSM-IV Axis I psychiatric disorders [158]. We used the following DSM-IV diagnoses: major depressive episode, generalized anxiety disorder, comorbid MDE and GAD and no diagnosis of MDE or GAD. Based on these MINI diagnostic categories, we defined a diagnostic gold standard whose positive cases were patients with either pure or comorbid MINI diagnoses of MDE or GAD and whose negative cases were patients without an active MINI diagnosis of the above-mentioned disorders.

The number of MDE/GAD symptoms was assessed with the Inventory of Depression and Anxiety Symptoms - Depression scale (INS-D) and the Inventory of Depression and Anxiety Symptoms - Anxiety scale (INS-G), two symptom checklists based on DSM symptom criteria [159].

The severity of mental disorders was determined with the following clinician-administered measures: INS-D, INS-G, the Hamilton Rating Scale for Depression (HRSD) [160] and the Hamilton Rating Scale for Anxiety (HAM-A)[127]. We also used two self-reported indicators for the severity of depression and anxiety disorders: the Patient Health Questionnaire (PHQ-9) [129] and the Beck Anxiety Inventory (BAI) [127].

Disability was measured with both clinician-administered and self-reported measures. We used the Global Assessment of Functioning (GAF) [161], a one-item scale, the World Health Organization Disability Scale 2.0 (WHODAS 2.0) [162] the 12-item version and an analogue scale of functioning based on clinical GAF [163].

2 PUBLICATIONS

In response to specific objectives 1 and 2 of this thesis, we systematically assessed the evidence available on detection levels of anxiety disorders in primary care in the following article:

Detection of anxiety disorders in primary care: a meta-analysis of assisted and unassisted diagnoses

Elena Olariu, Carlos García Forero, José Ignacio Castro-Rodríguez, María Teresa Rodrigo-Calvo, Pilar Álvarez, Luis Miguel Martín-López, Alicia Sánchez-Toro, Núria Duran Adroher, María Jesús Blasco-Cubedo, Gemma Vilagut, Miquel Àngel Fullana, Jordi Alonso.

Olariu E, Forero CG, Castro-Rodríguez JI, Rodrigo-Calvo MT, Álvarez P, Martín-López LM, Sánchez-Toto A, Adroher ND, Blasco-Cubedo MJ, Vilagut G, Fullana MA and Alonso J. [DETECTION OF ANXIETY DISORDERS IN PRIMARY CARE: A META-ANALYSIS OF ASSISTED AND UNASSISTED DIAGNOSES](#). *Depress Anxiety*. 2015; 32(7):471–84.
doi:10.1002/da.22360

In response to specific objective 3 of this thesis, we validated and determined the diagnostic accuracy, the ability to assess severity and to detect changes of two clinician-administered scales based on DSM-symptom criteria in the following article:

Validation of clinical symptom IRT scores for diagnosis and severity assessment of common mental disorders

Elena Olariu, José Ignacio Castro-Rodríguez, Pilar Álvarez, Carolina Garnier, Marta Reinoso, Luis Miguel Martín-López, Jordi Alonso, Carlos García Forero, on behalf of INSAyD Investigators.

Olariu E, Castro-Rodriguez JI, Álvarez P, Garnier C, Reinoso M, Martín-López LM, Alonso J and Forero CG. [Validation of clinical symptom IRT scores for diagnosis and severity assessment of common mental disorders](#). Qual Life Res 2014; 24(4):979–92. doi: 10.1007/s11136-014-0814-5.

In response to specific objective 4 of the thesis, we explored the contribution of functional disability measures to diagnose major depressive episode and generalized anxiety disorder in the following article:

Asking patients about their general level of functioning: Is IT worth IT for common mental disorders?

Elena Olariu, Carlos García Forero, Pilar Álvarez, José-Ignacio Castro-Rodríguez, María Jesús Blasco-Cubedo, Jordi Alonso, on behalf of INSAyD Investigators.

Olariu E, Forero CG, Álvarez P, Castro-Rodríguez J-I, Blasco MJ, Alonso J, et al.
[Asking patients about their general level of functioning: Is IT worth IT for common mental disorders?](#) Psychiatry Res 2015, 73(1): PSYD1500387.

Olariu E, Forero CG, Álvarez P, Castro-Rodríguez JI, Blasco MJ, Alonso J;INSAyD Investigators. [Asking patients about their general level of functioning:Is IT worth IT for common mental disorders?](#) Psychiatry Res. 2015 Oct 30;229(3):791-800. doi: 10.1016/j.psychres.2015.07.088.

In response to the secondary objective of this thesis, we explored the potential use of functional disability measures to predict the course of depression in the following manuscript:

Early Trends of Patient-Reported Functioning Predict 12-Month Course of Depression

Carlos García Forero , Elena Olariu, Pilar Álvarez, José-Ignacio Castro-Rodriguez, Àngels Pont, María Jesús Blasco-Cubedo, Gemma Vilagut, Jordi Alonso

Submitted to *Quality of Life Research* in September 2015

This secondary objective was suggested by clinicians and other members of the INSAyD research team. It sprang from the need to investigate other potential uses for functional disability measures besides diagnosis. Also, it responds to other post-conference comments we have received in relation to the INSAyD project.

Early Trends of Patient-Reported Functioning Predict 12-Month Course of Depression

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Short title: Functioning as Depression predictor

Keywords: Disability; Mental; Affective Disorders; Primary Care; Assessment/Diagnosis;

Latent Class Analysis.

Early Trends of Patient-Reported Functioning Predict 12-Month Course of Depression

ABSTRACT

Aims: Functioning is a compulsory criterion in the diagnosis of mental health disorders.

DSM5 functioning assessment moved from clinician-rated to patient-reported outcomes (PROMs), but the ability these measures to predict disorder course remains uncertain.

Methods: Longitudinal study (four assessments: baseline, 1-, 3- and 12-months) of 179 patients with major depression symptoms. We assessed the presence of active MDE using DSM5 criteria, as well as clinician-reported functioning (Global Assessment of Functioning, GAF) and two PROMs (World Health Organization Disability Assessment Schedule, WHODAS, and Analogue Scale of Functioning, ASF). Functioning trends in the first three months were modelled using Growth Mixture Models. Person trend parameters served as predictors of 12-month MDE status (absent/present) in a logistic regression model, adjusted by sex, age, physical and mental comorbidities and MDE status at the 3rd month. Predictive ability of clinicians and PROMs was compared with Area Under the Curve obtained in ROC analysis.

Results: We found a homogeneous pattern of trajectories progressing towards functioning recovery (improvement in points/month: GAF: 1.97; WHODAS: 0.46; ASF: 2.43). Individual functioning course was the best predictor of 12-months MDE; steeper functioning recovery indicated lower probability of depression at follow-up. WHODAS had good predictive accuracy ($AUC_{WHODAS}=0.79$), but was significantly outperformed by GAF and ASF measures ($AUC_{WHODAS}=0.76$; $AUC_{GAF}=0.92$; $AUC_{ASF}=0.93$).

Conclusion: Early functioning trends may predict 12-month course of MDE as accurately as clinical assessment, supporting the feasibility of PROMs for mental health monitoring in non-specialized services. Longitudinal modelling opens a promising line of research about PROMs as predictors of mental health.

INTRODUCTION

Since the introduction of the multi-axial system in DSM-III, functioning assessment has been a part of routine mental health diagnosis. Axis V in the DSM-IV was devoted to the assessment of functioning by means of the Global Assessment of Functioning (GAF) that reflects the clinician's judgment of a patient's overall level of psychological, social and occupational functioning [1]. Due to the ample diffusion of the DSM, the GAF scale has been the main instrument for evaluating functioning and quality of life in psychiatric patients [2, 3]. The GAF is applicable to a wide range of ages [4]. It is easy [5] to apply [6], relatively inexpensive and it has an appealing clinical interpretation. These characteristics have made it widely used in both clinical and research contexts [7].

Important limitations about the GAF have been acknowledged. Even though it has shown good reliability in research settings [1, 8, 9], the GAF has received criticisms for its low inter-rater reliability in clinical settings [3]. Its reliability and validity is highly dependent on rater's training and clinical experience [1, 6, 10–12]. There is also evidence that the GAF is overly sensitive to symptom severity, even to a higher degree than it is to impairment [1, 6, 11, 12], which flaws its construct validity [6, 10, 11] and questions its value over symptoms when predicting the outcomes of patient care [13, 14].

