Universitat Autònoma de Barcelona

CULTURAL DIFFERENCES IN THE EXPRESSION OF DEPRESSION ASSESSED WITH THE HAMILTON SCALE

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CULTURAL DIFFERENCES IN THE EXPRESSION OF DEPRESSION ASSESSED WITH THE HAMILTON SCALE

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Abreviations

APA: American Psychiatric Association

BDI: Beck Depression Scale

CDS: Carroll Depression Scale

CFI: Cultural Formulation Interview

CDSS: Carroll Depression Severity Scale

CES-D: Center for Epidemiological Studies of Depression

DALY: Disability Adjusted Life Years

DSM: Diagnostic and Statistical Manual of Mental Disorders

EHIS: European Health Interview Survey

EMA: European Medicines Agency

ENSE: Encuesta Nacional de Salud de España

FDA: Food and Drug Administration

HAMD: Hamilton Depression Scale

HMI: Hamilton and MADRS interview

ICD: International Statistical Classification of Diseases and Related Health Problems

ICH: International Council for Harmonization

IHME: Institute for Health Metrics and Evaluation

MADRS: Montgomery and Asberg Depression Scales

MDD: Major Depression Disorder

MRCT: Multi regional clinical trials

RWE: Real World Evidence

RWD: Real World Data

SIGH-ADS: Hamilton Depression Rating Scale with Atypical Depression Supplement

SIGH-D: Structured Interview Guide for the Hamilton Depression Scale

WASO: Wake time After Sleep Onset

WHO: World Health Organization

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ABSTRACT

Abstract

INTRODUCTION

Major Depressive Disorder (MDD), affects 121 million people in the world according to WHO. This is a major health issue which affects people worldwide hence a cross-national approach is needed to better understand the nature of MDD.

A psychiatric clinical interview serves to identify the depressive symptoms, stablish a diagnostic and apply a treatment intervention. During such interview, the clinician needs to explore the patient and obtain the answers that will lead to symptoms' identification. It is therefore crucial to conduct a correct assessment exercise as the diagnostic and subsequent treatment will depend on the outcome of the interview.

When working in transcultural settings, it is fundamental to be aware of the potential distinct expressions of depression from the patient. Likewise, the way the assessor interprets patient's responses can be mediated as well by his/her own cultural background. Clinician needs to have robust cultural competences. A psychiatric interview is therefore a 2 ways interaction with two critical aspects which might vary depending on the cultural background:

- Patient: How depression is expressed.
- Clinician: How depression is assessed.

METHODOLOGY

This project approaches both sides of the clinical interview with two differentiated studies:

STUDY 1: Assessment of depression; **STUDY 2:** Expression of depression

STUDY 1: Psychiatrists from different countries will assess the very same clinical interview, in a videotaped format, as part of the Rater Training program in a large multi-national clinical trial with MDD patients. The assessment tool will be the HAMD, 17 items version.

STUDY 2: MDD patients attending to the Psychiatry Transcultural Unit of Hospital Vall d'Hebron will be assessed with the HAMD17. A subjective depression assessment will be done by subjects completing the CDS. Most of these patients reside in Barcelona but are originally from foreign countries. Acculturation attitude will be captured with ACM

RESULTS

STUDY1 shows that despite the culturally diverse backgrounds of raters, acceptable consistency was reached for all HAMD-17 items. The individual ANOVA analyses revealed significant main effects for region (Country, Continent or Western/Non-Western) for the same six HAMD-17 items: Insomnia-Early, Agitation, Anxiety-Psychic, Somatic Symptoms-GI, Somatic Symptoms-General and Insight.

Data suggest that raters from different geographic regions and cultures can observe the same patient and provide consistently different ratings on certain HAMD-17 items. Differences in rater expectations, based on culturally-specific disease conceptualization and experience of «typical» patient presentations, may underlie these discrepancies in ratings.

STUDY2 results show that HAMD6 sub-scale total results are not influenced by the geographic origin of the subjects. As expected, HAMD17 Somatic items would be prone to be rated higher for non-Western subjects. CDS and HAMD showed a positive, moderate and statistically significant correlation. However, CDS is systematically overrated over HAMD independently of geographic origin of the subject. When analyzing Acculturation groups, the Segregation category showed different symptoms pattern when compared with the rest of the groups.

CONCLUSIONS

STUDY 1: Somatization of symptoms is one of the most described differences in the clinical expression of depression and anxiety between Western and Non-Western cultures, with Non-Western patients expressing greater somatic symptoms and fewer psychic symptoms. Differences in expectations between Western and Non-Western raters regarding somatic disease features may have contributed to differences we observed on more somatic HAMD-17 items (Somatic-General, Somatic-GI and Agitation).

In Non-Western countries, depression is often understood as a social or moral problem. Reluctance to consider psychological/biological/medical causes of depression could underlie differences in ratings among Western and Non-Western raters for the Insight item.

STUDY 2: In this study we can see that similar conclusions can be reached with HAMD17 and HAMD6 when evaluating a multi-cultural population. The fact that HAMD17 Somatic items are prone to be rated higher for non-Western subjects should be taken into consideration when designing Rater Training programs for multi-national Depression clinical trials and try to minimize the over-rating on somatic items. CDS is sometimes used instead of the HAMD interview in order to save time in the clinical setting. Care must be

taken as there might be an overrating during the CDS completion. Acculturation attitude needs to be taken in consideration when assessing individuals who are having adaptation problems to the host country as the expression of their depressive symptoms could be different from the rest of groups.

RESUM

RESUM

INTRODUCCIÓ

El Trastorn Depressiu Major, afecta 121 milions de persones al món segons l'OMS. Aquest és un problema de salut important que afecta les persones a tot el món, per la qual cosa es necessita un enfocament transnacional per entendre millor la naturalesa de la depressió.

Una entrevista clínica psiquiàtrica serveix per identificar els símptomes depressius, establir un diagnòstic i aplicar un tractament. Durant aquesta entrevista, el metge ha d'explorar el pacient i obtenir les respostes que condueixin a la identificació dels símptomes. Per tant, és fonamental realitzar un correcte exercici d'avaluació ja que el diagnòstic i el tractament posterior dependran del resultat de l'entrevista.

Quan es treballa en entorns transculturals, és fonamental ser conscient de les diferents possible expressions de depressió del pacient. De la mateixa manera, la forma com l'avaluador interpreta les respostes del pacient també pot estar mediada pel seu propi bagatge cultural. El metge ha de tenir competències culturals sòlides. Per tant, una entrevista psiquiàtrica és una interacció bidireccional amb dos aspectes crítics que poden variar segons l'origen cultural:

- Pacient: Com expressa la depressió.
- Clínic: Com avalua la depressió.

METODOLOGIA

Aquest projecte aborda ambdues vessants de l'entrevista clínica amb dos estudis diferenciats:

ESTUDI 1: Avaluació de la depressió; **ESTUDI 2:** Expressió de la depressió

ESTUDI 1: Psiquiatres de diferents països avaluaran la mateixa entrevista clínica, en un format gravat en vídeo, com a part del programa de Rater Training en un assaig clínic multinacional amb pacients de depressió. L'eina d'avaluació serà l'HAMD, versió de 17 ítems.

ESTUDI 2: Els pacients amb depressió que atenen a la Unitat Transcultural de Psiquiatria de l'Hospital Vall d'Hebron seran valorats amb l'HAMD17. Es farà una avaluació subjectiva de la depressió per part dels subjectes completant el CDS. La majoria d'aquests pacients resideixen a Barcelona però són originaris d'altres països. L'actitud d'aculturació es captarà amb l'ACM.

RESULTATS

L'ESTUDI 1 mostra que, malgrat els orígens culturalment diversos dels avaluadors, es va aconseguir una coherència acceptable per a tots els ítems HAMD-17. Les anàlisis ANOVA individuals van revelar efectes significatius per a la regió (país, continent o occidental/no occidental) per als mateixos sis ítems HAMD-17: insomni-precoç, agitació, ansietat-psíquica, símptomes somàtics-GI, símptomes somàtics-generals i Insight.

Les dades suggereixen que els evaluadors de diferents regions geogràfiques i cultures poden observar el mateix pacient i proporcionar puntuacions diferents de manera consistent en determinats ítems HAMD-17. Les diferències en les expectatives dels evaluadors, basades en la conceptualització de la malaltia

culturalment específica i l'experiència de les presentacions «típiques» dels pacients, poden ser la base d'aquestes discrepàncies en les valoracions.

Els resultats de **l'ESTUDI 2** mostren que les puntuacions totals de la subescala HAMD6 no estan influenciats per l'origen geogràfic dels subjectes. Com era d'esperar, els ítems somàtics HAMD17 serien propensos a ser valorats més alts per a subjectes no occidentals. CDS i HAMD van mostrar una correlació positiva, moderada i estadísticament significativa. Tanmateix, el CDS està sistemàticament sobrevalorat respecte a HAMD independentment de l'origen geogràfic del subjecte. Quan s'han analitzat els grups d'aculturació, la categoria de segregació va mostrar un patró de símptomes diferent en comparació amb la resta de grups.

CONCLUSIONS

ESTUDI 1: La somatització dels símptomes és una de les diferències més descrites en l'expressió clínica de la depressió i l'ansietat entre les cultures occidental i no occidental, amb pacients no occidentals que expressen més símptomes somàtics i menys símptomes psíquics. Les diferències en les expectatives entre els evaluadors occidentals i no occidentals pel que fa a les característiques de la malaltia somàtica poden haver contribuït a les diferències que hem observat en els ítems de la HAMD-17 més somàtics (Somàtic-General, Somàtic-GI i Agitació).

Als països no occidentals, la depressió s'entén sovint com un problema social o moral. La reticència a considerar les causes psicològiques/biològiques/mèdiques de la depressió podria ser la base de les diferències en les puntuacions entre els evaluadors occidentals i no occidentals per a l'ítem Insight.

ESTUDI 2: En aquest estudi podem veure que es poden arribar a conclusions similars amb HAMD17 i HAMD6 quan s'avalua una

població multicultural. El fet que els ítems somàtics HAMD17 siguin propensos a ser valorats més alts per a subjectes no occidentals s'hauria de tenir en compte a l'hora de dissenyar programes de Rater Training per a assaigs clínics de depressió multinacionals i intentar minimitzar la sobrevaloració dels ítems somàtics. De vegades s'utilitza CDS en lloc de l'entrevista HAMD per estalviar temps a la pràctica clínica. Cal anar amb compte, ja que pot haver-hi una sobrevaloració durant la puntuació del CDS. L'actitud d'aculturació s'ha de tenir en compte a l'hora d'avaluar les persones que tenen problemes d'adaptació al país d'acollida, ja que l'expressió dels seus símptomes depressius podria ser diferent de la resta de grups.

RESUMEN

RESUMEN

INTRODUCCIÓN

El Trastorno Depresivo Mayor, afecta a 121 millones de personas en el mundo según la OMS. Éste es un problema de salud importante que afecta a las personas en todo el mundo, por lo que se necesita un enfoque transnacional para entender mejor la naturaleza de la depresión.

Una entrevista clínica psiquiátrica sirve para identificar los síntomas depresivos, establecer un diagnóstico y aplicar una intervención de tratamiento. Durante esta entrevista, el médico debe explorar al paciente y obtener las respuestas que conduzcan a la identificación de los síntomas. Por tanto, es fundamental realizar un correcto ejercicio de evaluación ya que el diagnóstico y el tratamiento posterior dependerán del resultado de la entrevista.

Cuando se trabaja en entornos transculturales, es fundamental ser consciente de las distintas posibles expresiones de depresión del paciente. Del mismo modo, la forma en que el evaluador interpreta las respuestas del paciente también puede estar mediada por su propio bagaje cultural. El médico debe tener competencias culturales sólidas. Por tanto, una entrevista psiquiátrica es una interacción bidireccional con dos aspectos críticos que pueden variar según el origen cultural:

- Paciente: Cómo expresa la depresión.
- Clínico: Cómo evalúa la depresión.

METODOLOGÍA

Este proyecto aborda ambos aspectos de la entrevista clínica con dos estudios diferenciados:

ESTUDIO 1: Evaluación de la depresión; **ESTUDIO 2:** Expresión de depresión

ESTUDIO 1: Psiquiatras de diferentes países evaluarán la misma entrevista clínica, en formato de video, como parte del programa de Rater Training en un ensayo clínico multinacional con pacientes de depresión. La herramienta de evaluación será la escala HAMD-17.

ESTUDIO 2: Los pacientes de depresión que acudan a la Unidad de Psiquiatría Transcultural del Hospital Vall d'Hebron serán evaluados con el HAMD17. Los sujetos completerán el CDS para una evaluación subjetiva de su depresión. La mayoría de estos pacientes residen en Barcelona pero son originarios de países extranjeros. La actitud de aculturación se capturará con la ACM.

RESULTADOS

El **ESTUDIO1** muestra que a pesar de los antecedentes culturalmente diversos de los evaluadores, se alcanzó una consistencia aceptable para todos los ítems de HAMD-17. Los análisis de ANOVA individuales revelaron efectos significativos para la región (país, continente o occidental / no occidental) para los mismos seis ítems del HAMD-17: insomnio temprano, agitación, ansiedad psíquica, síntomas somáticos GI, síntomas somáticos generales y Insight.