These limitations, along with the intention to increase coordination with the ICD, led to the suppression of Axis-V in the new DSM-5 and, thus, to the exclusion of the GAF. Instead, the DSM-5 adhered to the International Classification of Functioning, Disability, and Health (ICF) [15], for clinical and diagnostic use [16]. In the ICF, mental diseases are separated

from functioning and the latter is conceptualized as a multidimensional construct encompassing impairment, that leads to activity restrictions, and social restrictions as the result of a disorder.

Instead, DSM-5 proposes to assess disability using WHODAS 2.0, a patient reported outcome measure (PRO) in six domains of functioning. While WHODAS has excellent psychometric properties [11, 17] even for subthreshold patients [18], its performance across in different mental disorders is uncertain. It has good results in specific pathologies, such as depression [19], but it may not in detect change when there is good premorbid baseline functioning [11]. Forensic professionals criticize WHODAS 2.0, arguing that it is not possible to assess the trustworthiness of patient's responses [20], and that the lack of clear cut-offs difficult score interpretation.

The usefulness of PRO measures for monitoring mental health patients is not well-known. PRO measures could be used for efficiently follow patient course and burden of disease. Their incremental value over disorder symptoms to predict treatment outcome has not been studied in depth, either. Moreover, PRO measures have not have not been compared with the GAF in these grounds. In this study, we aimed to determine the homogeneity among early trajectories of PRO functioning measures, as well as their ability to predict clinical status in patients demanding attention for affective problems one year after first use of health services. Additionally, we compared PRO measures with clinical GAF assessment. We hypothesized that the initial changes in PRO measures of functioning will predict clinical course of MDE, and that they perform similarly to clinical assessment.

METHODS

Design

Observational, prospective study (baseline, 1-, 3- and 12-month assessments) of patients consulting health services because of mood and anxiety symptoms in three

different health care levels: primary care, outpatient mental health centers and acute psychiatric inpatient facilities/hospitals. They pertained to 7 collaborating centers.

Patients were recruited according to the following inclusion criteria were: adults older than 18 years old demanding attention for incident or aggravated episodes of affective or anxiety symptoms. Psychotic symptoms, syndromes attributable to organic or substance origin, or significant cognitive impairment were excluded. Further details on recruitment procedures have been published elsewhere [18].

Procedures

Patients were assessed at baseline in a personal computer-assisted clinical interview including in-depth psychiatric assessment, and administered a series of self-reported instruments. Patients were re-assessed at 1 and 3 months after initial evaluation. The final assessment, a year after the initial visit, was a phone interview exploring the presence of active MD symptoms and at the end, the same self-reported instruments were administered.

At any time point during the follow-up, patients were considered dropouts if they missed the appointment or couldn't be reached in more than 5 occasions.

Functioning Assessment

Clinical and self-reported measures of functioning were collected during the baseline, 1-month and 3rd month interviews. Clinical assessment was conducted using DSM-IV axis V criteria with the Spanish version of the Global Assessment of Functioning (GAF) [21], a scale ranging from 0 to 100, from inability to superior functioning (Greenberg, Rosenheck 2005). A 10-point tabulation guideline aids clinicians to make their decisions.

Self-reported assessment of functioning was carried out with two PRO measures. Firstly, following DSM-5 recommendations, the 12-item Spanish version of the World

Health Organization Disability Assessment Scale 2.0 (WHODAS 2.0) [22]. The WHODAS 2.0 has a total score ranging from 12 to 60 [17], higher scores reflecting lower functioning (i.e. higher disability). The WHODAS 2.0 has shown good psychometric properties [23].

The second PRO measure was an analogue scale of functioning (ASF), a one item-scale asking for the overall level of functioning due to the mental condition on a scale from 1 (lowest) to 100 (highest) (“*On a scale from 1 to 100, how would you currently rate your overall level of functioning?*”). The ASF was developed by the authors to capture the patient’s own estimates of his level of functioning. It has shown good discriminant and criterion validity [24]. Similar scales have been reported in the literature with good performance in clinical samples [25, 26].

Clinical status

Symptoms were assessed using the PHQ-9 [27], a 9-item questionnaire with scores ranging from 0 (none) to 27 (highest) severity [28]), with excellent reliability and validity. PHQ-9 items are DSM symptoms and it can be interpreted according to DSM criteria: an item score reaches 2 or higher (in a 4-point likert scale) indicates that the symptom/criterion is present. In this study, patients were considered as having active MDE symptomatology if they fulfilled DSM-5 criteria for MDE, that is five present MDE symptoms (i.e., 5 items scored as 2) and one of them is either item 1 or 2 (compulsory DSM-5 MDE criteria). All other patients were classified as not having active MDE symptoms. PHQ-9 measures were also used to define a group of stable patients for reliability assessment; we considered stable those with score differences below the standard error of measurement (5 points) in the first month [24]

Statistical Analysis

Modelling functioning trajectories

As a first step, we studied whether there were significantly different trends of functioning evolution using a longitudinal growth mixture model (GMM) to characterize trajectories of functioning from baseline to the 3rd month of follow-up. GMM is a case-centered approach using latent mixture models to assign individuals into inferred subpopulations (classes). GMM finds clusters of sample trajectories grouping cases into homogenous classes, and allowing heterogeneity between them. The evolution in time of each individual within each class [29] is modeled by individual parameters: intercepts (i), represent the starting value whereas slope (s) is the rate of change over time. Slopes were fixed to reflect time since the baseline in months, thus indicating the rate of monthly functioning change. As only three timepoints were available, we modelled linear change and did not attempt to model curvilinear trends in functioning across time.

Detection of functioning evolution classes

Fig 1 shows the tested model structures. Solid lines represent the mixture part of the structure, and dashed lines the overall predictive model. Latent classes (c) are inferred from individual trajectory heterogeneity, indicated by i and s parameters. We compared different number of clusters in the functioning models, starting with single-cluster model (assuming that individuals shared the same overall trajectory), then adding clusters for each successive model. Individual allocation in classes was based on maximum posterior probability. In order to select a number classes in c , we used the proportion of subjects in the smallest cluster (>10%), and sample size adjusted Lo-Mend-Rubin log-likelihood test (Adjusted LMR_LRT) to assess differences in the log-likelihood between models with k and $k+1$ clusters; p -values below than 0.01 indicated that the addition of a supplementary cluster [30, 31] improves fit with respect to the k cluster solution. When cluster frequency was too small or Adjusted BLRT did not reach significance, the hypothesis that the $k+1$ cluster solution improves fit over the k -cluster solution cannot be rejected, so the simplest solution was chosen.

In order to avoid biasing the results we considered patients with information at all time points. Sensitivity analyses showed that including and excluding individuals with missing data resulted in the same cluster structure. Models were estimated with 2000 randomly starting values using MPLUS software version 7.0 (Muthén and Muthén, Los Angeles, CA).

FIGURE 1 ABOUT HERE

Prediction of 12-month status using individual functioning trends

The best fitting GMM model was used to estimate individual intercept and slopes, representing individual functioning trajectory. Parameters were then introduced as predictors of MDE 12-month status in a binary logistic regression model to determine the predictive ability of functioning trajectories on MDE status [32]. One model was developed for each measure, thus using GAF, WHODAS and ASF separately to predict patient clinical status (MDE active/inactive) at the 12-month follow-up. Functional measures entered the models as continuous variables using a logit link and specifying a binomial outcome distribution. We included patient status at 3 months to control for the clinical status due to initial patient response to treatment. Age, sex and presence of number of chronic physical comorbidities were also included as adjusting variables in the predictive models because of their known influence in functioning and MDE.

In order to check for incremental effects of functional assessment over active MDE symptomatology at the third follow-up up, we estimated the same models using a hierarchical approach, including active MDE symptomatology at 3rd follow up as baseline model, and then we added functioning measures [33]. Six models were estimated in total:

three types of functional assessments, considering and not considering disorder status at 3rd month. All models were adjusted for age, number of chronic conditions and sex.

Model performance was assessed by computing model parameters, standard error and significance (using Wald's test), as well parameter OR for interpretation. Model fit was assessed using Nagelkerke's Pseudo R-squared values and Hosmer-Lemeshow fit test using 8 groups. Predictive ability was checked by computing model-based probabilities of MDE presence at the follow-up and performing ROC analysis versus actual MDE symptom status. For each predictive model of each measure, with and without MDE status at 3-months, we computed the AUC, Standard Errors and their confidence intervals. To avoid over-fitting, predictive analyses were conducted using a 10-fold cross-validation sample. Given that GAF and ASF higher scores reflect higher functioning, while the WHODAS goes in the opposite direction, we inverted WHODAS score direction to match the positive functioning direction of the GAF. In this regard, all ORs were expected to be below 1 as they would indicate improvements in functioning associated with less likelihood of a disorder. All analyses were conducted using MPlus 7.2 and SPSS 20.0.

RESULTS

In total, 233 patients completed the baseline assessment, with average age 49.1 years old (SD=14.8), 69% were women. More than half of the sample (57%) fulfilled DSM-5 symptom criteria for active MDE symptomatology at baseline, 37% of them with comorbid mental disorders. The average number of physical conditions was 1.13 (SD=1). Table 1 shows the descriptives of the sample considered by measurement occasion.

TABLE 1 ABOUT HERE

As it can be seen in table 2, the proportion of active MDE symptomatology decayed linearly during the 4 measurement times ($F_{1,139}=30.36, p<0.00$), from 57.9% to 21%. Self-reported measures showed a significant trends toward improved functioning during the first three assessments (GAF $F_{1,162}=22.73, p<0.00$; WHODAS $F_{1,142}=24.1, p<0.00$; ASF $F_{1,161}=12.80, p<0.00$), a trend that PRO measures continued up to the final follow-up. In the N=109 group of stable patients, test-retest reliability of the functioning measures resulted in 0.52, 0.83, 0.57 for the GAF, WHODAS and ASF, respectively. Notice that The GAF and ASF are single-item measures, so that their lower reliability was to be expected.

 TABLE 2 ABOUT HERE

Table 3 shows GMM model selection and parameters. For all measures, the $c=1$ class solution was preferred over solutions with more classes, as they had either very low frequencies in the smallest cluster (GAF=2.8% ; WHODAS=49.2% ; ASF=3.2%) or a non-significant test for 1 vs 2 clusters solutions (Adjusted LMR_LRT: GAF 17.97 $p= 0.07$; WHODAS=23.78 $=0.05$; ASF=21.45, $p=0.03$). Table 2 shows good fit in the simplest 1-cluster model according to chi-square and SRMSR values, indicative of homogeneous trends. All functioning models started in values above the latent intercept average, with the GAF showing the highest standardized intercept value (5.51) and WHODAS showing the lowest deviation from average (3.0). As regards the slope parameters, all measures showed an average change towards functioning recovery, (GAF 1.97 points/month; WHODAS= -0.46 points/month; ASF= 2.43 points/month). Standardized slopes showed the GAF had the fastest change rate (0.57), followed by WHODAS (-0.47), and ASF (0.36). Intercept and slopes showed significant negative correlations, a typical result of regression towards the mean in severe cases. The 1-class model explained a great amount

of indicator variance in all three occasions, with a minimum of 51% in the 1st month ASF and a maximum 87% in the 3rd month ASF.

TABLE 3 ABOUT HERE

Table 4 shows the predictive value of patient MDE symptom status (active/inactive symptom criterion) at the 3rd month assessment of individual trajectory parameters 12 months after the initial assessment. An active MDE 3rd-month status significantly increased the likelihood (OR=7.44) of active MDE symptomatology at 12 months. However, when individual functioning trajectories were included in the model, 3-month MDE symptomatology became non-significant in case of the GAF and ASF measures, and substantially reduced its predictive value in the case of the WHODAS (OR=3.89). For all measures, a higher intercept value (indicative of milder disability at baseline) indicated reduced likelihood of 12-month MDE symptoms. Initial GAF intercept was highly predictive of 12-month MDE (OR=0.79), followed by ASF (OR=0.84). The models indicated that a 1-point increase in the individual slope parameter, (indicative of steeper patient improvement) predicted lower probability of active MDE at 12-month. Noticeably, while changes in PRO measures were likely to predict MDE at 12-month (GAF OR=0.22; ASF=0.41), individual slopes were not significant predictors in the case of the WHODAS (OR=0.93, $p=0.62$).

TABLE 4 ABOUT HERE

Figure 2 compares predictive ability of each measure measures using the ROC curves in the 10-Fold cross-validation sample by assessment, taking and non-taking into account the MDE status information at the 3rd month.

FIGURE 2 ABOUT HERE

ROC analysis and AUCs indicate that functioning trends predicted MDE symptom status at 12 months. Active MDE symptoms were quite associated with MDE 12-month status ($AUC_{MDE3m}=0.72$). The trends of all measures performed quite well in predicting 12-month symptoms, ($AUC_{WHODAS}=0.76$, $AUC_{GAF}=0.92$; $AUC_{ASF}=0.93$). Including 3-month symptom status in the trajectory model significantly improved WHODAS predictive ability ($AUC_{WHODAS}=0.79$), but did not have significant impact on GAF and ASF predictive ability.

DISCUSSION

Recently, the DSM-5 moved the focus of disability assessment from clinical observation to patient-reported information, with the intention to get closer to the standards proposed by the ICD [14] and increasing the quality of disability assessment [9,5]. Notwithstanding, the usefulness of PRO measures in patient management needs [13] and their ability to predict clinical outcomes remain underexplored. In this paper, we investigated the trajectories of clinical (GAF) and PRO measures (WHODAS2.0 and Analogue Scale of Functioning), in sample of patients demanding attention for affective symptomatology to predict active DSM Major Depression symptomatology a year after the demand.

Results showed that considering the evolution patients' functioning during the first three months might help anticipating clinical MDE remission and new onsets after patient contact with health services. When considered in isolation of other mental health

information, GAF, WHODAS and ASF achieved a predictive value with Areas Under the Curve over 0.75. Moreover: adding information about MDE status at 3rd month did not increase: the trend of PRO measures had better predictive ability than MDE status. Once the patients express a demand for attention regarding affective distress, the evolution of subjective perceptions of functioning is associated with their future clinical status.

These results must be interpreted in the light of its limitations. First, the sample is a composed of patients demanding attention for mental symptomatology and conducting some kind of treatment [33] and thus the results cannot be generalized to MDE sufferers outside clinical settings. This strategy might be representative of clinical course after patient demands, after they alert the professional of some kind of mental distress. Secondly, the sample was not large enough to validate our prediction in an independent dataset for the selection of the models and estimating the generalization error[34]. Nevertheless, the use of a 10-fold cross-validation sample for testing prediction accuracy minimizes the risks of overfitting [35]. Thirdly, only three time points were used in patient assessment, which avoided us from testing higher order recovery effects indicating steeper recoveries at the initial treatment.

At the same time, our study design counts with some strengths. We measured and compared functional disability with the two standard instruments proposed the DSM-IV (GAF), and DSM-5 and ICD (WHODAS 2.0). To our knowledge, this is the first comparison of these instruments in a longitudinal predictive design in sample of demanding patients: a case that confronts two different approximations to assessment (clinical vs. PROMs) in a naturalistic situation regarding the patient demands. Moreover, it is known that there is a lag between symptom and in functioning recovery, the latter improving after symptoms have begun to diminish [36]. The predictive 12-month time-window used in this study allows enough time for functioning recovery after symptom remission.

PRO methods have received criticisms regarding their objectivity and validity in mental health assessments [10, 24][20], but there are high expectations on the possibilities they might offer [37]. The role of disability in the course of depression has been depression has also received attention [38], but it has been mainly treated as an outcome. In our study, functioning assessment was a useful outcome to predict patient status in MDE. Our results indicate that monitoring early functioning changes allow accurate prediction about disorder course with 12 month anticipation. Little research has been devoted to the predictive value of disability and functioning, which is mostly considered as an outcome to be predicted. However, there's been a certain amount of evidence indicating that the course of subjective functioning is related with patient evolution in specific populations, for instance comorbid affective disorders in chronic fatigue [39], or in late life depression disorder [40].

Our study points at the usefulness of PRO measures of functioning as predictors of clinical course. This result adds to previous evidence of the usefulness of PRO instruments in MDE [19], but also stresses its advantages. Clinical assessment of functioning requires specialized training [10]. The PRO measures herein presented have established validity, and they depend only on patient responses, not on rater's ability. Given this, make PRO measures a better election for monitoring disability caused by MDE. Concerns about patient trustworthiness [20] might be not well grounded, given predictive ability of a simple question such as the one implied by the ASF.

The ASF is also as good a predictor as the GAF. Surprisingly, it was an even better predictor than the WHODAS, a standardized questionnaire. A possible explanation is that while the ASF is totally specific of patient demands and the patients assess their functioning in relation to their demand. Conversely, the WHODAS unspecific, and explores both physical and mental components, which might hinder its predictive ability. The ASF , and might be adequate enough to be used in non-specialized care services under pressure

from rising demand, such as Primary care [24]. Its simplicity, independence from the rater, and predictive ability deserve further studies to confirm it as one useful tool for monitoring patients in other mental disorders and populations.