Los datos sugieren que los evaluadores de diferentes regiones geográficas y culturas pueden observar al mismo paciente y proporcionar calificaciones consistentemente diferentes en ciertos elementos del HAMD-17. Las diferencias en las expectativas de los evaluadores, basadas en la conceptualización de la enfermedad culturalmente específica y la experiencia de las presentaciones

«típicas» de los pacientes, pueden ser la base de estas discrepancias en las calificaciones.

Los resultados del **ESTUDIO2** muestran que los resultados totales de la subescala HAMD6 no están influenciados por el origen geográfico de los sujetos. Como era de esperar, los elementos somáticos de HAMD17 serían propensos a tener una calificación más alta para los sujetos no occidentales. CDS y HAMD mostraron una correlación positiva, moderada y estadísticamente significativa. Sin embargo, CDS se sobrevalora sistemáticamente sobre HAMD independientemente del origen geográfico del sujeto. Al analizar los grupos de Aculturación, la categoría de Segregación mostró un patrón de síntomas diferente en comparación con el resto de los grupos.

CONCLUSIONES

ESTUDIO 1: La somatización de los síntomas es una de las diferencias más descritas en la expresión clínica de la depresión y la ansiedad entre las culturas occidentales y no occidentales, y los pacientes no occidentales expresan mayores síntomas somáticos y menos síntomas psíquicos. Las diferencias en las expectativas entre los evaluadores occidentales y no occidentales con respecto a las características de la enfermedad somática pueden haber contribuido a las diferencias que observamos en elementos más somáticos de HAMD-17 (Somático-General, Somático-GI y Agitación).

En los países no occidentales, la depresión a menudo se entiende como un problema social o moral. La renuencia a considerar las causas psicológicas / biológicas / médicas de la depresión podría ser la base de las diferencias en las puntuaciones entre los evaluadores occidentales y no occidentales para el ítem Insight.

ESTUDIO 2: En este estudio podemos ver que se pueden llegar a conclusiones similares con HAMD17 y HAMD6 al evaluar una

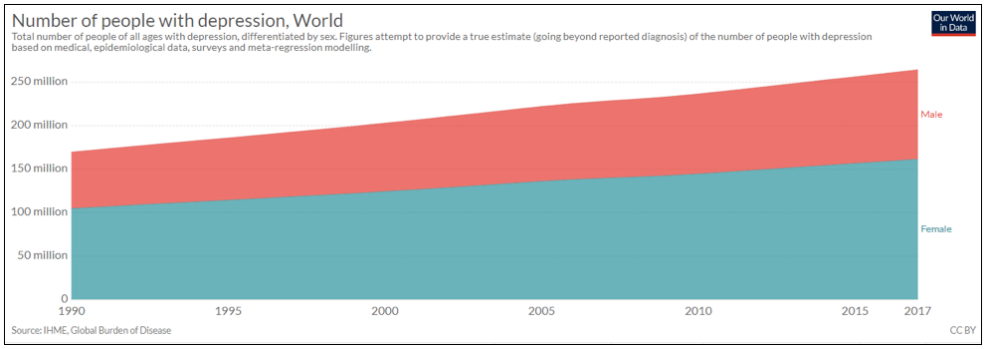
población multicultural. El hecho de que los elementos somáticos de HAMD17 sean propensos a tener una puntuación más alta para los sujetos no occidentales debe tenerse en cuenta al diseñar programas de Rater Training para ensayos clínicos multinacionales de depresión y tratar de minimizar la sobrevaloración de los elementos somáticos. A veces se utiliza CDS en lugar de la entrevista HAMD para ahorrar tiempo en la práctica clínica. Se debe tener cuidado ya que podría haber una sobrevaloración en la puntuación del CDS. Es necesario tener en cuenta la actitud de aculturación a la hora de evaluar a las personas que están teniendo problemas de adaptación al país de acogida, ya que la expresión de sus síntomas depresivos podría ser diferente a la del resto de grupos.

CHAPTER I:
Major Depression Disorder

1. SOCIAL AND ECONOMIC IMPACT OF DEPRESSIVE DISORDER

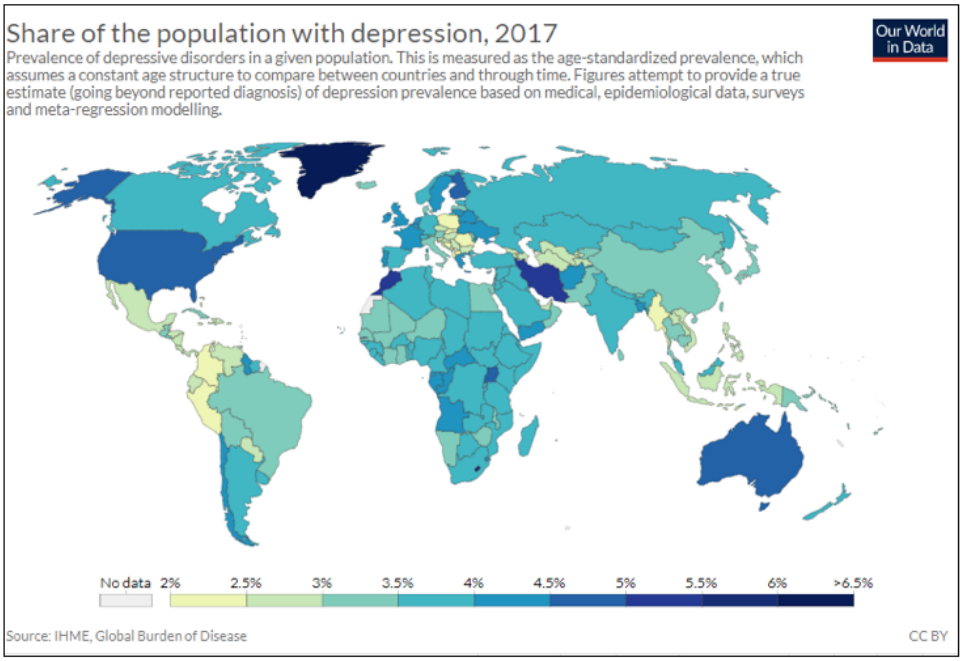
According to data from WHO more than 300 million of people suffer from depression (WHO1) representing 4.4% of the world's population (Friedrich 2017). Depression can be mild, moderate or severe depending on the intensity of its symptoms, but it can become a very serious health condition. Suicide is a dramatic outcome of such condition, especially amongst the younger patients where suicide is the second leading cause of death (WHO1). Depression typically affects female more than male. (WHO1, IHME 2018)

Figure 1. Number of people with depression, male vs female (IHME 2018).



Data shows that affectation of Depression reaches all countries in the world. Although potential cultural differences will be discussed later in this research work, a clear statement can be made that depression does exist at worldwide level.

Figure 2. Worldwide prevalence of depression (IHME 2018).



Depression is the leading case of disability worldwide (Friedrich 2017). Such disability can be measured by using DALYs (Disability Adjusted Life Years). It shows the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability (Ustun 2004). According to data from IHME, (IHME 2018) in 2017 depression was causing significant DALY rates worldwide. Data from 1990 is showing that DALYs were already an important problem, thus depression worldwide impact is documented since long ago.

Figure 3. DALYs due to depression in 2017 (IHME 2018).

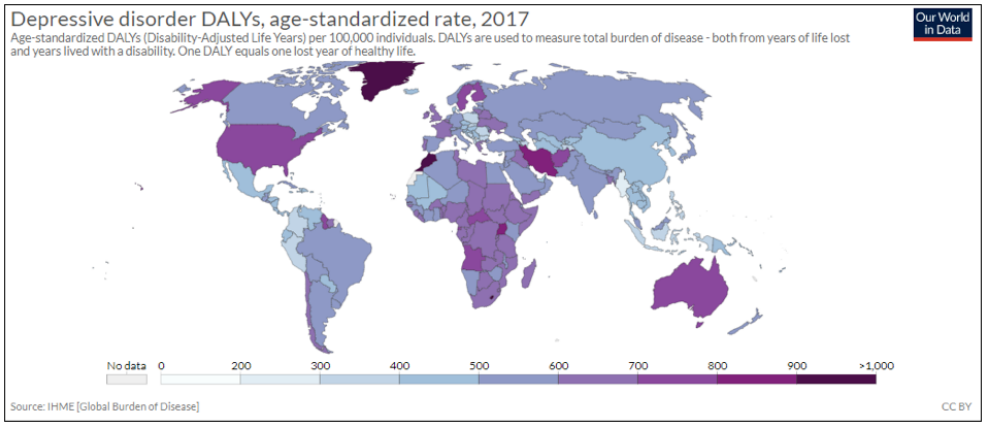
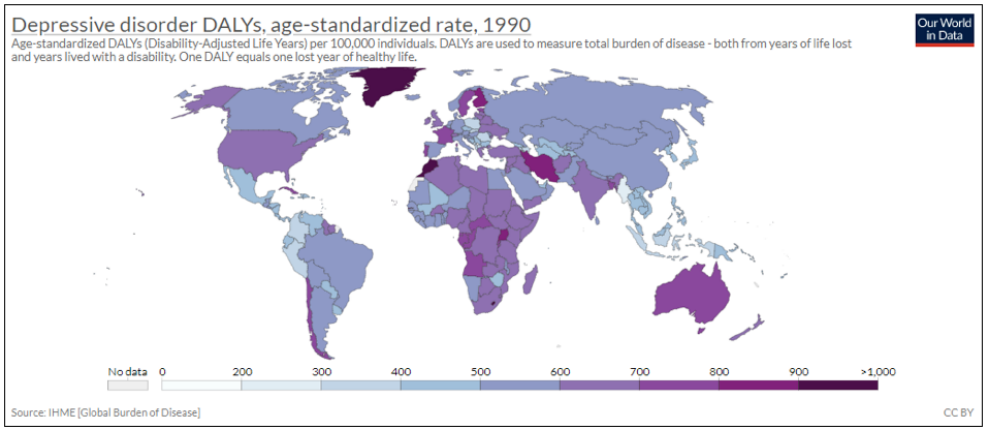
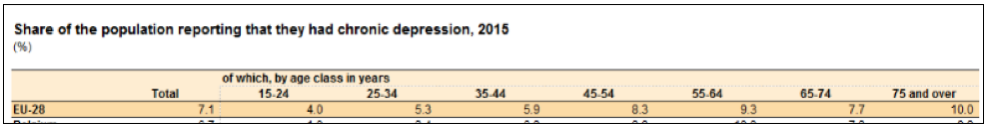


Figure 4. DALYs due to depression in 1990 (IHME 2018).



If we move the focus to the European continent, we find that 7.1 % of the EU-28 population reported having chronic depression, being the proportion higher in women than in men. (EHIS 2015). The lower proportions are found in the younger age range (15-24 years old subjects report 4%) and it gradually increases until reaching 10% in subjects aged 75 years and over.

Figure 5. Proportion of European population reporting chronic depression by age.



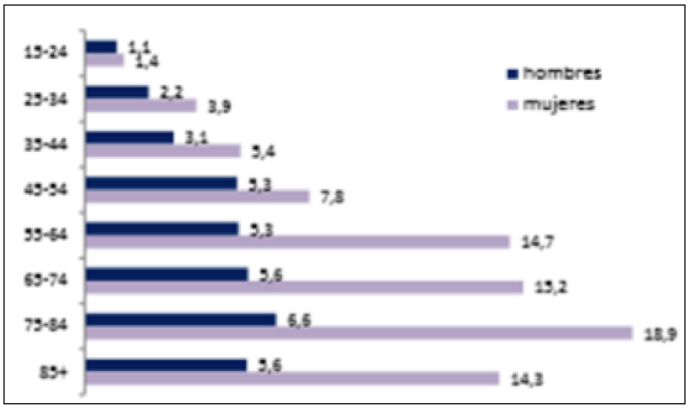
Share of the population reporting that they had chronic depression, 2015
(%)

	Total	of which, by age class in years 15-24	25-34	35-44	45-54	55-64	65-74	75 and over
EU-28	7.1	4.0	5.3	5.9	8.3	9.3	7.7	10.0

Depression is present in both rural and urban environments. According to EHIS in 2014 7.8% of population living in the cities reported depression whereas 7.1% was reported by people living in the suburbs. The percentage decreased down to 6.2% for population living in rural areas. Seems therefore that the higher the population density is, the higher depression prevalence is present.

If we explore depression in Spain, we find similar rates than at European level: Depression is present in 6.7% of the population and is significantly higher in women than in men. Likewise, the proportion of depression increases as age becomes older. (ENSE 2017).

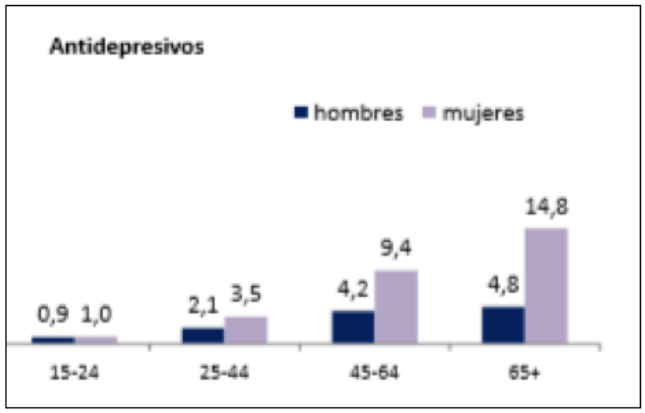
Figure 6. Percentage of population reporting chronic depression by age and gender (Spain 2015).



Unemployed population shows 7.9% depression rate whereas working population presents 3.1%. Amongst subjects who suffer a disability and are not able to work this rate goes up to 30%.

The use of antidepressants is associated with suffering of depression, with the subsequent economic burden for the public health system. As age increases, the use of medication increases, being substantially higher in women than in men.

Figure 7. Percentage of population using antidepressants by age and gender (Spain 2015).



Numerous parameters show the cost of depression. What follows is a list of depression consequences which are in direct relation to the patient's quality of life (Kessler 2012).

- Education: Provided the early age of onset of depression, the chances of finishing education are lower in depression patients independently of whether they live in developed countries like the US or low-middle income countries. (Lee 2009, Breslau 2008).
- Family Functioning: Marital problems are associated to depression, independently of whether the patient is man or woman. (Whisman 2001). Parenting functioning is also affected again independently whether the patient is the mother or the father. Negative influence is more evident at younger ages of the children.

- Work/Financial success: Depression has been defined as the fourth cause leading to work absenteeism (after migraine, other pain conditions and cardiovascular disease). Another interesting parameter is the «presenteeism» referring to the fact that the patient is at work but having a low performance (Stewart 2003). In regards the financial success, it is difficult to say whether this is a cause or a consequence of depression. It is known that low income environments bring to a higher chance to suffer from depression. However, depression patients suffer an impairment of their ability to work and consequently have a lower income. (Muntaner 2004).

2. TRANSCULTURAL CONSIDERATIONS OF MDD

It is evident that MDD is a worldwide health problem which has no distinction of gender, age, employment status or place or living. At different rates, MDD is present in all these groups causing disruption at individual, family and social level.

WHO has several workforces dedicated to increase worldwide awareness of the importance of the mental health, especially in developing countries where the access to treatments and resources dedicated to depression are dramatically limited. Health care providers need to be trained and investment needs to be increased in these areas of the world. However, attention is to be given as well to the developed countries where nearly 50% of people with depression do not have treatment. WHO reports that high-income countries dedicate 5% of their budget to mental health whereas the investment drops to less than 1% in developing countries. (WHO 2018)

To improve this situation, WHO has created the mhGAP (mental health Gap Action Program), dedicating its World Health Day 2017 to Depression. This campaign was called «Depression: Let's talk» and emphasis was given to the fight against the taboo surrounding mental health in general and particularly depression.

This campaign defines depression as a feeling of sadness and loss of interest in activities that were normally enjoyable for the subject. There is inability to carry on with daily activities for at least 2 weeks. Also, some of the following symptoms should be present:

- Loss of energy.
- Appetite changes.
- Sleep disturbance.
- Anxiety.
- Decreased ability to concentrate.
- Hesitation.

- Fatigue.
- Feelings of incapacity, hopelessness, guilt.
- Self-inflicted injury thoughts or suicide or suicide ideation.

These symptoms are clearly aligned with the diagnostic systems from Western countries: DSM and ICD. It is rather notable that a global campaign is using western-based diagnostic criteria and is obviating depression features which are culturally specific from non-western cultures.

It is commonly recognized the fact that depression in non-western cultures show a somatic profile when compared with western cultures which are prone to display a psychological component when suffering from depression. This can be itself a bias as it is based in the western dichotomy between mind and body. Causes for these different symptom's patterns can be various: e.g. fear to recognize emotional problems due to the social stigma or simply lack of vocabulary to elaborate on emotions. (Kirmayer 1998, Kirmayer 2000).

Despite the westernized definitions, WHO issued culturally adapted promotion materials for this campaign, which would be distributed in Arabian, Chinese, English, French, Russian and Spanish. However, when campaign posters are compared, again one can see the western bias provided that the cultural adaptation in some cases is just the change of the skin color and some facial features.

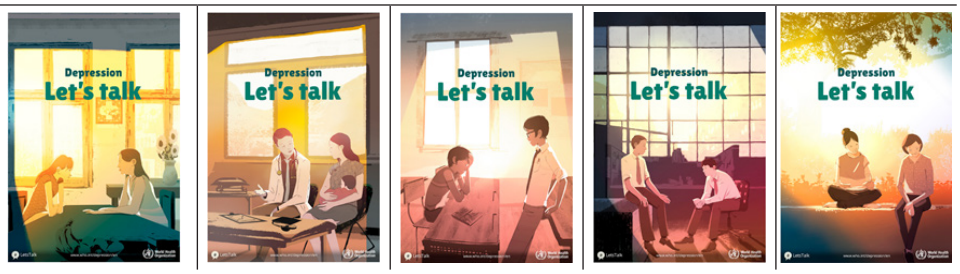
Figure 8. WHO promotion posters for «Depression: Let's talk» campaign.

EUROPE

SOUTHEASTERN ASIA

AFRICA

WESTERN PACIFIC



It is therefore crucial to be conscious of the frequent biases in the definition of depression if we want to have a global approach covering all cultures worldwide.

An enormous effort has been done in DSM to capture cultural considerations not only in depression but in all diagnostic categories. In DSM-IV one could find the «Cultural Bound Syndromes» section which was criticized because it was just an Appendix covering 25 different syndromes considered rather localisms, cultural-dependent and very heterogeneous, becoming a sort of box of curiosities.

DSM-V has a more comprehensive classification and definition of the former «Cultural Bound Syndromes». Such definitions are set as follows:

1. Cultural Syndrome: Groups of symptoms which tend to occur simultaneously in individuals belonging to certain cultural groups or communities. They have local recognition and follow the same pattern. DSM-V includes nine of them:

    a. Ataque de nervios («attack of nerves»): Present in Latin groups.
    b. Dhat syndrome («semen loss»): Present in South Asia. However similar believes have been identified in western cultures where religion identifies masturbation as a sin.
    c. Khyâl cap («wind attack»): Present in Cambodia.
    d. Kufingisisa («thinking too much»): Present in Zimbabwe.
    e. Maladi moun («human caused illness»): Present in Haiti.
    f. Nervios («nerves»): Present in Latin groups.
    g. Shenjing shuairuo («weakness of the nervous system»): Present in China.
    h. Susto («fright»): Present in Latin groups.
    i. Taijin kyofusho («interpersonal fear disorder»): Present in Japan.

2. Cultural Idioms of distress: This is a way of expression to show discomfort and does not necessarily has to mention symptoms or syndromes. These idioms are used within a collectivity to share the same experience and express personal or social worries. This is a subjective way of expression, in contrast with previous «cultural bound syndromes» which acted rather as labels. (Hertog 2016).

3. Cultural distress explanations: Explicative models implemented in a community to understand locally recognized symptoms and syndromes.

It is important to mention that the cultural formulation guideline in DSM-IV was just 4 items which were difficult to apply during a clinical interview and did not have in consideration especial populations like refugees, children, elderly, illiterate or homeless. (Lewis-Fernandez 2014).

DSM-V presents de Cultural Formulation Interview (CFI) which is a semi-structured interview where the clinician can explore different domains which will provide the needed information to conduct a complete cultural formulation. Interestingly, CFI has two versions, one for assessing the patient and another one for an informant. Lastly, there are some supplemental modules that can be used by the clinician to deeper explore some of the domains (e.g. Module 5: Spirituality, Religion and Moral Traditions) or concrete populations (e.g. Module 11: immigrants and refugees). (APA 2013).

Coming back to depression, it becomes fundamental to understand the different clinical expressions that can be found across the globe. Diagnostic tools are having in consideration these potential differences, but a literature review would be needed to understand how depression is perceived and expressed in different regions of the world.

2.1. Depression in Maghreb countries

(Balbo, 2004; Caballero 2008; Stein, 2000; AOUTTAH, 1992; Okasha 1999; Ktiouet, 2004)

Western medicine was implemented in Maghreb at the beginning of XX century, with French protectorate. In '30 decade there were already several Hospitals in the region which were based in Western medicine. Both French and local patients were attended at these facilities, although segregated. In 1956 the French administration retired from the region leaving a western psychiatry heritage which would coexist with old local traditions that would never be replaced by the new biomedical model brought by the French psychiatrists.

Depression in Maghreb was believed to be lower than other countries during '50 and '60 decades. It was not until '70 decade, when migratory flow from France started, that the presence of depression syndromes in this population was recognized. Such depression was defined as follows:

- High prevalence of somatic complaint.
- Frequent persecutory ideation.
- Low affective expression, particularly depressed mood.
- Rare expression of guilt.

Should the interviewer explore deeper, some depressive mood symptoms would emerge, however they are not as detailed as the spontaneously described somatic complaints.

In Maghreb the common language is classical Arabian, which is highly diverse from a semantic point of view. However, a dialect is used in the streets as well as in the medical consultation. Such dialect lacks the description capacity of classical Arabian. Therefore, there are no words to describe feelings like «sadness» or «anxiety». This leads patients to use circumlocutions or metaphors to describe such feelings, giving the appearance of somatization and hypochondriac complaint.

It is noteworthy the low expression of guilt which is explained by the religion. In Maghreb it is believed that mental disease occurs because of God designation or evil possession; making the patient a victim of this circumstance. There is, therefore, a clear external locus of control, in which the patient does not feel responsible for what is happening to him; hence no guilt feeling is present. This is an essential difference with Christian cultures where the subject is made responsible of what is happening to him by the «mea culpa» way of thinking.

Religion plays a key role in the understanding of mental disease for people living in Maghreb. Mental disease is commonly assumed as a divine punishment this is why they call it «*Iahmaq min ghadah Allah*» (i.e. human folly is the anger of God). Mental illness can be caused by spirit possession or a witchery sent by a third person with special powers. As this is an extended common believe, subject's family understands mental illness and provides protection to the affected relative. The disease will become a family matter and, as a group, they will seek a solution, that being a spiritual healer. Different local traditional methods can be applied:

- FQUIH: Mosque leader, master of the Koranic school. His methodology goes from fabricating talismans to conducting exorcisms to expel spirits using Koran readings.
- MARABOUTISM: Veneration of the saints. Family members travel to the holy places to ask for the healing of the affected member.
- DANCE THERAPY: Performed at religious brotherhoods it is thought to be especially effective in cases of possession.

It is obvious that traditional and biomedical pathways are clearly separated not only by the methodology per se but also by the places where they are practiced. Still, some families and healers recommend seeing a psychiatrist when the local solutions do not

work, leading to a model of co-existence between the traditional and biomedical medicine practices.

2.2. Depression in Egypt

(Okasha 1999, Okasha 2005, Okasha 2004)

Descriptions of mental illness and depression have been found on ancient Egyptian papyrus.

Mental diseases were thought to be a consequence of physical dysfunction in organs like the heart or the uterus. «Soma» and «Psyche» were intimately connected, and they influenced each other within the human being. The soul was repaired within the body overnight. This is the reason why funerary rituals are so important for Egyptians, the body must be preserved for the purpose to have a rested soul on it.

At a later stage Islam was implemented in Egypt and some explanatory models were inherited. For this reason, some Egyptian beliefs about mental health are very similar to those found in Maghreb region, especially the existence of evil possessions which underlie mental disease.

Mental disease in Egypt is considered a family problem. Affected family members are protected by the group and a solution is sought as a group. The first contact for help is the local healer who will apply witchcraft and amulets.

It is noticeable, though, the use of psychiatry services once the traditional procedures are unsuccessful. Egypt is one of the Arabic countries with more psychiatry attention. It is estimated that 50% of psychiatric patients go directly to a hospital.

Moving to the clinical symptomatology of depression, in Egypt one can observe a higher prevalence of somatic symptoms over the emotional expression. Emotional expression could be misunderstood, and social repudiation is feared, specially by male patients.

Literature shows that the most common symptoms expressed by depressive patients are agitation, somatic symptoms, libido decrease, anorexia and insomnia. Amongst the less frequent symptoms are listed feeling of guilt, sin and self-reproach, again due to the low presence of Christian confession in Egyptian culture.

2.3. Depression in India

The Bhagavad Gita sacred scriptures already describe a balanced individual as someone who controls his mind, emotions and senses. If this internal balance is disrupted, pain and suffering will be caused to self and others. (Prakash, 2013).

Depression presence is well documented in India, where it is linked to a profound social stigma. Evil possession or punishment for something wrong done in a past life could be the root of depression. Indian population strongly believes in reincarnation. (Keedwell 2008, Avasthi 2011, Wig NN 1970).

Still, the family is a vital factor to fight depression as a group and will bring the affected relative to the local healers. Local healers use techniques ranging from Ayurveda therapies with herbs, to exorcisms conducted by the priest (Kakar 2003).

Psychiatrist will be rarely approached as they do not think of depression like a medical problem. Likewise, it would be a social shame to make public a family problem of this nature. (2011 Avasthi). At most, the family will visit a family physician, as psychiatrist are often seen as eccentric doctors who cannot help (2011 Kishore).

In India the influence of the local traditions is very powerful, to the extent that some psychiatrists are still influenced by Hindu beliefs. An investigation showed that 18% of interviewed psychiatrists believed that divine punishment is related to some mental pathologies, and 24% believed that evil possession plays a role in mental disease (Almanzar 2014).

During the '80 decade several studies took place about the clinical expression of depression in Indian patients and it was concluded that somatic symptoms, agitation and hypochondriasis were more prevalent in Indian group that in the European controls (Kirmayer, 1984).