The application of longitudinal modeling in series of PRO measures opens a promising line of research where PRO measures can be considered as predictors of health status, instead of a health outcome. Further research in this line would require longitudinal studies about the performance of PRO mental health functioning measures in other populations and psychopathologies. In summary, monitoring functional disability in MDE is a successful way to predict disorder course after 12-months. Such predictions may have important implications for treatment, allowing the clinician to advance aggravation and chronification. Functioning trends can be a key outcome in non-specialized services for patient management. The simplicity of PRO measures is promising in this regard, stressing the need for investigation on the effectiveness of self-reported measures as predictors of mental health and other disorders.

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Table 1 – Sociodemographic and clinical characteristics of the study sample

Sociodemographic variables	N (%)	Active mental disorders			
		No active mental disorder N (%)	Pure MDE N (%)	MDE + comorbid ^b N (%)	Other Disorders ^b N (%)
Total	233 (100)	75 (32.2)	79 (33.9)	56 (24.0)	23 (9.9)
Age, <i>M</i> (<i>SD</i>)	49.1 (14.8)	50.5 (16.1)	51.1 (13.3)	46.1 (15.2)	45 (13.2)
Sex					
Men	72 (30.9)	26 (34.7)	23 (29.1)	15 (26.8)	8 (34.8)
Women	161 (69.1)	49 (65.3)	56 (70.9)	41 (73.2)	15 (65.2)
Nationality					
Spanish	212 (91.4)	69 (92.0)	72 (91.1)	49 (89.1)	22 (95.6)
Not Spanish	20 (8.6)	6 (8.0)	7 (8.9)	6 (10.9)	1 (4.4)
Education level					
Less than Primary & Primary	92 (39.5)	32 (42.7)	30 (38.0)	25 (44.6)	5 (21.7)
Secondary	97 (41.6)	25 (33.3)	38 (48.1)	21 (37.5)	13 (56.6)
Higher	44 (18.9)	18 (24.0)	11 (13.9)	10 (17.9)	5 (21.7)
Employment status					
Working	106 (45.5)	34 (45.3)	30 (38.0)	27 (48.2)	15 (65.2)
Non-working	118 (50.6)	40 (53.3)	43 (54.4)	27 (48.2)	8 (34.8)
Others	9 (3.9)	1 (1.3)	6 (7.6)	2 (3.6)	0 (0)
Civil status					
Never married	61 (26.2)	18 (24)	22 (27.9)	12 (21.4)	9 (39.1)
Married or living with a partner	132 (56.6)	42 (56)	47 (59.5)	33 (58.9)	10 (43.5)
Divorced or separated	30 (12.9)	12 (16)	8 (10.1)	7 (12.5)	3 (13)
Widowed	10 (4.3)	3 (4)	2 (2.5)	4 (7.2)	1 (4.4)
Setting					
Primary Care	91 (39.0)	31 (41.3)	15 (19.0)	30 (53.6)	15 (65.2)
Outpatient mental health centers	122 (52.4)	42 (56)	47 (59.5)	25 (44.6)	8 (34.8)
Hospital	20 (8.6)	2 (2.7)	17 (21.5)	1 (1.8)	0
Patients with physical comorbidities	175 (77%)	55 (73%)	59 (74%)	47 (83)	20 (86)
Average physical conditions (<i>SD</i>)	1.13 (1.01)	0.96 (0.94)	1.24 (1.20)	1.18 (0.94)	1.17 (0.65)
Mental disorders					
MDE ^b	135 (57.9)	0 (0)	79 (100)	56 (100)	0 (0)
Dysthymia	10 (4.3)	0 (0)	0 (0)	0 (0)	10 (13.3)
(Hypo)mania	12 (5.2)	0 (0)	5 (6.3)	6 (10.7)	1 (1.3)
Panic	33 (14.2)	0 (0)	10 (12.6)	18 (29.9)	5 (21.7)
GAD ^b	79 (33.9)	0 (0)	0 (0)	56 (100)	23 (100)

^a Major Depressive Episode; ^b Generalized Anxiety Disorder, Panic Disorder, Dysthymia, Hypomania

M mean, *SD* standard deviation

Table 2. Functioning descriptives at baseline and follow-ups.

	Assessment											
	Baseline (N= 233)			1-month (N = 190)			3-month (N = 174)			12-month (N=179)		
	Mean [%]	SD [SE]	Min/Med/ Max	Mean [%]	SD [SE]	Min/Med/ Max	Mean [%]	SD [SE]	Min/Med/ Max	Mean [%]	SD [SE]	Min/Med/ Max
Active MDE cases	[57.9%]	[0.03]	--	32%	[0.03]	--	26%	0.03	--	21%	[0.03]	--
GAF	66.38	[0.99]	10/70/100	70.52	[1.07]	7/70/100	72.52	[1.08]	30/75/100	--	--	--
WHODAS	28.63	[0.75]	12/17/56	26.68	[0.83]	12/24/57	24.82	[0.84]	12/23/52	20.37	0.65	12/17/48
ASF	50.08	[1.52]	0/50/100	56.12	[1.60]	0/60/100	58.20	[1.09]	30/75/100	59.34	1.58	7/60/100

Table 3. Model fit and estimated parameters of GM model

		Functioning		
		GAF	WHODAS	ASF
Fit indices	Chi-2 (1 gl) p	2.37 (0.12)	1.55(0.21)	3.43(0.06)
	SRMSR ¹	0.04	0.02	0.03
Parameter estimates	Intercept(SE)	66.87(0.95)	28.42(0.72)	50.95(1.46)
	Standardized intercept	5.51	3.00	2.84
	Slope(SE)	1.97(0.37)	-1.14(0.19)	2.43(0.60)
	Standardized slope	0.57	-0.46	0.36
	Parameter correlation ³	-0.47(0.17)	-0.32(0.13)	-0.45(0.12)
	Baseline explained variance	0.66(0.11)	0.74(0.06)	0.61(0.10)
	1st month explained variance	0.53(0.10)	0.74(0.04)	0.51(0.05)
	3rd month explained variance	0.70 (0.20)	0.60(0.07)	0.87(0.21)

GAF: General Assessment of Functioning; *WHODAS*: WHO Disability Schedule 2.0; *ASF*: Analogue Scale of Functioning

¹Standardized Root Mean Square Residual

² Adjusted Lo-Mendel Rubin Likelihood Ratio Test (bootstrapped)

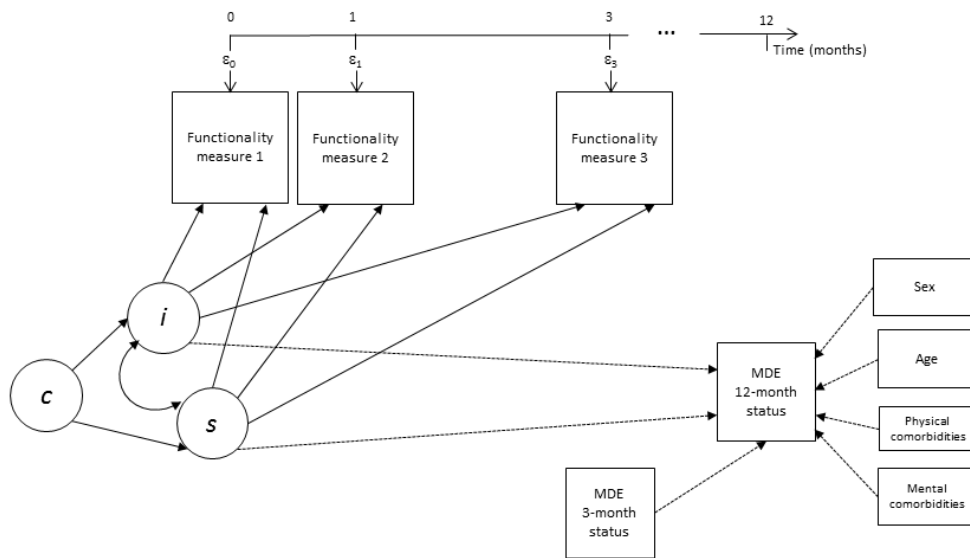
³Intercept-Slope correlation

Table 4. Model estimates (SEs), Wald test and parameter Odd Ratios (95% CIs) and goodness of fit of 12 month MDE status as predicted with GAF, WHODAS and ASF. Functioning models are added hierarchically to baseline MDE 3-month model. All models adjusted by age, sex, presence of mental comorbidities and number of physical comorbidities.

Model	Parameter Estimate	Parameter SE	Wald	Wald p-value	OR (95% IC)	Model p-value	Nagelkerke Pseudo R ²	H-L ^b test (p)
Baseline MDE 3 rd month model	2.01	0.44	19.41	0.00	7.44(3.08/17.94)	--	0.21	--
GAF								
MDE_3M	0.31	0.6	0.26	0.61	1.36(0.42/4.44)	<0.001 ^a	0.57	2.12(0.97)
I	-0.24	0.05	19.74	0.00	0.79(0.71/0.87)			
S	-1.53	0.33	21.31	0.00	0.22(0.11/0.41)			
WHODAS								
MDE_3M	0.26	0.54	6.18	0.01	3.89(1.33/11.98)	<0.001 ^a	0.28	6.24 (0.62)
I	-0.08	0.03	7.11	0.01	0.92(0.90/0.95)			
S	-0.07	0.14	0.24	0.62	0.93(0.81/1.07)			
ASF								
MDE_3M	0.40	0.74	0.31	0.58	1.49(0.16/2.81)	<0.001 ^a	0.62	5.50(0.70)
I	-0.17	0.04	20.64	0.00	0.84(0.78/0.90)			
S	-0.90	0.18	24.19	0.00	0.41(0.28/0.58)			

^aStep significance from MDE baseline model.

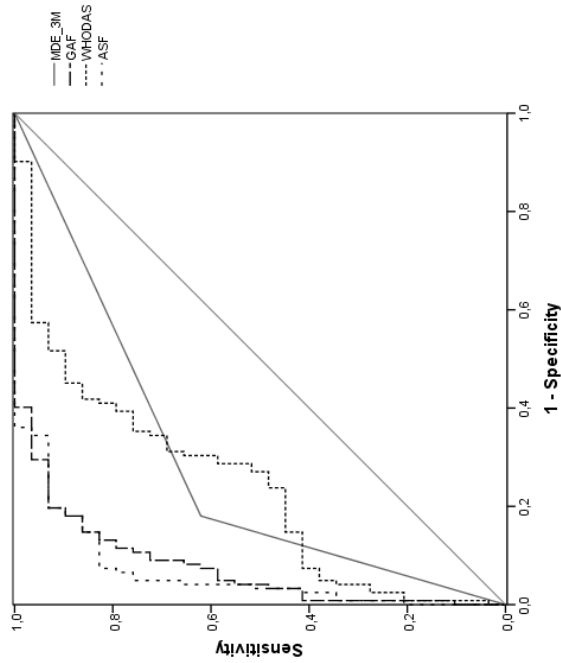
^bHosmer-Leshmeshow Goodness of fit test



c Latent Classes; i : Intercept; s : slope, *MDE*: Active Major Depressive Episode

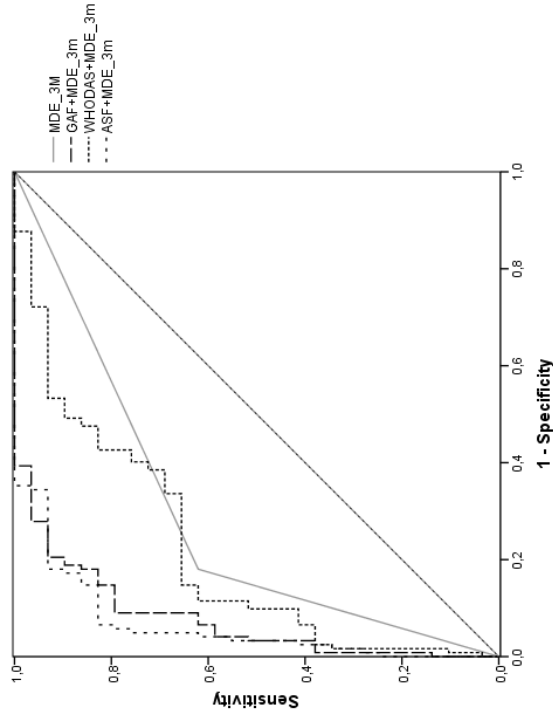
Figure 1: GMM tested. Three functioning measures (GAF; WHODAS and ASF) were tested at each time point.

(a) ROC curves for MDE Status at 12th month as predicted by functioning trends



	AUC	SE	95% CI
MDE 3month only	0.72	0.06	0.61/0.83
GAF	0.92	0.02	0.88/0.96
WHODAS	0.76	0.05	0.67/0.85
ASF	0.93	0.02	0.89/0.97

(b) ROC curves for MDE Status at 12th month as predicted by functioning trends and MDE status at 3rd month



	AUC	SE	95% CI
MDE 3month only	0.72	0.06	0.61/0.83
GAF + MDE 3m	0.92	0.02	0.88/0.96
WHODAS + MDE 3m	0.79	0.05	0.70/0.89
ASF + MDE 3m	0.93	0.02	0.89/0.97

Figure 2. Receiver Operator Curves, Areas Under the Curve (AUC) and SEs of model estimated probabilities of active MDE at 12th month, using functioning measures only (a) and functioning added to known MDE status at 3rd month (b). Dashed lines are curves for GAF, WHODAS and ASF models adjusted for age, sex, presence of mental comorbidities and number of physical comorbidities. MDE status at 3rd month (active/inactive) is shown as reference. Diagonal line represents random prediction.

3 SUMMARY OF FINDINGS AND DISCUSSION

In this thesis, we extended the knowledge on the recognition of common mental disorders in non-specialized healthcare settings exploring whether patient-reported outcome (PRO) measures are a valid and effective solution for improving detection rates. In this chapter we will briefly summarise and discuss the main findings of this thesis. The discussion will initially tackle the recognition of common mental disorders in non-specialized healthcare settings in general and then it will gradually narrow down to discussing the first and second specific objectives of the thesis. Afterwards, general considerations on the use of PRO measures in non-specialized healthcare settings will be presented and then the focus will shift on the third and fourth specific objectives and finally onto the secondary objective of the thesis.

3.1 Recognition of common mental disorders in non-specialized healthcare settings

Mental disorders are largely unrecognized in non-specialized healthcare settings [78, 79, 90, 91]. Mitchell et al [79] had already highlighted the magnitude of the problem in case of depression. We have done the same for anxiety disorders. So, it is clear that general practitioners need to improve their detection rates (even though they might be better at detecting mental disorders in an unspecific way) [89]. Our results indicate that strategies of improvement should focus more on increasing their ability to include potential cases, given that they are already highly specific.

The low recognition rates, as supported by our results and by other studies, might mistakenly guide one into questioning the appropriateness of non-specialized healthcare settings to deliver a high quality mental health care. However, several studies support the fact that primary care is an appropriate setting for identifying, treating and managing all types of disorders including common mental disorders [84, 164]. The distinctive features of primary care facilitate a higher intake of psychiatric patients compared with specialized care. Also, an early detection in primary care is associated with lower levels of perceived stigma [165] and increased accessibility and social integration [164].

Hence, it is sensible to promote interventions that improve case detection at this level of care. Finally, the recognition problems at this level might not necessarily imply that a better job is being done in specialized care: it might be that the same level of evidence is not readily available yet for specialized care [84].

The greater reliance on physical aspects of the patient-doctor relationship as well as shorter appointment times are some of the general factors that make primary care a unique setting. Most probably some of them are behind the poor recognition rates. Out of these, two are of more relevance to the topic of this thesis: the form in which patients' express their complaints and suffering and how the diagnostic process is understood, operationalized and put into practice by the healthcare professional. In primary care, patients often express unspecific complaints. This happens for common mental disorders and also for certain somatic disorders, such as hypertension. Hypertension has also been reported as underdiagnosed in primary care [166]. Hence, it can be argued that unspecific complaints combined with time constraints can easily make GPs overlook symptoms that otherwise might raise their degree of suspicion. This is extremely relevant for mental disorders whose assessment has greatly and traditionally relied on the clinician's observations and interrogations of the patient. In our studies we have provided evidence that a higher reliance on outcomes reported directly by the patient might remove this barrier and lead to a more comprehensive and feasible assessment for this setting. This aspect will be discussed further in the following subchapter (3.2) where ways of facilitating the diagnostic process will be tackled.

Finally, controversy exists on whether knowledge on recognition rates is actually relevant to the management and outcomes of patients with common mental disorders. Evidence exists supporting the fact that patients who are accurately diagnosed have a higher likelihood of getting appropriate treatment and hence have better outcomes and course [167, 168]. According to other studies, outcomes can only be improved provided that detection is coupled with an improved management of detected cases [169]. Another study has shown that primary care patients with recognised mood disorders had poorer health related quality of life in the mental health domain than patients whose disorders had not been recognized [170]. Additionally, diagnosis did not seem to influence the 12-month outcome in case of depression according to another study

conducted in general settings: unrecognised depressive symptoms seem to resolve by themselves over a twelve month period in approximately 70% of the cases [171, 172]. Nevertheless, the remaining cases are most probably more severe and have a more chronic future course [173], underlining the importance of diagnosis in these cases in order to avoid future complications.