As previously mentioned, an important social stigma is associated to depression diagnosis, making somatic symptoms more prone to be shared. (Raguram, 1996; Grover 2010). During the clinical interview, the first description of symptoms is somatic. The clinician must probe further in the exploration until reaching the potential interpersonal problems and emotional sphere (Raguram 1996, 2001). By doing this, some other studies demonstrate that Indian patients present western-like symptoms which could fit with ICD/DSM diagnostic criteria (Gupta 2010, Chatuvedri 1985). According to this research the main difference between western and Indian patients would be the explanatory model underlying such symptoms. Indian patients attribute the psychological symptoms of depression to the natural course of life and seek comfort in the religion. However somatic symptoms are more prone to be cured by a physician hence those will be expressed in a clinical setting. But these patients do not realize that psychological and somatic symptoms are both sides of the same thing. For them both are disconnected (Bhugra 1997). Of note is the poor adherence to pharmacological treatment, despite a patient might decide to see a doctor, the believing on medication effectiveness is still low (Grovers, 2010).

2.4. Depression in Africa

This section is focused in sub-Saharan Africa as Northern Africa has been covered in the section dedicated to Maghreb region.

To understand depression in Africa, it is necessary to step back and comprehend the history and reality of the continent. Currently existing countries gained their independency when colonialism left

the region. However, since then, political instability and corruption have troubled the region (Njenga 2006; Njenga 2002) causing wars, massive exodus and famines. This already devastating scenario is accompanied by critical public health problems (e.g. HIV/AIDS) and extreme weather conditions (e.g. prolonged droughts ruining the tenuous agricultural-based economy).

In this desolate situation, mental health is underestimated. Only 50% of African countries do have a mental healthcare policy and most of them are obsolete and insufficient. 90% of African countries have less than 1 psychiatrist per 100.000 inhabitants (Bird, 2011; Hanlon 2010, Fournier 2011). These countries dedicate their scarce resources to high mortality rate diseases, leaving to a second term the pathologies causing morbidity and/or social impact. (Bird, 2011; Hanlon 2010).

In many countries simply there is no data about mental health. Its impact is not documented; hence the need is not quantified. Consequently, the mental health problem does not exist; so no resources are dedicated. Since no resources are dedicated, objective mental health data is not generated. This situation generates a vicious circle by which mental health results neglected as a whole (Bird 2011, Hanlon 2010, Ehiemua 2014).

In Africa mental health is still seen as something spiritual or supernatural. Thus, it is nor perceived as a health problem and it is managed at family level. Healers or religious leaders might be consulted (Amuyunzu-Nyamongo 2013, Alem 2008); in some cases, even performing craniotomies as Kisii community in Kenya (Njenga 2002, Furnas 1985). However these local remedies are decreasing due to the change of paradigm in the traditional family. People is gradually moving to the cites pursuing more opportunities, hence families are separated and relatives safeguard is no longer available. Individuals are not used to face problems by themselves and have no resources to manage difficult situations. Often alcohol

and/or drugs are used, even in adolescent age group. (Amuyunzu-Nyamongo 2013, Njenga 2002).

Is therefore expected the existence of supra-natural explanations for mental disease, as shown in several research works: In Ghana mental disease is considered a punishment for a bad behavior (Bird 2011); in Tanzania is believed to be an incurable incantation leading to fear and rejection towards the patients (Njenga 2002); in Uganda there is no word to name «depression» which is not culturally accepted (Gordon 2013). A study conducted in Nigeria searched for the cause attribution for mental disease (Arboleda-Florez, 2002) and the more frequent explanations were drug consumption, God's wrath and spirit possession.

Stigma associated to mental disease is significant, not only for the ill person but for his/her family members. It becomes a family shame (e.g. a woman has more difficulties to be married if there is a mentally ill person in her family) and this is the reason why they keep the patient within the family. In some cases where the disease is severe or the family is not cohesive, patients might end up chained or totally neglected in prayer camps. (Njenga 2002, Fournier 2011).

Some efforts are done to address mental health problem in Africa, despite the lack of resources. In Liberia the ministry of health is trying to settle mental health attention points in the 15 regions of the country; in Sierra Leone there are centers looking after the war children, and in Democratic Republic of Congo there are «listening houses» for gender-based violence victims. (Amuyunzu-Nyamongo 2013, Ehiemua 2014).

There are initiatives to generate regionalized attention points for covering the rural areas. Psychiatry attention in Africa is basically sitting in cities, whereas an important portion of the population is still located in rural areas. Communications between cities and regions are minimal hence making unreachable to rural population

the already scarce psychiatry resources (Duthé 2016, Alem 2008, Ehiemua 2014).

Therefore, some authors advocate for providing a basic training on psychiatry to the already existing primary care points sitting in rural areas. These trainings would be short, frequent and very practical. Whereas such training needs to have a scientific basis, one cannot totally neglect the local believing followed in rural areas of Africa, otherwise this initiative would be unsuccessful. Some actions involve the local healers, so psychiatry is gradually integrated in the local practices. Some countries do have a sub-section for «Traditional Medicine» within the Health Ministry. Western imposition model would not be the way to follow as social reality has to be considered. But it is fundamental to build some scientific knowledge and institutional recognition. Only then mental disease will officially start existing and social stigma will be truly fought. (Alem 2008, Ehiemua 2014, Njenga 2002).

Some registers have been done already, for example, Accra Hospital in Ghana declares having depression as first cause for admission (33.1% of cases) closely followed by schizophrenia (29.8% of cases) (Fournier 2011). Some additional registers are gradually evidencing the existence of depression in Africa (Pérez 1998, Tomlison 2007). Following prevalence for depression have already been reported: Nigeria 1%, South Africa 4.9%, Ethiopia between 7 and 11%, Burkina Faso 4,3% (Duthé 2016).

Africa is gradually modernizing, and hybrid cases might be described, showing locally known symptoms (i.e. traditional concepts which remain in African culture) merged with biomedical symptoms more linked to Western ways of assessment (Pérez 1998). In order to obtain more accurate data on depression prevalence and clinical evidences, an improvement in the screening and diagnostic tools is still needed. Despite these limitations, some research shows that there are «core» symptoms in African patients' depression those

being somatic and behavioral symptoms (Majodina 1983). Symptoms are not displayed at a cognitive level (Sweetland 2014). Emotions and worries are related to the heart, leading to a confusion when describing the symptoms, moving from a psychological / emotional origin to a somatic level.

2.5. Depression in Latin America

When referring to depression in Latin patients, it is common to find a significant volume of research conducted in immigrant population in the US. In these cases, acculturation process has a crucial role in the clinical outcomes (Torres 2010, Alegría 2007). For this reason, in this section only Latin patients living in their original country will be addressed.

In Latin American countries depression is accepted as a mental health problem. There are registries and prevalence is known. Such prevalence will vary depending on the socio-economic circumstances of the country (García-Álvarez 1986).

As per explicative models, depression is seen as a reaction to the adverse life circumstances, depression is not really seen like a medical diagnostic. They believe depression will heal via conversation and only those very severe cases will need some medication.

Latin American patients usually present a somatic profile for their depression. For both depression and anxiety, the physical component is major. This somatic expression can vary greatly in terms of localization and intensity. This trend to express more somatic symptoms has been shown as well when using scales covering both somatic and psychological symptoms, like HAMD-17 (Jorge MR 2003, Munoz 2005-1, Muñoz 2005-2). It is crucial that clinicians are aware of this bias, so depression symptoms are not overlooked under many somatic complaints coming from Latin American patients (Tamayo 2007).

Of note is the numerous Cultural Syndromes that are already captured in DSM-V (see previous section of this work) like «ataque de nervios», «susto» or «nervios» showing the many localisms existing in Latin America in regards mental health.

2.6. Somatization Vs Psychologization

What precedes is a brief overview of the geography of depression that makes no claim to completeness but nevertheless demonstrates its global distribution.

What becomes evident is that many researchers on this field associate the depressive symptoms' somatization to the non-Western countries. The approach is that «THEY» somatize and neglect the psychological symptoms. Of note is that «THEY» (non-Western) is opposed to «WE» (Western). This demonstrates that there is a bias to consider the Western approach as the «official» and leave the non-Western approaches as the ones deviating from the official standard.

In scientific literature there is an evident bias towards scientific production coming from European and American countries (Kirmayer 2000). Amongst scientific publications in psychiatry, 90% of research published in relevant journals is coming from either Europe or North America (Patel 2001 A, Patel 2001 B). Consequently, the biomedical model has been taken as the standard and is extrapolated to the rest of the planet. The other 10% of research production from other countries are considered localisms and regionalisms; and extrapolating them to the global knowledge is not even considered (Avasthi 2011).

The cultural factor is normally used on the patient's perspective to justify lack of understanding between patient and clinician, strange believing from the patient or value differences (Kirmayer 2000). However, cultural factor should be applied to both patient

and clinician as they both can have different cultural frames which will impact the diagnostic. It is about patient symptoms but also about clinician's cultural competences.

At this point is needed to stop and take some distance to utterly understand what is meant by «somatization».

Somatization is the presence of a physical symptom without an evident organic cause. During a clinical interview one must understand why the patient is using somatic symptoms to express his discomfort and why the observer reaches the conclusion that there is no organic basis, and he is witnessing a somatization (Kirmayer 1984). The cultural component in this interaction is fundamental. Also, the cultural competences of the observer are crucial.

Several research works demonstrate that somatization is a universal mechanism. When it has been looked for, it has been found. Somatization is not a phenomenon only happening in non-Western countries or in rural-collectivist societies. (Kirmayer 1984, 1991, 2001).

In Western countries one can find several examples of somatization like Hysteria or Briquet Syndrome, described already during XIX century.

At the present time there are numerous diseases known as somatic and present in Western countries: fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, to name a few.

Kirmayer and Robbins (Kirmayer 1991) categorize the somatic symptoms depending on the causal attribution of the symptom:

1. Somatic symptom with no medical explanation.
2. Hypochondriacal concern.
3. Clinical presentation of affective disorders, anxiety or other psychiatric disease.

Some authors describe the term «Somatic Depression» (Robbins 1997), where affective symptoms are neglected, and physical symptoms prevail. Sometimes these physical symptoms would be aligned with melancholic profile of depression. Robbins highlights as Somatic Depression symptoms the following vegetative signs: fatigue, weight loss/gain, poor appetite, sleep disturbance, constipation, restlessness.

Some other authors provide a different perspective in this matter. We do not have to discuss only about somatization in non-Western countries. We must consider that a «Psychologization» is done in Western countries too. If we consider this, we will be getting away from the Western-centric approach and consider that both Somatization and Psychologization are expressions of the same thing but from different perspectives (Western vs Non-Western cultures) (Ryder 2008, White 1982).

Ryder conducted a study where North American and Asiatic patients were compared. Independently from the utilized assessment tool, North Americans showed a higher prevalence of psychological symptoms. This trend was stronger than the one showed by Asiatic towards somatic symptoms. Hence one can conclude that psychologization done by North Americans was stronger than somatization done by Asiatic subjects (Ryder 2008).

As a matter of fact, psychologization processes are also found in non-Western countries. If the clinical interview is conducted in this direction and idiomatic barriers are overcome, psychological symptoms will also be reported. (Ryder 2008, Patel 2001 C, Patel 2001 A, Patel 1995B, Raguram 2004).

The Western biomedical model defines depression disorder based on psychological symptoms. DSM V requests de presence of depressive mood or loss of interest /anhedonia in order to give an MDD diagnostic. In Western countries, where MDD is understood

under a biomedical model, the associated stigma is lesser. This also helps patients to show psychological symptoms and use the emotional level (Ballenger 2001).

2.7. Western vs Non-Western. Pooling strategies

So far, we have discussed the somatization and psychological processes for depression in Western and non-Western cultures. However, one could question what it is understood by Western and non-Western. If we consider our own countries, we will find differences already across regions, within the same country. Some other variables are involved, like socio-economic level, educational degree, etc.

However, research is global since years ago and is working at global level. A clear example of this are clinical trials, which are conducted worldwide. International clinical trials will give global results which will be used by local countries' Health Authorities to approve the use of a drug on their population. This is also true for clinical trials in psychiatry, where primary efficacy outcomes are usually the change on time of certain scales' scoring.

Following questions arise:

- Patient: How will the subject answer to the study specific questions? Will there be differences across subjects from different regions? Will this impact the global results of the trial?
- Assessors: How are psychiatrists utilizing the study scales? All assessors across the study will use the same assessment tool, however, psychiatrist will be sitting at different countries which are following different psychiatry models.

Regulatory agencies and ICH (international body that defines a set of standards, which governments can then transpose into regulations for clinical trials involving human subjects) have developed guidelines to overcome the above described transnational obstacles.

ICH guideline E17 (REF) has been developed by EMA to provide guidance on how to approach research at global level, i.e. covering different countries across the globe.

EMA establishes that data obtained via MRCT (multi regional clinical trials) can be accepted by local Regulatory Authorities to provide approval of a given medicine to their local population. MRCTs can deliver more robust evidence for extrapolation of results than single regional trials. The basis of this statement is the regional pooling of subjects, which is a valid strategy if there are enough similarities with respect intrinsic / extrinsic factors relevant to the disease. Even distant regions can be pooled. Thanks to this pooling, extrapolation of results to real life will be more reliable and it will avoid unnecessary duplication of studies, leading to a quicker access to study results and conclusions.