All in all, there is no one good for all explanation or solution to the complex problem of the recognition of common mental disorders. But multiple actions, such as a greater reliance on patient reported outcomes or the use of questionnaires, can be taken at several levels in order to improve the general understanding and knowledge of the diagnostic process in non-specialized healthcare settings.

a Specific objectives 1 and 2:

To critically assess the evidence regarding the accuracy of diagnoses of anxiety disorders made by general practitioners

To compare the accuracy of the diagnoses that general practitioners make when they use severity scales or instruments to detect anxiety disorders with the accuracy they have when they don't use such tools

Summary of findings:

The recognition of common mental disorders is the first necessary step in accessing health care services. To fully understand the magnitude of recognition problems as a barrier to accessing healthcare services, we conducted one of the first systematic reviews on the diagnostic accuracy of GP's assisted (i.e., using severity scales/diagnostic instruments) and unassisted (without such tools) diagnoses of anxiety disorders.

Our results showed that, when diagnosing anxiety disorders, general practitioners'(GPs) ability to correctly classify patients as "diseased" was approximately two times lower than their ability to correctly identify non-cases as not having the disorder (Sensitivity= 44.5%; Specificity=90.8%). When diagnoses were unassisted, their sensitivity was of 30.5% (95% CI 20.7 – 42.5%) and their specificity was 91.4% (95% CI 86.6 – 94.6%).

When questionnaires were used to guide the diagnostic process, GPs' sensitivity rose to 63.6% (95% CI 50.3 – 75.1%), but at the expense of a loss in specificity levels (87.9%, 95% CI 81.3 – 92.4 %). Diagnostic accuracy did not seem to vary with the type of anxiety disorder identified or with the type of instrument used (e.g. diagnostic, screening or severity scale) when diagnoses were assisted.

Discussion:

Overall, GPs are better at ruling out cases of anxiety disorders rather than at identifying true cases. This finding is in line with Mitchell et al. [79] results on depression in primary care: sensitivity 50.1% and specificity 81.3%. Comparable results were obtained in case of mild depression as well: GPs correctly identified 33.8% (95% CI=27.3% to 40.7%) of people with mild depression and had a detection specificity of 80.6% (95% CI=66.4% to 91.6%) for the non-depressed [174]. However, their accuracy seemed to improve significantly in case of moderate-severe depression [174]. Another systematic review [175] on the clinical recognition of alcohol disorders in primary care revealed similar results: a sensitivity of 41.7% (95% CI 23.0 – 61.7) and a specificity of 93.1% (95% CI 86.7–97.6).

As already commented, specificity results are constantly being reported as high in the literature: this is also the case for our results. Additionally, as shown by our results, specificity did not vary substantially with the use of questionnaires in case of anxiety disorders. Other studies have reported specificity levels to remain fairly constant in other circumstances as well: in the case of depression, for example, accuracy does not seem to vary with age either [176]. Still the approximately 3.5% loss in specificity levels associated with the use of questionnaires in anxiety disorders cannot be overlooked. This might lead to an increase in the false positive rates of diagnosis, with a number of patients undergoing unnecessary treatment, thus probably increasing costs and lowering the overall quality of care. Assuming a prevalence rate of 9.4% of any anxiety disorder, the fraction correct for 1,000 consecutive patients presenting to a Spanish primary care centre would be of 85.7% and the number of false positives would increase by 39.7% if the practitioner used questionnaires to detect anxiety.

Low detection rates in non-specialized healthcare settings are registered across a wide variety of mental disorders as suggested by our results and by the literature already

available. Hence, it is reasonable to believe that the low detection rates are independent of the type of the disorder. The delays within the care pathway reported for psychosis might support this hypothesis [177, 178]. Still, future research exploring detection levels in case of severe mental disorders is needed in order to confirm that the type of disorder might not be the cause of the low detection rates [179].

The different characteristics of non-specialized healthcare settings must be kept in mind when trying to understand the low recognition rates registered at this care level: the lack of specificity of patients' complaints and the high healthcare demands in terms of time and volume of patients. The majority of patients in primary care present with unspecific complaints or with mixed depression and anxiety symptoms that very rarely reach the DSM threshold for diagnosis of a mental disorder. Additionally, there are more patients who meet some but not all criteria for a diagnosis than in other healthcare levels [104]. Therefore, detection might be facilitated in this setting if common mental disorders were perceived more like a continuum [180], with detection focusing more on identifying people suffering from broader mental problems, but who require professional help rather than on a diagnosis per se [181, 182]. Likewise, patients' complaints are determinant for recognition. For instance, even though the DSM system gives equal weight to all symptoms, physicians do not actually consider exploring the possibility of a mental diagnosis unless the patient him/herself expresses a clear mental complaint or looks notably sad [104]. This underlines the need to use severity, dimensional measures in primary care, as patients with subthreshold symptoms are very rarely identified when a pure categorical diagnostic approach is used. Hence, in these patients categorical diagnosis might act as a barrier to accessing a correct treatment and management of the disorder.

A general limitation of the research that supports the low recognition rates of common mental disorders, including our own review, is the fact that the pooled summaries of sensitivity and specificity mostly come from cross-sectional studies. Assessments in primary care have a clear longitudinal component. Also, GPs' accuracy varies according to the number of contacts the patient makes: practitioners usually revise their opinions based on further examinations especially when they are in doubt. Hence the possibility of the disorder being recognized at a later stage cannot be fully excluded [183], with diagnostic accuracy rates eventually improving.

3.2 The use of PROs: a way of improving the recognition of common mental disorders in non-specialized healthcare settings

The results of the INSAyD project have shown that a greater reliance on patients' reports is a valid and sensitive alternative in the field of mental health. Even though the clinical approach is an invaluable method for detecting psychopathology, its complexities and demands make it unfeasible for early assessments at patients' first contact. Our meta-analysis, in line with other results [79], indicate that a PRO approach can facilitate a more thorough assessment and ease the diagnostic process of common mental disorders for non-specialized clinicians.

The assessment of common mental disorders has traditionally been driven by the clinician's views and opinions on the patient's condition. This characteristic is very common in the assessment undertaken in psychiatry (e.g. specialized care) [184] and has been largely maintained in its simplified version adopted in non-specialized healthcare settings. Therefore, the use of PROs might still be perceived with scepticism in clinical practice [185] in spite of them being the gold standard for assessing outcomes in subjective experiences [186]. Given that PROs reflect more precisely the views and concerns of the clinical population, relating a specific individual to particular population, some have questioned their role in facilitating the patient-physician communication. By bringing into light problems that otherwise might have been overlooked, practitioners might be forced into discussing areas over which they have little control. Thus they might cause patients unnecessary distress [187]. Finally, clinicians still have problems in adapting to a process in which patients' statements are as equivalent to, and as salient as the psychological symptom profile that they themselves have constructed for the patient seated in front of them [184].

Thus, clinicians are skeptic of the use of PRO measures, but mostly because of lack of familiarity and cultural barriers. Efforts should be put into changing this given that PROs can be a powerful means of collecting data on large numbers of patients who are

representative of typical, everyday practice, if used in routine clinical practice [188]. Additionally, different studies have shown that they can help clinicians to better understand patients' and families' situations, to monitor change and to evaluate interventions [189, 190].

Notwithstanding, some controversy still persists regarding the use of PROs and its implications for mental health care. For instance, several clinical trials have shown that the use of PRO improved recognition and diagnosis [187], with the clearest benefits found in the diagnosis of depression [191]. Also, when it comes to routine use, practitioners prefer self-reported instruments to clinician ratings for practical reasons [192]. On the other hand, self-reported and clinician-rated measures of depression severity have been found not to be interchangeable when assessing response and remission in major depressive disorder [193]. Additionally, when measuring depression severity, self-reported and clinician measures provide unique information. Each method captures information not captured by the other method, but that information is fully relevant to clinical prognosis [192]. In our opinion, these concerns are not applicable to the patient's first contacts with the clinician, when the diagnostic assessment usually takes place.