Such pooling must be carefully conducted. ICH guideline E5 (REF) has been developed by EMA to describe the ethnic factors in the acceptability of foreign clinical data. By «ethnic» EMA understands the original Greek definition (Ethnos means Nation or People). Hence ethnic factors relate to populations grouped by common traits and customs. This definition gives ethnicity a broader meaning than just racial. These factors can be categorized as Intrinsic and Extrinsic.

1. Intrinsic: Genetic and Physiology factors.
2. Extrinsic: Environment and culture. More culturally and behaviorally determined.

EMA recommends pooling strategies for MRCT being that from pivotal trials to exploratory studies. For early exploratory studies regional pooling will allow a qualitative analysis of certain traits which could be further tested in future confirmative studies.

Regional pooling, though, could also be a source of variability which needs to be mitigated. Care must be taken because too much mitigation (e.g. narrowing study population to small groups) may

reduce the external validity of the study results in certain regions. EMA guidelines suggest following strategies to reduce the variability within a pooled group of subjects:

1. Disease definition: It is well known that disease definitions may vary between regions. For a multi-regional study, it is crucial to define from the beginning the nature of the disease under study and clear inclusion and exclusion criteria need to be set. Only then subjects showing the same disease will be recruited, independently of the region where they come from.
2. Standardized Protocol: Protocol procedures must be defined in advance. Not only the actual assessments to be conducted to the subjects but also the sequence of assessments and the tools to be used for obtaining such data. All subjects must undergo the same procedures in the same way, independently of the region where they come from.
3. Training of investigators: As said above, investigators are also a source of variability. In order to ensure that they will apply study procedures in the same manner, training must be conducted before the start of the study. This is especially important in psychiatry trials, where the subjective component of the assessor may play a role. Therefore, EMA has also developed some guidelines indicated for psychiatry studies, in order to avoid variability coming from the study assessors.

Coming back to our topic (MDD) the EMA does have guidelines to conduct international clinical trials in MDD (REFx3). On their versions 1 and 2 the following conditions are indicated, in line with the general principles outlined in ICH E17 and ICH E5:

1. Disease definition: MDD diagnosis should be done by using a recognized diagnostic classification method, being DSM the preferred system.

2. Standardized Protocol: To characterize MDD symptoms severity, validated scales should be used being HAMD (17 items version) and MADRS the preferred tools.
3. Training of investigators: Guidelines establish that investigators should be trained in evaluating the patients. Moreover, Inter Rater Reliability Scores (kappa) should be documented for each assessor, in order to guarantee the integrity of the data collected.

There is currently a concept paper highlighting the improvements that version 3 of this Guideline will have to show, in order to give an answer to the current challenges in MDD research. Interestingly, a section is foreseen for the cross-cultural differences in the definition of the target population.

3. THE ASSESSMENT OF MDD

This section will address some of the existing instruments available to assess depression severity. Both interview format and auto-administered scales will be covered; and a mention will be done to the cultural component of the scales. Once more, it is important to note that cultural component affects not only the subject but also the assessor. Both sides of the clinical encounter are potentially affected by the cultural bias.

Observer variability can be overcome with an increase of the cultural competency of the clinician. The assessor must be conscious of the differences existing among patients with different cultural backgrounds. Likewise, the assessor must be aware of the differences existing between those cultural backgrounds and oneself. Assessors also have their own cultural background. An increase on the cultural competence will help the clinician to be more objective on his assessment. By cultural competence it is understood that the assessor will challenge the preconceived knowledge and attitudes towards other cultures (Qureshi 2008). It is important to escape from stereotypes. The cultural particularities must be used by the assessor to understand what the subject is expressing. It is very important not to use cultural particularities to predict what the subject is showing. The difference is subtle, but crucial: if we use culture as a predictor, we will be falling in the stereotype.

Scales can also have cultural bias. Van de Vijver (Van de Vijver, 2004) describes de construct bias, referring to the fact that a construct (e.g. depression, or intelligence) might have different understandings across cultures. The scales are usually shaped under Western parameters (e.g. depression is defined by DSM criteria) and those do not exactly match what is understood in non-Western countries under that construct. Several strategies are suggested to overcome this obstacle, which are mostly in line with suggestions provided by regulatory authorities:

1. Extensive training of assessors
2. Detailed protocol in regards administration, scoring and interpretation
3. Utilize bilingual population. This suggestion, thought, must be taken with care. Whereas bilingual population bridges the potential gap between western scale and non-western subject, these subjects will not be representative of their origin population. Bilingual subjects usually belong to higher educated groups and have been probably exposed to other cultures. This will benefit the value of the assessment; however, they do not fully represent the cultural group where they are coming from.

EMA recommends using HAMD (17 items version) and MADRS to assess severity of depressive symptoms. These scales will be detailed in next section. Also, auto-administered version of HAMD will be discussed (CDSS- Carroll Depression Severity Scale) as well as BDI (Beck Depression Scale) due to its extended use in the clinical setting.

3.1. Hamilton Depression Scale

In 1960 «A Rating Scale for Depression» was published by Max Hamilton, presenting his scale to assess the severity of depressive symptoms (Hamilton 1960). This scale was designed to assess patients who were already diagnosed with depression and its value entirely depends on the capacity of the interviewer in eliciting the information from the patient during the interview. This scale allows the interviewer to consider other sources of information in order to conduct a final assessment.

Some items are scored from 0 to 2 whereas some other items are scored from 0 to 4. In the first group of items the scoring would be as follows:

- 0. Absence
- 1. Mild
- 2. Obvious

In the second group of items the intensity of the symptom can be specified, should the symptoms be present:

- Absence
- Dubious
- Mild
- Moderate
- Severe

Hamilton shows in his publication an exhaustive description of the items, which is helpful for the interviewer to apply the scale. Later in 1967 (Hamilton 1967) Hamilton published another work where additional detail on the items are provided. This time he used a larger sample and included both men (n= 152) and women (n=120). In his original work sample were 49 women.

What follows is a compilation of definitions for all HAMD items, based in both first Hamilton publications. Hamilton emphasizes the importance of rating each symptom under the correct item. Sometimes items might seem similar, however they are qualitatively distinct, therefore care must be taken when allocating each symptom from the patient under each item of the scale. As an example, Hamilton mentions the «Depression Triad» embracing Item 1 (Depressive Mood), Item 2 (Guilt) and Item 3 (Suicide ideation).

Item 1: Depressive Mood. Scoring 0-4

The most common symptom under this item is the tendency to weep. Hamilton already remarks that this symptom might be expressed differently across cultures, therefore the assessor must be skilled when evaluating it. Other symptoms to be explored

would be melancholia, pessimism over the future and hopelessness feelings. Occasional weeping during the interview would be rated as «2», frequent weeping would be rated as «3». «4» would be used for severe cases and «0» would most probably indicate absence of depression diagnostic.

Item 2: Guilt. Scoring 0-4

Pathological guilt must be differentiated. In some circumstances it is normal to feel guilt (e.g. wrong decision taken by the subject) but in some other circumstances there is a pathologic component. Following guide can be used for rating severity of guilt: «0»- Absence of guilt, «1» –Self-reproach, «2» –Guilt ideation, «3» –Believing that depression is a punishment, «4» –Guilt delusion.

Item 3: Suicide. Scoring 0-4

Any suicide attempt will be scored as a «4» unless the patient has never shown suicide ideation where the rating would be a «3». It is important to differentiate between true suicide attempt and acts intended to receive attention. Rater must be skilled to make such a judgment. Following guide can be used for rating severity of this item: «1» –life is not worth living, «2» –wishes to be dead, «3» –suicidal ideation, mild attempts «4» –serious attempts.

Items 4, 5 and 6. Insomnia (early, middle, late). Scoring 0-2

When insomnia problem is serious normally the 3 items are affected. Care must be taken with middle insomnia as there might be artifacts (e.g. waking up for voiding). If insomnia is not frequent or mild, a «1» should be scored. Only for severe cases «2» will be used.

Item 7: Work and Loss of interest. Scoring 0-4

If the subject has quit his job or stopped job hunting due to depression, this is scored a «4». If the patient still works, the impact

on its performance must be assessed. It is important to cover in this item social life and hobbies and determine whether there has been a decrease of activities or a loss if interest.

It is important not to embrace here symptoms of lack of energy or tiredness, as those must be scored under Item 13 «Somatic Symptoms».

Item 7 is meant to capture the performance on work and hobbies, independently of whether the patient is feeling tired or not. We need to evaluate in item 7 whether the patient can overcome tiredness in order to continue his normal life.

Item 8: Retardation (0-4):

A «4» would be awarded if the subject is silent and the interview cannot take place. If the interview can occur after perseverance of the interviewer, that would be a «3». As a general guide the following can be considered: «1» –rigid facial expression, flat expression «2» –Retard in providing answers, monotonous voice, tendency to be sitting still «3» –interview is nearly impossible «4» –interview is impossible.

Interviewer might ask the subject whether he feels slowed down. Sometimes what subject feels is not in line with what interviewer observes. This item is an observational item therefore the rating must be based in observation only.

Item 9: Agitation (0-4):

In the original article Hamilton mentions that this item can not be rated from 0 to 4 but from 0 to 2 (Absent-Mild-Obvious). However later Hamilton recognized that he was biased in this rationale because he had only seen British patients. When he assessed patients from other countries, he acknowledged that there are different shades in the expression of Agitation and he allocated then the 0-4 range to this item (Guy, 1976).

Following descriptors can be used: «1» –unrest, «2» –hands movements, picking at clothing, «3» –subject can not be sitting and stands up «4» –interview is dominated by the subject's agitation.

It is important to consider that retardment and agitation can be both present simultaneously during the interview, on mild forms.

Item 10: Anxiety (psychic symptoms) (0-4):

It is needed to know whether the subject had anxiety traits before the depression. This item is intended to capture the anxiety associated to depression (difficulty to relax, tension, irritability, worrying for little things, feeling tense. Difficulty to get concentrated).

Item 11: Anxiety (somatic symptoms) (0-4):

This item assesses the autonomous system activity, i.e. symptoms in the following areas: respiratory, cardiovascular, gastrointestinal, urinary system. Blurry vision, tinnitus.

Item12: Gastrointestinal symptoms (0-2):

A common symptom in depression is loss of appetite. Further versions of HAMD will have into account the gain of appetite. However, this is not covered in the original scale.

Item 13: Somatic Symptoms General (0-2):

Somatic symptoms due to depression use to be vague with no concrete description from the patient. Fatigability needs to be explored under this item, as well as loss of energy. How difficult it is for the patient to start an activity and to finish it.

Item 14: Loss of libido (0-2):

To be assessed independently of the patient status (e.g. single person, elderly person). What is to be rated here is not the actual

behavior but the level of interest which might be affected because of depression.

Item 15: Hypochondriasis (0-4):

Care must be taken not to mix Hypochondriac thoughts with Guilt feelings. As a general guidance the following can be used: «4» to be scored when delusions or hallucinations. «3» to be scored when subject believes that depression is caused by an organic disease. «2» for worries about somatic symptoms and «1» for questionable symptoms.

Item 16: Insight (0-2):

It is crucial to differentiate between lack of acceptance of the disease from shame to admit patient is suffering from a mental condition.

Item 17: Weight loss (0-2):

This item can be rated based on subject declaration or the actual registered weight. If loss of weight is evident, a «2» will be rated. If is not clear, a «1» will be scored.

Besides the core 17 items, there were 4 additional items in the original publication of 1960, however Hamilton did not include then in the total scoring of the scale because they added qualitative information about the nature of the depression, rather than indicating how severe the episode was (Hamilton 1960). In the following lines a description of this additional 4 qualitative items is provided:

Item 18: Diurnal Variation (0-2):

As per Guy's manual from 1976 this item is not included in the Hamilton scale total scoring because it does add information about patient's disability. The most common pattern is that the patient feels worse during the morning, although some patients refer to feel

worse in the evening. If the variation is clear a «2» will be rated. If no variation a «0» will be scored. «1» will be used when variation is not clear cut.

Item 19: Depersonalization and Derealization (0-4):

Patient refers having a distance with his surroundings, it is an extreme lack of interest in his environment. Normally patients recognize such symptoms when they happen. If they don't have the symptom, they don't understand this question very well. Extreme cases of depersonalization are rare in depressive patients.

Item 20: Paranoid symptoms (0-4):

A suspicious attitude needs to be explored. The patient might say that others talk about him and that might be true. What needs to be clarified is whether the patient makes a negative intentionally intention from the others. This attitude already would score a «1». If the patient believes that others want to harm him that would be a «2». If the patient mentions than others are doing things for harming him that would rate a «3». Lastly, if there are hallucinations, a «4» would be awarded.

Item 21: Obsessive symptoms (0-2):

Obsessive symptoms need to be differentiated from guilt or hypochondriasis explored in other items. Obsessive thoughts are described by the patient as coming from his own mind, as thoughts that are not normal for the patient and that he cannot stop them. These thoughts generate anxiety on the patient.

Later, a 24 items version was developed, including the 21 items already defined by Hamilton plus 3 additional items which evaluated the cognitive symptoms of depression: Helplessness, Hopelessness and Worthlessness. (Guy 1976, Riskind 1987, Paykel 1985). Like in the original scale, the total scale scoring was still based in the

original 17 items and the rest of the items were just to add qualitative information. In 2003 Dr. Janet Williams expanded the scale up to 29 items, generated a structured interview which would add 8 factors covering the Seasonal Affective Disorders. Later in this work details will be provided about this structured guide.