The results of the INSAyD project also support the beneficial use of PROs in mental health assessment. The instruments developed in this project (INSAyD depression: INS-D; INSAyD Generalized Anxiety: INS-G; Analog scale of functioning: ASF) adequately measure symptom severity and functioning, thus having a positive impact in clinical practice, as other studies have already indicated [187]. Given the ever increasing time pressures and patient demands in non-specialized healthcare settings, ideal diagnostic instruments for this setting need good content validity (do they measure what we think they do?), test-retest reliability (reliability over time), good inter-rater reliability (agreement between clinicians), and high specificity (few false-positives) [194]. The instruments developed and validated as part of the INSAyD project are short, reliable and responsive to short-term change. Additionally, they have good diagnostic validity and most probably the costs of their routine uptake might be quite minimal. Hence, we believe that the instruments we have proposed respond adequately to the realities of the clinical practice: they have good psychometric properties and very short times of administration. They are responsive and allow prediction of patients' clinical course. In contrast with the currently established process, INSAyD tools are less

demanding on healthcare professionals, don't require much of their time and neither does their administration need a high level of knowledge or very good interviewing skills. This eases considerably their use given that the aforementioned time and training requirements are precisely what practitioners don't have in non-specialized health care settings.

Unfortunately, the acceptability of the tools developed as well as the views of the clinicians on their use could not be assessed as part of the INSAyD project. In spite of their benefits, PROs have been very slowly implemented in clinical [190, 195] and especially in mental health care [196]. This might partially be due to clinicians not being very convinced of the benefits of their use [190]. Undoubtedly, the controversy caused by the questionable impact of the use of PROs measures as routine screeners on the detection and management of mental disorders [197, 198] has also contributed to these rather unfavourable views. Nevertheless, the tools we developed are not meant for screening, they are diagnostic tools. They assist clinicians in making a decision about diagnosis, thus easing clinical judgement. Given their very short administration times and minimal administrative burden, we believe that their routine uptake will be easily accepted by practitioners. However, future research is needed in order to confirm our hypothesis and also to determine the costs of their implementation.

The concept of mental health and the strategies to improve mental health care have always fuelled rather interesting debates concerning over-diagnosis and over-treatment [199]. One might think that the use of questionnaires to improve detection rates might lead to over-treatment due to the increase in the number of false positive cases detected. Until further research is available on over-diagnosis and on harm from over-treatment, one might legitimately think that over-treatment is closely linked with under-recognition as well. For instance, people with undetected anxiety can undergo unnecessary treatments for physical disorders they don't suffer from [200]. This is so because the practitioner might associate and recognize more easily anxiety's somatic symptoms as being caused by a physical disorder rather than by a mental one. Nevertheless, dimensional measures, like the ones devised in the INSAyD project, are known to guide more precisely treatment decisions than categorical measures [201].

In this thesis we addressed the problem of low recognition rates in non-specialized healthcare settings through the development of better diagnostic tools. Nevertheless, other strategies have also been proposed to improve recognition rates. They vary from educational interventions to more structural, organisational ones. Even though the results of certain interventions, such as guideline implementation strategies or educational campaigns for healthcare professionals or the general public were rather modest [202, 203], promising results were obtained with organisational strategies like collaborative care [204, 205] and stepped collaborative care [206, 207]. Future research is needed to determine the effectiveness of our instruments and the costs associated to the increase in sensitivity and specificity.

a Specific objective 3:

To study the psychometric properties of a continuous (dimensional) severity scoring system based on DSM-IV-TR symptom criteria for major depressive episode and generalized anxiety disorder

Summary of findings:

The two DSM-IV symptom-based severity scales, INS-D and INS-G, showed very good psychometric properties in a clinical sample of patients seeking care for mood and anxiety disorders symptoms. They had a very high diagnostic accuracy level, with a sensitivity of 0.90 and a specificity of 0.85 in case of MDE (INS-D) and of 0.85 and 0.87 respectively in case of GAD (INS-G). They also showed good construct validity: the highest correlations were registered with other severity measures and the lowest correlations with instruments that measured other concepts than severity with different methods (clinician versus self-administered). They were highly responsive to short term clinical change and had very short times of administration (INS-D: 2 minutes; INS-G: 4 minutes).

Discussion:

Our results show that INS-D and INS-G are as reliable as some of most used scales like the Hospital Anxiety and Depression Scale [208], the Hamilton Rating Scale for Depression [209] or GAD-7 [210]. They also have an incremental validity over other

criterion measures. The sensitivity and specificity of INS-D are higher than the levels reported in systematic reviews for PHQ-9 as a diagnostic algorithm (Sensitivity=0.69; Specificity=0.95) [211] or for The Hospital Anxiety and Depression Scale (depression scale) (Sensitivity=0.70; Specificity=0.83) [211]. INS-G also performed better than The Hospital Anxiety and Depression Scale (anxiety scale) according to the results of a systematic review (Sensitivity=0.78, 95% CI 0.68–0.85; Specificity=0.74, 95% CI 0.64–0.82 [212]. Their accuracy levels are better than the ones reported for screening tools, such as CES-D [213] or the Zung self-rated scale of depression [214] while having a lower response burden. In terms of responsiveness, their performance was somewhat lower than that of PHQ-9 [215] or HAM-A for example [216].

All in all, the psychometric properties of our scales are comparable and sometimes better than the ones of other well established instruments. Additionally, they don't require extensive training, only a minimal one in administering and interpreting the results. They are also short and easy to use, characteristics that not all of the tools we compared them with have. For example, the Hamilton scales have very long administration times. For HAM-A, structured interview guides had to be developed in order to ease its administration [217]. The Hospital Anxiety and Depression Scale has a difficult reading level [218] and the mix of positive and negative items of the Zung self-rated scale of depression may confuse patients [219]. Hence, we believe that the use of INS-D and INS-G will have a beneficial impact in the daily routine of clinical practice.

One general limitation of this study is the fact that the recruited sample might not be representative of the clinical population from the respective healthcare levels, affecting the generalizability of our results. The recruitment strategy of the study favoured the inclusion of cases over non-cases with an overestimation of disorder prevalence. However, we ensured like this a wide range of symptom severity levels that allowed testing more adequately the diagnostic properties of our questionnaires. Hence, the INSAyD project was specifically designed to test and validate the psychometric properties of our questionnaires in “controlled conditions”. But, it remains to be tested whether these properties hold in “real life” conditions of clinical practice. Nevertheless, this research will serve as a basis for future randomized clinical trials that are needed in order to determine the properties of our questionnaires in routine clinical practice.

b Specific objective 4 and secondary objective:

To explore the contribution of functional disability measures to diagnose major depressive episode and generalized anxiety disorder

To explore the contribution of functional disability measures to diagnose major depressive episode and generalized anxiety disorder

Summary of findings:

Functional disability measures discriminated well between cases and non-cases of either MDE or GAD. The method of assessment did not influence the diagnostic accuracy of the studied measures for either MDE or GAD (MDE: $AUC_{ASF} = 0.84$; 95% CI 0.77 – 0.90; $AUC_{GAF} = 0.83$; 95% CI 0.76 – 0.89; GAD: $AUC_{ASF} = 0.79$; 95% CI 0.71 – 0.87; $AUC_{GAF} = 0.79$; 95% CI 0.71 – 0.87). As seen, the diagnostic accuracy of functional disability measures was better in MDE than in case of GAD. In terms of sensitivity and specificity, self-reported methods had the highest sensitivity and specificity for MDE (0.79 and 0.81 respectively), whereas clinician-rated methods had the highest levels for GAD (0.77 and 0.78 respectively).

When evaluated together with symptom assessment, self-reported measures of functional disability improved GAD detection ($AUC_{ASF} = 0.92$, 95% CI 0.87 – 0.97), but not MDE or comorbid MDE & GAD detection. When symptoms were present, both methods of assessing functional disability had similar AUC values for MDE and comorbid cases of MDE & GAD.

Discussion:

Our results concerning the discriminatory ability of functional disability measures in the absence of symptoms are similar to the ones reported by Luciano et al. [220] in a primary care sample with depression. In this case, the accuracy levels of WHODAS 2.0 for detecting “depression caseness” were also good with levels very similar to ours.

When evaluated together with symptoms, functional disability measures tended to improve, but not significantly, the diagnostic accuracy of symptoms in the case of GAD. No such trend was observed for MDE or for comorbid cases of MDE & GAD. The

complex relationship between symptoms and functional disability in anxiety disorders might account for this difference. In anxiety disorders, functioning seems to be less affected by the number of symptoms [22, 221, 222], but when it comes to measuring treatment outcomes functioning is as informative as symptom severity [223]. More exactly, in the case of anxiety disorders the relationship between symptom and functional improvement is bidirectional: symptom severity predicts functional impairment and conversely functional impairment predicts anxiety symptoms [223].

On the other hand, in MDE the information on functioning status apparently overlapped with that given by the disorder symptoms. This might be due either to the fact that MDE symptoms already collect information on functional disability and/or that their mere presence implies an impaired level of functioning. Future research should contemplate why the level of functioning—either clinical or self-reported—is not as specific as symptoms in common mental disorders in spite of it being a compulsory criterion.