In 2008 Dr. Williams developed a new tool to use the Hamilton Scale: GRID-HAMD (Williams 2008) where the assessment of frequency and intensity are separated for each item, forming a grid which allows for a faster administration and a better definition of the anchor points for each item.

The above are the most well-known version of HAMD, which are typically used in MDD Clinical trials. However, when reviewing literature one can find numerous HAMD versions with different combinations of items. HAMD27 was developed including some atypical symptoms items (Galenberg 1990) and HAMD36 was further developed onto the CDI (Clinical Interview for Depression) (Paykel 1985, Guidi 2011).

Carrozzino et al recently conducted a review of different HAMD versions showing which items were shared or not by all of the versions. The study concluded that HAMD is still a reliable tool but it is crucial to use the structed guide during the interview and that assessors receive appropriate training on the use of the tool. Otherwise the validity of the results obtained with the scale might be compromised. (Carrozino 2020).

Figure 9. Items for most widely used HAMD versions.

Number	Items	Range of scores											
		Hamilton [2] $HAM\text{-}D_{21}$ unstructured version with ratings only	Hamilton [2, 3] $HAM\text{-}D_{17}$ unstructured version with ratings only	Bech et al. [13, 14] $HAM\text{-}D_{6}$ unstructured version with ratings only	Miller et al. [21] $MHRSD_{25}$ structured version with structured interview	Bech et al. [18] $HAM\text{-}D_{23}$ structured version with anchor points and item definitions	Williams [22] $SIGH\text{-}D_{21}$ structured version with structured interview	Potts et al. [24] $SI\text{-}HDRS_{17}$ structured version with structured interview	Gelenberg [11] $HAM\text{-}D_{27}$ unstructured version with ratings only	Williams et al. [26] $SIGH\text{-}SAD_{29}$ structured version with structured interview	Moberg et al. [27] $HAM\text{-}D_{24}$ structured version with structured interview	Morriss et al. [19] $HDRS_{17}$ structured version with semi-structured interview and anchor points	Timmerby et al. [20] $HAM\text{-}D_{6}$ structured version with semi-structured interview and anchor points
1	Depressed mood	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4
2	Feelings of guilt	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–3	0–4	0–4	0–4
3	Suicide	0–4	0–4	–	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	–
4	Insomnia, early	0–2	0–2	–	0–2	0–2	0–2	0–2	0–2	0–2	0–2	0–2	–
5	Insomnia, middle	0–2	0–2	–	0–2	0–2	0–2	0–2	0–2	0–2	0–2	0–2	–
6	Insomnia, late	0–2	0–2	–	0–2	0–2	0–2	0–2	0–2	0–2	0–2	0–2	–
7	Work and interests	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4
8	Psychomotor retardation	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4
9	Psychomotor agitation	0–2	0–2	–	0–2	0–4	0–4	0–4	0–4	0–4	0–4	0–4	–
10	Anxiety, psychic	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4
11	Anxiety, somatic	0–4	0–4	–	0–4	0–4	0–4	–	0–4	0–4	0–4	0–4	–
12	Somatic symptoms, GI	0–2	0–2	–	–	0–2	0–2	–	0–2	0–2	0–2	0–4	–
13	Somatic symptoms, general	0–2	0–2	–	–	0–2	0–2	0–4	0–2	0–2	0–2	0–2	–
14	Genital symptoms	0–2	0–2	–	0–2	0–2	0–2	0–2	0–2	0–2	0–2	0–2	–
15	Hypochondriasis	0–4	0–4	–	0–4	0–4	0–4	0–4	0–4	0–4	0–4	0–4	–
16	Loss of weight	0–2	0–2	–	0–2	0–2	0–3	–	0–2	0–2	0–3	0–2	–
17	Insight	0–2	0–2	–	0–2	0–2	0–2	0–2	0–2	0–2	0–2	0–2	–
18	Diurnal variation	0–2	–	–	0–2	–	0–2	–	0–2	–	0–2	–	–
19	Depersonalization/derealization	0–4	–	–	–	–	0–4	–	0–4	0–4	0–4	–	–
20	Paranoid symptoms	0–4	–	–	–	–	0–3	–	0–3	0–3	0–3	–	–
21	Obsessive/compulsive	0–2	–	–	–	–	0–2	–	0–2	0–2	0–2	–	–
22	Tiredness and pains	–	–	0–2	0–2	0–4	–	0–2	–	–	–	–	0–2
23	Distinct quality of mood	–	–	–	0–2	–	–	–	–	–	–	–	–
24	Lack of reactivity	–	–	–	0–2	–	–	–	–	–	–	–	–
25	Worthlessness	–	–	–	0–4	–	–	–	–	–	0–4	–	–
26	Helplessness	–	–	–	0–4	–	–	–	–	–	0–4	–	–
27	Hopelessness	–	–	–	0–4	–	–	–	–	–	0–4	–	–
28	Loss of appetite	–	–	–	0–2	–	–	0–2	–	–	–	–	–
29	Weight gain	–	–	–	0–2	–	–	–	0–2	0–2	–	–	–
30	Loss of interest	–	–	–	0–2	–	–	–	–	–	–	–	–
31	Insomnia, general	–	–	–	–	0–4	–	–	–	–	–	–	–
32	Retardation (motor)	–	–	–	–	0–4	–	–	–	–	–	–	–
33	Retardation (verbal)	–	–	–	–	0–4	–	–	–	–	–	–	–
34	Retardation (intellectual)	–	–	–	–	0–4	–	–	–	–	–	–	–
35	Retardation (emotional)	–	–	–	–	0–4	–	–	–	–	–	–	–
36	Loss or gain of weight	–	–	–	–	–	–	0–2	–	–	–	–	–
37	Fatigue	–	–	–	–	–	–	–	0–4	0–4	–	–	–
38	Social withdrawal	–	–	–	–	–	–	–	0–4	0–1	–	–	–
39	Appetite increase	–	–	–	–	–	–	–	0–2	0–3	–	–	–
40	Carbohydrate craving	–	–	–	–	–	–	–	0–3	0–3	–	–	–
41	Hypersomnia	–	–	–	–	–	–	–	0–4	0–4	–	–	–
42	Increased eating	–	–	–	–	–	–	–	–	0–3	–	–	–
43	Diurnal variation type A	–	–	–	–	–	–	–	–	0–2	–	–	–
44	Diurnal variation type B	–	–	–	–	–	–	–	–	0–2	–	–	–

HAM-D, Hamilton Rating Scale for Depression; GI, gastrointestinal.

From: The Hamilton Rating Scales for Depression: A Critical Review of Clinimetric Properties of Different Versions. Danilo Carrozzino, Chiara Patiernoa, Giovanni A. Favab Jenny Guidia. Psychother Psychosom 2020;89:133–150.

3.1.1. Notes about hamd and gender

Original Hamilton scale (1960) was developed in a sample of women. The next work on 1967 was based in a sample of men and women and Hamilton already points out that the items descriptors should be equally used for both genders. However, Hamilton added some annotations to be considered when assessing female patients.

Care must be taken when reading these notes, as they are coming from a '70 society showing stereotypes and social circumstances from that time. Nevertheless, they are included in the present research work in order to show a complete picture of the evolution of the Hamilton scale.

Item 1: Depressive mood (0-4): It is believed that women cry more easily than men, but this is not true for depression. Both men and women cry equally when they are depressed, hence the assessor must avoid bias when rating this item.

Item 7: Work and Activities (0-4): Women are usually housewives, so they can module the frequency and intensity of her activities, they can even get help from other family members. If the women have a work outside her house, she might even have to reduce her hours or even quit the job. Women have less hobbies than men, hence the loss of interest in activities can be less obvious for women.

Item 11: Somatic Anxiety (0-4): The three last symptoms are more often present in women tan in men: (cardiovascular, gastrointestinal and urinary systems).

Item 13: General Somatic symptoms (0-2): When women present back pain, it is common they attribute it to pelvic disorders. This attribution needs to be explored in deep before scoring this item.

Item 14: Loss of libido (0-2): In women with a satisfactory sexual life this item is easy to assess, as the rater must quantify whether this satisfaction has decreased with depression. However, for women

with certain degree of frigidity the rater needs to explore whether it has become worse since depression is present. This item is more difficult to assess for women with no previous sexual experience, or widows. In women loss of libido appears not as a loss of drive but as a decrease on her responsiveness, which can not be evaluated in women with no sexual activity. If there is not enough information, this item will be rated as «0». Of note is that in some cases of severe depression, menstrual alterations could be present too.

3.1.2. Notes about hamd and cultural differences

Hamilton references to cultural differences are scarce. However, one must consider that Hamilton research is developed in the '60 and '70 decades, where the world was not yet global and interculturality was still far from what would become in the decade of '90.

This makes even more valuable some cultural considerations that Hamilton already presented in his work. See following notes:

Item 9 Agitation: At the beginning it was rated from 0 to 2. However, Hamilton changed it to 0-4 when he recognized he was biased by his experience on British patients. Hamilton recognized that outside United Kingdom patients could express their agitation in a range of intensities more diverse than those expressed on his own country, so he decided to change the rating range for this item.

Item 1 Depressed Mood: For this item Hamilton already made remarks for the gender aspect, which were complemented by the cultural aspect comments. Crying behavior is something which varies substantially amongst cultures; therefore the rater needs to become familiar with the culture where the patient is coming from so a proper evaluation of crying intensity can be made.

Item 16: Insight: Mental health perception can vary depending on the culture of the patient. Therefore, the rater needs to have this in consideration before rating this item.

3.1.3. Research by Dr. Janet Williams

As time went by, the use of HAMD became more popular, not only in clinical practice but also in clinical trials for MDD therapy investigation. In 1988 Janet Williams published a Structured Interview Guide for HAMD, (SIGH-D) in order to support the correct administration of the scale (Williams, 1988). Until then, several research works had been published on the validity of the scale but mainly considering the total scoring of the scale. According to Williams, there was a need to improve the validity of the scale at item level too, as these are providing qualitative information about the depressive patient. In other words, at equal levels of severity (i.e. Total Score) there could be different symptomatic profiles, therefore the item-per-item analysis is fundamental.

This tool was developed by Dr. Williams' team with the support of Dr. Max Hamilton himself. Results showed that data obtained with the structured interview had higher validity at item level than when guide was not used. The use of the guide did not imply a larger amount of time for administration (L. Baer 2009; Muller 2003; Kobak 2003).

Dr. Williams continued her research work until HAMD29 was created in 2003. It was made up from the original 17 items plus 4 qualitative items plus 8 factors designed to assess the Seasonal Affective Disorder. An interview guideline was developed like the one generated on 1988 for HAMD17, called Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS) (Williams 2003). In this guideline, the original items are identified by «H» and the seasonal factors are identified by «A» letter. Lastly, there are 2 additional items covering difficulty waking and temperature discomfort, identified by «E» letter. This scale has been used to assess depressive disease with seasonal factors. Some authors have published some scoring rules to help understand how to use this guideline (Rohan 2016).

Hereafter a description is found for each one of the items for HAMD29:

H1 Depressed Mood (0-4):

Depressed mood symptoms are captured in this item, by using both verbal information from the patient and non-verbal. At the end of the interview the rater must come back to this item and score it considering the observational information gathered during the interview.

The SIGH-ADS includes questions about Hopelessness, Helplessness and Worthlessness, which were not included in SIGH-D which only asked in general whether the patient had felt down or depressed. These terms were included in order to cover all symptoms described by DSM for MDD diagnosis, as this was one of the criticisms that HAMD17 had received (Bagby 2004).

H2 Work and Activities (0-4):

This item rates the time and interest dedicated to work activities and / or house care or hobbies. This item has not changed substantially from how it is defined in the original HAMD17 publication.

A1 Social withdrawal (0-4):

This is the first seasonal affective disorder added by Dr. Williams in 2003. The exploration starts with a straightforward question to be answered YES or NO: «have you been spending less time with people, or talking to people less than when you feel well?» If the answer is YES, interviewer needs to probe further in order to evaluate the extent of the symptom.

H3 Genital Symptoms (0-2):

This item is scored in the same manner as the original scale. The key is to determine whether there is a reduction in the interest rather

than in the actual behavior. Some authors (Morriss 2008) suggested to extend the timeframe for this item back to 1 month. However, this suggestion was not successful as the dysfunction must come on the interest, not in the sexual behavior. Also, consistency needs to be maintained with the rest of the items, where the time frame is the past week.

H4 Somatic Symptoms Gastrointestinal (0-2):

There are no significant differences in how this item is rated in HAMD29 and the original HAMD17. If the subject has less interest than normal in food, however he is still able to eat, a «1» will be scored.

This item has been criticized because it only captures the decrease of appetite, whereas in depression, an increase of appetite might also happen. HAMD29 solves this problem by adding a new item (A3) where increase of appetite is captured.

H5 Loss of Weight (0-3):

As in the original scale, this item scores the loss of weight due to depression. In both 1960 and 1967 publications, Hamilton recommended to have an objective registry of patients' weight. If this doesn't exist, only an obvious loss would be scored as «2». If not obvious, a «1» would be rated.

Dr. Williams changed the way this item was scored in SIGH-D: She generated Form A and Form B. Form A was intended for patient's feedback whereas Form B was meant to capture the actual weight of the patient. In both forms the rating was increased up to «3» (original scale ranged from 0 to 2) to be used only when it is not possible to assess the loss of weight.