The analogue scale of functioning that we developed and tested in our study showed good diagnostic accuracy and relative fair test-retest reliability in a subgroup with stable severity level at 1-month (ICC=0.64). This is in line with other studies' results that have reported that self-reported measures of functioning are valid and reliable [224, 225]. Nevertheless, the test-retest reliability of our measure still needs to be evaluated in a shorter, non-therapeutic time window, such as one week for example. It is likely that our patients, even if they were clinically stable, still might have tended to improve as they were all in treatment.

The use of a self-reported measure of functioning, as proposed by us in the INSAyD project, goes in line with the change from a clinician-administered measure of functioning (GAF) to a self-reported one (WHODAS) that was brought by the recent edition of the DSM-5. With this change, the American Psychiatric Association adhered to the International Classification of Functioning framework that conceptualizes functioning as a dynamic interaction between health, environment and personal factors. This transition, from clinical to self-reported measures, has once again highlighted the importance PRO measures will acquire in the clinical practice in the near future. Nevertheless, there are still many steps to be taken before the full benefits of PRO measures of functional disability will be established and determined in areas of mental health like patient management and outcome monitoring. More clinical studies, proofs

of concept and longitudinal follow-ups are needed to estimate the effectiveness, the costs and the contribution of functional disability measures to assess the long-term course of mental disorders. Until then, our results encourage the use of self-reported measures of functional disability in diagnosing and potentially bring new strategies yet to be explored for patient communication. They might be an alternative to traditional diagnostic tools in those patients who may not be open to systematically complete depression ratings scales due to stigma and/or an unwillingness to discuss a psychiatric diagnosis [226].

One important limitation of our results was the reduced sample size. This did not allow us to validate the models we used to determine the diagnostic ability of functional disability measures in a true dataset. Nevertheless, the models were defined a priori and not developed from the sample. Also, the 10-fold cross-validation techniques have been shown to have minimal effects of sample characteristics [227] and to achieve stable values of the prediction error [228].

The results of the third article of this thesis showed that functional disability, as a diagnostic criterion, contributes to establishing a diagnosis in a lesser extent than symptoms. This raises questions about the role functional disability plays in mental disorders. Hence, we explored the potential use of functional disability measures (clinician rated and PROs) to predict the course of depression at 12-months. This was also done at the suggestion of the clinicians that were members of the INSAyD research team. It is also the result of different post-conference discussions that we had with clinicians following the presentation of the results of the INSAyD project. Hence, models similar to the ones used to determine the contribution of functional disability measures to diagnosis were used to determine the role of functional disability measures in predicting clinical status after 12-months for depression. Our results showed that the change in the functional status of a patient at 3-months with respect to baseline can be used to predict both remission and new onsets or relapses at 12-months for depression. PRO measures of functional disability were as good as clinician-administered measures in predicting MDE course after 12-months. Hence, PRO measures of functional disability can be a simple and easy way to monitor remission: they predict more accurately the patient's status after 12 months than the very symptomatologic course of the patient's disorder.

3.3 Directions for future research

This thesis showed that common mental disorders are under-diagnosed in non-specialized health care settings. It also provided, by means of the INSAyD project, the proof of concept to support the use of dimensional instruments in “controlled conditions” of clinical practice. Further research is needed in order to:

- a) Review the characteristics of patients that go undetected with detailed information on the treatment pathways they follow, on how they progress and on the costs that they generate at health care system level.
- b) Investigate possible gender differences in diagnostic accuracy levels and in unrecognized cases of common mental disorders.
- c) Estimate the accuracy of GPs’ diagnoses of common mental disorders based entirely on prospective ratings and longitudinal assessments.
- d) Assess the costs associated to the use of INSAyD instruments in real primary care practice conditions. This can be done either with the help of simulation models or by using data from clinical trials.
- e) Estimate the effectiveness of the use of INSAyD measures in real primary care practice conditions. A randomized clinical trial would provide the best evidence to support the benefits of their routine use in detection, patients’ and practitioners’ satisfaction, cost containment or in other clinical processes, such as adherence to treatment.
- f) Determine the long-term ability of INSAyD severity scores to distinguish case trajectories of remission, aggravation or chronification. This would support their use as prioritization instruments at different health care levels.
- g) Finally, more studies are needed on the long-term use of functional disability measures to explore their potential as predictors and not only as outcomes in mental health.

4 CONCLUSIONS

- a) Common mental disorders are largely underdiagnosed in non-specialized health care settings. This is the case with anxiety disorders as well. The accuracy of anxiety recognition in primary care is low: at a prevalence rate of 10%, the general practitioner will correctly identify 86% of the patients, misclassifying 8% as false positives and 6% as false negatives.
- b) GPs are better at ruling out anxiety in patients without anxiety than at recognizing true cases. This suggests that interventions to improve detection rates in primary care should focus on increasing the GPs' ability to identify true cases.
- c) GPs have an improved diagnostic accuracy when they use questionnaires to assist their diagnoses: they identify almost 50% more cases, at the expense of a somewhat higher false-positive rate.
- d) GPs' detection levels do not vary with the type of questionnaire used or the type of disorder identified. This fact should facilitate the development of interventions to increase detection rates that are more responsive to the needs and preferences of the practitioners, potentially improving the acceptability of such interventions.
- e) Instruments for primary care and non-specialized healthcare settings should have very low burden of administration. In the INSAyD project we developed short, reliable, valid and responsive measures with high diagnostic accuracy:
 - i. INS-D has excellent reliability (0.92), very good diagnostic properties for detecting major depressive episode (sensitivity 0.90; specificity 0.85), and its administration takes only two minutes.
 - ii. INS-G has excellent reliability (0.93), good levels of sensitivity and specificity for detecting generalized anxiety disorder (0.85 and 0.87 respectively), and it takes four minutes to administer.

- f) INSAyD instruments are dimensional measures based on symptom distribution in the general population, validated in a clinical context. They allow dimensional assessment of psychopathology both in general and clinical samples, they are simple and easy to use tools and do not require previous training in psychiatric evaluation.
- g) As dimensional measures, INSAyD instruments support the current trend in psychiatry towards a psychiatric assessment based on a continuum from mental wellbeing to psychopathology.
- h) In the absence of symptom evaluation, functional disability measures have acceptable diagnostic accuracy for detecting major depressive and generalized anxiety disorders.
- i) Trends of change in functioning in the first 3 months after patient demand for health care are highly related with the course of depression symptomatology either whether they are clinician or patient-reported. They allow the prediction of psychopathological status after 12 months with a predictive accuracy from 0.76 to 0.93.
- j) Our proposal of an Analogue Scale of Functioning, based on a simple, self-reported question of functional disability, is a reliable tool for patient monitoring in major depressive episode. Its routine use could facilitate assessment and provide better outcomes for mental health in non-specialized health care settings.
- k) In summary, Patient-Reported Outcome (PRO) measures are a valid and feasible solution to the detection problems of common mental disorders in non-specialized health care settings: they can adequately increase the diagnostic performance of general practitioners. Given the wider context of effective treatment for common mental disorders, they should always be associated with other changes in practice structure, such as multimodel intervention programs.

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ANNEXES

Annex 1 - INS-D, INS-G and ASF questionnaires

INS-D questionnaire – English translation from Spanish

Over the past 2 weeks, has the patient presented any of the following symptoms?

ID01	Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful)	Yes	No	Not assessable
ID02	Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)	Yes	No	Not assessable
ID03	Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.	Yes	No	Not assessable
ID04	Insomnia or hypersomnia nearly every day	Yes	No	Not assessable
ID05	Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)	Sí	No	Not assessable
ID06	Fatigue or loss of energy nearly every day	Yes	No	Not assessable
ID07	Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)	Yes	No	Not assessable
ID08	Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)	Yes	No	Not assessable
ID09	Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide	Yes	No	Not assessable

INS-G questionnaire – English translation from Spanish

Over the past 6 months/1 month, has the patient presented any of the following symptoms?

IAG01	Excessive anxiety and worry (apprehensive expectation) about a number of events or activities	Yes	No	Not assessable
IAG02	The individual finds it difficult to control the worry	Yes	No	Not assessable
IAG03	Restlessness or feeling keyed up or on edge	Yes	No	Not assessable
IAG04	Being easily fatigued	Yes	No	Not assessable
IAG05	Difficulty concentrating or mind going blank	Yes	No	Not assessable
IAG06	Irritability	Yes	No	Not assessable
IAG07	Muscle tension	Yes	No	Not assessable
IAG08	Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)	Yes	No	Not assessable

ASF questionnaire – English translation from Spanish

“On a scale from 1 to 100, how would you currently rate your overall level of functioning?”