A2 Weight Gain (0-2):

This is the second seasonal factor added by Dr. Williams in 2003. This item covers (along with other ones that will be reviewed later)

the fact that HAMD17 is not considering the reverse symptoms of depression: increase of appetite, weight gain, etc. (Bagby 2004)

This item will be explored only if the previous item (H5 Loss of weight) has been scored a «0». In case no weight gain is present either, a «0» will be scored too for item A2

In case there is weight gain, same criteria than used for H5 will be used: if doubtful, a «1» will be rated, if obvious, a «2» will be scored. There will not be ratings of «3» for those cases where assessments could not be done.

A3 Appetite Increase (0-3)

This is the third seasonal factor, covering the reverse symptoms of depression. It is important to consider only the increase of desire for food. Actual increase – or not- of eating must not be captured in this item. Increase of desire for food will be rated as «1» for mild, «2» for moderate or «3» for severe.

A4 Increased Eating (0-3)

Item A4 will be rated only if A3 has been positive. In A4 the real increase of food intake will be rated as «1» for mild, «2» for moderate or «3» for severe.

A5 Carbohydrate Craving or Eating (0-3)

For assessing this item, the interviewer must ensure that the patient understands which foods are carbohydrates. «1» Will be scored if the subject has more appetite than normal. If such increase is significant, a «2» will be rated. If the appetence is craving, a «3» will be rated.

H6 Insomnia Early (0-2)

Insomnia items are the same as the original scale, however there is a substantial change in the way they are explored in SIGH-ADS.

The subject is asked in a systematic way how was the sleeping before the depression, and how is it now. In order to quantify the current sleeping habits, questions are made about the naps, total time slept, the WASO (Wake time After Sleep Onset).

Rohan criticized the insomnia assessment in HAMD29 because, despite all these additional details, it is unclear what is «early», «middle» and «late» insomnia (Rohan 2016). The scale simply mentions «at the beginning», «in between» and «at the end» of the night. Rohan suggests dividing the night in three thirds which would correspond to «early», «middle» and «late». It is also unclear what is the latency needed to fall asleep. Morriss establishes as a normal latency time 30 minutes. If the patient needs more time to fall asleep, insomnia will be considered (Morriss 2008).

There are also discussions on how to define «occasional» difficulty to fall asleep, as this is the descriptor used to rate a «1». For the original HAMD, «1» would be «occasional» difficulty and «2» would be difficulty all nights. However, SIGH-D defines as «1» having difficulties during 2-3 nights during the last week and «2» when 4 or more nights with difficulties. Other authors (Rohan 2016) define «1» as difficulties during 1-4 nights and «2» as difficulties during 5 or more nights.

H7 Insomnia Middle (0-2):

Only with one episode during the past week is enough to rate «1». If the interruption is just for voiding, it is not considered insomnia and a «0» is scored. If the patient wakes up in the middle of the night for any other reason and takes more than 30 minutes to fall asleep again, that would be scored «2».

E1 Difficulty in Awakening (0-4):

This is one of the new items in HAMD29 and evaluates how awake and alert the patient feels once he has wakened. If the patient feels

well, that would be a «0». If the patient still feels sleepy after 5 hours of waking up, that would be a «4».

Of note is that this item is not taking in consideration for the final total scoring and only provides qualitative information on patient's sleeping behavior.

A6 Hypersomnia (0-4):

This is the sixth seasonal factor added by Dr. Williams in 2003 and covering the reverse symptoms of depression (Bagby 2004).

In order to do a correct assessment of this item, one must determine how much the patient sleeps when he is not depressed. To note that euthymic mood must be assessed, i.e. there could be the situation where the patient has been hypomanic and was sleeping less than normal. This is not the baseline to be considered for assessing hypersomnia in HAMD29.

Once determined the «normal» number of hours for that patient, exploration of the current sleeping time will begin. It is important to differentiate between patients who are working and who are not as hours might differ during the weekends. In these cases, the average over the 7 days of the past week must be done. Naps are to be accounted as well in this total count.

The ratings will be conferred as follows: «0» no or less than 1 hour, «1» at least 1 hour, «2» at least 2 hours, «3» at least 3 hours, and «4» 4 or more hours.

H8 Insomnia Late (0-2):

Once again, this item needs to be rated in comparison with the normal habits of the patient when he was not depressed. If the patient wakes up at the normal time that is scored a «0». If the patient wakes up later than expected, that is still a «0» as hypersomnia is rated in item A6.

If the patient wakes up earlier than expected but falls asleep again in less than 30 minutes, that will be a «1». If more than 30 minutes are taken to sleep again, «2» will be rated.

H9 Somatic Symptoms General (0-2):

Hamilton already mentioned in his original publication (Hamilton 1960) that general somatic symptoms use to be vague but also frequent in depressive patients. It is very important to make the right questions to score this item correctly. As indicated by SIGH-D (Williams 1998) we need to first define how was the energy level during the past week. This is about fatigability, i.e. independently whether the tasks are done or not. We are assessing here the lack of energy of the patient. If the tasks are done or not this would be rated in item H2 «Work and Activities».

If the patient does not report any symptom, a «0» will be awarded. If symptoms are reported but they are vague, a «1» will be rated. Lastly, if there is a clear-cut symptom, a «2» will be scored.

It is important to take in consideration whether there are underlying medical conditions (Rohan 2016). If the medical condition is punctual (i.e. a broken bone) this item will be scored a «0». In case medical condition is a chronic disease, a «1» or a «2» will be scored depending on the clarity used by the patient. Other authors suggest scoring this item differently: if the patient spontaneously reports symptoms, a «2» will be rated. In case symptoms are expressed only when asked, a «1» will be scored. If there are no symptoms at all, a «0» will be rated (Morriss 2008).

A7 Fatigability (0-4):

In case Fatigability has been reported in item H9, the item A7 will be explored. Affectation of functionality will be explored. If even the patient reports fatigability, it is not impacting the functionality, a «0» will be scored. The rest of the ratings depend on the frequency

and duration of symptoms, when they affect functionality: a «2» is at least one hour/day on at least three days, and a «1» is fatigue that is less frequent than in «2». We interpret a «3» «much of the time on most days» as at least half of the day on at least 5 days and a (4) «almost all the time» as normal energy levels for no more than 2 hours per day every day.

H10 Feelings of Guilt (0-4)

If the patient feels he has disappointed others, a «1» will be scored. Same rating will be awarded when the patient feels guilty for things like not performing well at work or not conducting correctly the house keeping activities. When guilt is based in things from the past, a «2» will be rated. If patient thinks that depression is a punishment for something done wrong in the past, as this is already delusional. A «4» will only be given when patient clearly has delusions and hallucinations (e.g. accusation voices or visual threatening hallucinations).

H11 Suicide (0-4)

Anchor points for assessing suicide are very similar to those defined by Hamilton in 1960.

A «1» will be rated when patient feels that life is not worth living. If patient thinks of his own dead in a passive manner or he thinks it would be better to be off dead, that would be rated a «2». If patient already elaborates on a plan to commit suicide or harming himself, a «3» will be rated. A «4» is given if the patient committed a suicide attempt during the past week.

As per original Hamilton publication, suicide attempts happening without a clear previous tendency should be rated as «3». It is important to differentiate between true suicide attempts or actions intended to attract attention.

H12 Anxiety Psychic (0-4)

We rate this item as «1» if the participant endorsed feeling more tense, irritable, argumentative or impatient as compared to normal.

This item is rated as «2» if the participant reported worrying about little things they do not ordinarily worry about. Note that the probes ask for examples of the types of «little things» worried about. Here, we find that it is important to distinguish momentary worries about everyday things that are consistent with a «2» (e.g., where to go, what to do, what to wear, what to eat). A «2» is warranted if the participant endorsed worrying about serious matters that would similarly elicit anxiety during a euthymic mood episode (e.g., major financial stressors, relationship strain with partner).

Ratings of «3» or «4» were provided based on clinical presentation per the scoring stems provided.

H13 Anxiety Somatic (0-4)

This item shows a list of physical symptoms and the assessor needs to explore whether they are present and in which intensity. SIGH-D (1998) indicates that physical symptoms related to an underlying medical condition should not be rated. However, SIGH-ADS (2003) requests noting the symptoms independently if they are caused by a medical condition. If there is such a medical condition, an explanation should be added in the form (Williams 2003). Other authors do follow this interpretation as well (Rohan 2016).

Ratings will be awarded as follows, depending on the severity shown by the most intense symptom: «1» for mild, «2» for moderate,»3» for severe, or «4» for incapacitating.

E2 Temperature Discomfort (0-3)

This item will not be accounted for the final Total scoring as it only offers qualitative information. The patient will be asked whether he

is uncomfortable with the temperature even in places where other people is fine with the temperature. Both cold and hot sensations are explored, as well as the discomfort frequency.

H14 Hypochondriasis (0-4)

SIGH-ADS (2003) adds an additional probe in comparison with SIGH-D (1998). The patient is asked whether he had to ask for help in order to do things that he normally he does independently. With this, it is easier to evaluate whether hypochondriacal thoughts are interfering in the patients' functionality.

Hypochondriasis needs to be separated from the possible ruminations that a depressive patient could have. Even ruminations are present, if they are not related to the own health a «0» would be rated.

A «1» would be rated if the patient admits that he is paying more attention than normal to his body, thinking on how it is working. If patient expresses worry about the possibility of being sick, a «2» would be rated. A «3» would be rated if patient seeks help to do things that he used to do alone in the past. It is important to discriminate on the reasons why the patient seeks help. If the patient only mentions that he has no energy to do things, this would be rated under items H9/A7. We rate the item as «4» if the patient described symptoms indicative of hypochondriacal delusions.

H15 Insight (0-2), H16 Agitation (0-4), H17 Retardation (0-4)

These items are observational, hence there are no probe questions. They will be rated based on the thinking, behaviors and declarations provided during the interview. Other authors also follow this convention (Morriss 2008).

For Agitation and Retardation SIGH-ADS includes some additional questions for those cases where the scale is administered over the phone.

H18 Diurnal Variation Type A (0-2)

This term simply assesses whether diurnal variation exists or not. A «0» will be rated if there are no significant differences across the day. If such variations are present, a «2» will be rated. If they are not clear, a «1» will be awarded.

This item will help us to identify patients of morning type (they feel better during the morning) or the evening type (they feel better the rest of the day).

A8 Diurnal Variation Type B (0-3)

This is the eighth seasonal factor added by Williams in 2003. It also describes the diurnal variation but only in respect slumps occurred during the day. The rater needs to explore if slumps happen and whether there is a recovery. In order to consider a slump, recovery needs to happen at least one hour before going to bed.

If there are no slumps, a «0» would be rated. If there are slumps, ratings will be «1», «2» or «3» depending on whether they are mild, moderate or severe (Williams 2003). In case of doubt, the rating will be scored down (Rohan 2016).

H19 Depersonalization and Derealization (0-4)

In this item it is important not to account the potential cognitive symptoms that can be found in a depressed patient (i.e. attention problems, memory disturbance...).

If the patient refers spacey feelings with no additional symptoms of depersonalization, a «1» will be rated. If symptoms are more elaborated, ratings will be awarded depending on whether they are mild «1», moderate «2», severe «3», or incapacitating «4».

H20 Paranoid Symptoms (0-3)

This item was present already in the original Hamilton publication, and it was rated from 0 to 4 even though it did not account for the total scoring.

However, other authors do count this item in the total scoring (Williams 2003, Rohan 2016), but it is reduced to 0-3. A «1» will be rated when there are paranoid suspicious, a «2» when there are paranoid ideation and a «3» when there are self-referential delusions.

H21 Obsessional and Compulsive Symptoms (0-2)

Obsessions and compulsions need to be explored as they are described in DSM, i.e. we should not consider here ruminations about the own depression. Likewise, paranoid-like thoughts should be rated under item 20.

Depending on the severity and frequency of these symptoms, they will be rated as «0»-absent, «1»-mild or «2»-present. Impact on functionality needs to be explored and considered for rating severity.

An independent rating will be given for both obsessions and compulsions in separated boxes.

At the end of the SIGH-ADS interview, the following algorithm will be followed in order to score different totals:

- TOTAL 17-ITEM HAMILTON DEPRESSION SCORE (without starred items):
- TOTAL 8-ITEM ATYPICAL SYMPTOMS SCORE (starred items only):
- TOTAL 25-ITEM SIGH-ADS SCORE (17-item Hamilton score + 8 item Atypical Symptoms score):
- SIGH-ADS ATYPICAL BALANCE SCORE (total 8-item Atypical Symptoms score divided by total 25item SIGH-ADS score, multiplied by 100): ___ ___. ___%

- SCORE CORRESPONDENCES WITH EARLIER INSTRUMENT VERSIONS:
  - TOTAL 21-ITEM HAMILTON DEPRESSION SCORE (without starred items):
  - TOTAL 29-ITEM SIGHSAD SCORE (21-item Hamilton score + 8 item Atypical Symptoms score, as used in Seasonal Affective Disorder versions between 1988-2002):
  - SIGHSAD ATYPICAL BALANCE SCORE (total 8-item Atypical Symptoms score divided by total 29item SIGH-ADS score, multiplied by 100, as used in Seasonal Affective Disorder Versions between 1988-2002): ___. ___ %

3.1.4. Sub-Scales in Hamilton Depression Rating Scale

In 1975 Bech already questioned the capacity of HAMD17 for discriminating between severe and moderate depression. He proposed a sub-scale composed of 6 items which were more robust to evaluate the core symptoms of depression (Bech 1975). During years he worked in this sub-scale advocating for it as a better tool to assess symptom severity and more practical to use in the daily clinical practice where the consultation time is limited (Bech 1981). Below are listed the 6 items of this sub-scale as well as the cut-off points: (Bech 1996; Bobes 2003, Bobes 2004):

Items:

- Item 1 - Depressed Mood
- Item 2 – Guilt feelings
- Item 7 – Work and activities
- Item 8 - Retardation
- Item 10 – Anxiety Psychic
- Item 13 - Somatic Symptoms General

Cut off scores:

- No depression: 0 - 3 points
- Minor depression: 4 - 8 points
- Major depression: > 8 points

Other authors conducted similar research works with equivalent results. HAMD6 seemed to have good sensitivity to capture depression severity and is also able to identify changes across the time (O'Sullivan 1997, Hooper 2000). For clinical trials this shorter version was less influenced by the adverse events commonly reported with antidepressants. However, EMA insisted on recommending the use of the full HAMD17 rather than the shorter version HAMD6 (EMA 2013).

Bech indicated the existence of other indexes within the Hamilton scale which could provide more information in a more concise and fast way (Bech 1996):

- Anxiety Sub-Scale: Item 9 (Agitation), Item 10 (Psychic Anxiety) and Item 11 (Somatic Anxiety).
- Sleeping Sub-Scale: Item 4 (Early Insomnia), Item 5 (Middle Insomnia) and Item 6 (Late Insomnia).

Other authors defined the Vitaly / Slowness Factor (Tollefson 1993, Boves 2004), containing the following items: Item 1 (Depressed Mood), Item 7 (Work and Activities), Item 8 (Retardation) and Item 14 (Genital Symptoms).

This factor would assess the energy level of the patient, one of the hardest symptoms to mitigate in depression. Sometimes the patient overcomes depression but remains with a residual lack of energy (Targum 2011). Therefore, this factor is of special interest and has been explored in a preliminary way in some studies (Judge 2000).

Cut off ratings for this Vitality factor would be as follows:

- Low Slowness: Less than 8 points.
- High Slowness: 8 points or more.

3.1.5. Cut off Ratings of HAMD17

HAMD17 total score ranges from 0 to 52 points. Several authors have provided different cut-off criteria: Following ratings are generally accepted (Baer 2009):

- 0 – 6: No depression
- 7 – 17: Mil depression
- 18 - 24: Moderate depression
- > 24: Severe depression

Following ratings are proposed by Bech (Bech 1996):

- 0 - 7: No depression
- 8 - 12: Minor depression
- 13 - 17: Less than major depression
- 18 - 29: Major depression
- 30 - 52: More than major depression

Below follow other cut-off criteria (Zimmerman 2013):

- 0-7: no depression
- 8-16: mild depression
- 17-23: moderate depression
- More than 24 severe depression
- 3.1.6. Hamilton scale limitations

Some authors consider HAMD as a scale which is not adapting to the current definitions of depression and lacking the psychometric properties that nowadays are required to a scale (Bagby 2004).

The reversed neurovegetative symptoms of depression are not covered in the first versions of the Hamilton scale (L. Baer 2009) . It was not until HAMD29 was designed that all these aspects are taken in consideration (Williams 2003).

Whereas psychometric properties of the scale are good, such properties diminish when one goes down to the item level. There are items that are measuring similar constructs (e.g. irritability and anxiety; general somatic symptoms and somatic anxiety). It is difficult to replicate the factorial structure of the scale (Williams 1988, L. Baer 2009, Bagby 2004).

Janet Williams already pointed out in 1988 the low item reliability, therefore she developed the structured interview guide which led to an improvement of the scale reliability. There are other standardized interview guidelines to administer the Hamilton scale (Whisman 1989; Potts 1990), but Janet Williams' version is the most extended. Dr. Williams went beyond the structured interview guide and developed the GRID-HAMD, which is a tool capturing the frequency and intensity of each symptom in an independent manner. In this way, it is ensured that all raters are capturing the symptomatology in the same way (Williams 2008).

The fact that so many versions of Hamilton scale exist led some authors to consider if the Hamilton scale is a single tool or it has developed already in several different scales. Some authors advice the use of the HAMD6 (See previous sections for further details) (Grundy 1994, Bech 1981, Ianuzzo 2006, Bobes 2003).

3.2. Montgomery and Asberg Depression Scale

In 1979 MADRS was published as an alternative to the already existing HAMD scale, which had been used for over 20 years and had received already several criticisms (Montgomery 1979).

MADRS was designed thinking on clinical trials, in order to have a good sensibility to the changes in symptoms due to a pharmacological intervention. Until that moment the depression scales had been designed to show depression clinical characteristics.

Montgomery sustained that if his scale had a better sensitivity to change, this would allow for smaller sample sizes in clinical trials and avoid overexposure to treatments that were not yet demonstrated to be efficacious for depression.

MADRS administration is indeed faster than HAMD because it has 10 items representing the core symptoms of depression. In the same paper where the scale is presented it is acknowledged that not all depression symptoms are represented. However, this diminishes the spectrum of symptoms where pharmacologic treatment could have an effect. Preference is given to the items who have shown capacity to be changed with the treatment, leaving aside those items who has less chances to change with treatment and potentially masking the effects of a pharmacologic intervention.

It is also admitted that MADRS does not explore in deep the autonomic disturbances which are often affected in depression. However, the author argues that these symptoms are easily affected by treatment intervention and might be confounded with a true depression affectation. Therefore, it is better not to include them in the scale.

In the original paper it is demonstrated that MADRS is better than HAMD for identifying changes in severity after a treatment intervention. However, it must be mentioned that HAMD reliability values were still good, and there were good correlations between both the HAMD and the MADRS.

In the original paper the author is not doing a factor analysis, however, other authors have done it with mixed results. Some

authors have found only one factor, which was the original idea of Montgomery. However other authors have identified up to 2 or 3 factors (Galinowski 1995, Rocca 2002).

All 10 items of MADRS are rated in the same manner. Severity ranges from 0 to 6 and provide defined anchor points for ratings of 0,2,4 and 6. In general, these anchor points would be equivalent to:

- 0- Absence of symptoms
- 2- Mild symptoms
- 4- Moderate symptoms
- 6- Severe symptoms

If the rater is not clear on the level of severity of a symptom, then the scoring in between will be awarded: 1, 3 or 5.

The Original scale provides a descriptor for each of the anchors and for each one of the 10 items. They are to be scored over the course of the past week.

Item 1: Reported Sadness

Rater needs to ask the patient about feelings of sadness and only reported information needs to be considered, independently of the appearance the patient might have.

Item 2: Apparent Sadness

Montgomery allows to use information provided by an informant. Interviewer can ask the patient about how he thinks he looks like, but the observational information will be used.

Item 3: Inner Tension

Feelings of tension or anxiety are rated under this item. The interviewer must explore the frequency of these feelings and whether they have interfered in the normal life of the patient.

Item 4: Reduced Sleep

First the rater needs to determine how many hours the patient used to sleep when he was not depressed. With that, the assessor must determine for how many hours the sleep has been reduced.

Item 5: Reduced Appetite

Assessor must explore the reduction in the desire for food and whether the patient is actually eating less or not. It must be determined whether others have to push the patient for eating something.

Item 6: Concentration Difficulties

The rater must define first what are the regular everyday activities for the patient, and then assess how are they impacted by the concentration difficulties. The degree of incapacity needs to be determined. For this item is also important to consider the observational information obtained during the interview, i.e. how concentrated the patient during the course of the interview.

Item 7: Lassitude

This item captures the capacity of the patient for starting activities and whether he needs help for this. Once started, the interviewer needs to determine whether the patient can continue without effort or still the activity is slowed down or carried out with effort.

Item 8: Inability to Feel

The interviewer has to explore first what activities did the patient enjoy when he was not depressed, and then assess whether the interest on these activities is reduced. Montgomery requires to assess in this item the subjective experience of reduced interest hence the interviewer must be skillful to obtain this information. Not only the interest has to be rated but the capacity to enjoy such activities.

Item 9: Pessimistic Thoughts

Guilt is assessed in this item, about the current situation that the patient is suffering or for things done in the past. Pessimism about the future is also explored in this item. Should there be presence of delusions, the maximum rating would be scored.

Item 10: Suicidal Thoughts

The interviewer will start exploring the presence of feelings that life is not worth living and will escalate the intensity to see up to which point the subject is endorsing: presence of suicidal thoughts, and how frequent. Presence of plans for suicide and to which extent they are elaborated. Of note is that a previous suicide attempt is not rated in this item; only current thoughts about potential suicide episodes in the future are assessed.

This scale was published with no guidelines for the interview and Dr. Janet Williams developed a guide for it in 1988, which was improved in 2008 with the experience of raters using it (Williams 2008). The only change done in the scale with respect the original publication was the sequence of the items «Reported Sadness» and «Apparent Sadness» which were reversed in the interview guide, leaving in the second place the Apparent item which was not based in the patient verbal output.

Since MADRS was conceived to be used in clinical trials, the use of a guideline did help to improve reliability of the scale and harmonization of how it is used across different assessors participating in a trial.

MADRS is a tool to determine the severity of depression once the diagnostic is already made with a diagnostic tool. However, different authors have determined different cut-off points not only to determine the presence of depression but also to describe how severe it is (Boves 2004, Lobo 2002).

Recommended cut-off points are:

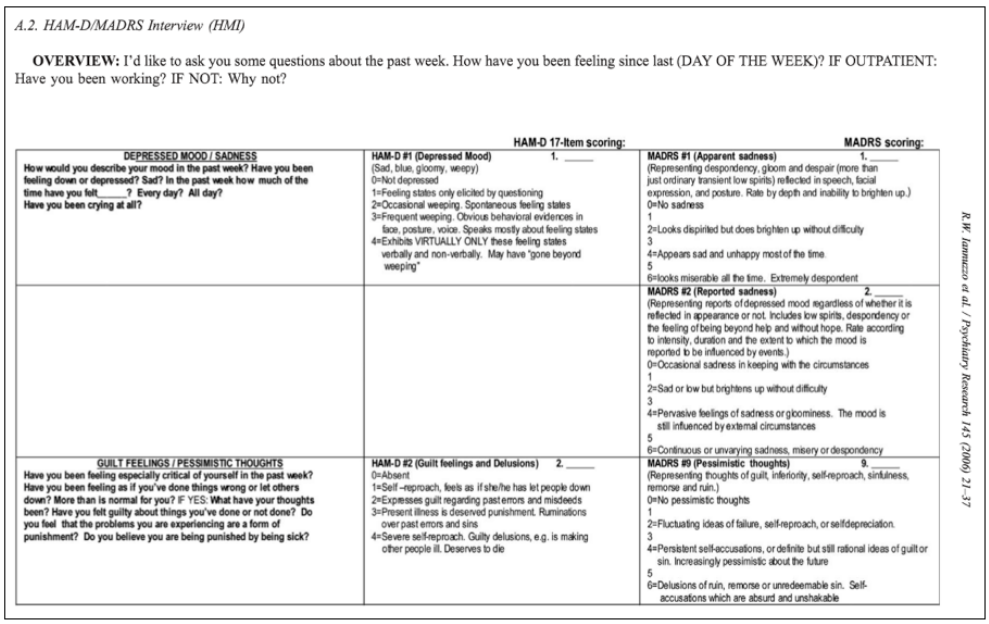
- 0-6: No depression
- 7-19: Minor depression
- 20-34: Moderate depression
- 35-60: Serious depression

In clinical trials the below criterion is often used:

- 0-12: no depression
- 13-26: mild depression
- 27-36: moderate depression
- 37-60: serious depression

One can conclude that both HAMD and MADRS do have advantages and disadvantages and the choice of the scale depends on the user objectives and the target population. In 2006 there was an attempt to merge both scales in one single tool, the HMI: Hamilton and MADRS interview (Ianuzzo 2006). The author used as a basis the SIGH-D and merged it with the MADRS, considering that some of the items were somehow repeated. For example, the HAMD item «Depressed Mood» was merged with the MADRS items «Reported Sadness» and «Apparent Sadness». As a result, the scale had 3 columns showing the main interview questions and secondary probes. The final outcome was a HAMD17 scoring and a MADRS scoring (see Figure 10).

Figure 10. Sample of HMI as per original publication



A.2. HAM-D/MADRS Interview (HMI)

OVERVIEW: I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF THE WEEK)? IF OUTPATIENT: Have you been working? IF NOT: Why not?

	HAM-D 17-Item scoring:	MADRS scoring:
DEPRESSED MOOD / SADNESS **How would you describe your mood in the past week? Have you been feeling down or depressed? Sad? In the past week how much of the time have you felt_____? Every day? All day? Have you been crying at all?**	**HAM-D #1 (Depressed Mood)** 1. _____ (Sad, blue, gloomy, weepy) 0=Not depressed 1=Feeling states only elicited by questioning 2=Occasional weeping. Spontaneous feeling states 3=Frequent weeping. Obvious behavioral evidences in face, posture, voice. Speaks mostly about feeling states 4=Exhibits VIRTUALLY ONLY these feeling states verbally and non-verbally. May have "gone beyond weeping"	**MADRS #1 (Apparent sadness)** 1. _____ (Representing despondency, gloom and despair (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.) 0=No sadness 1 2=Looks dispirited but does brighten up without difficulty 3 4=Appears sad and unhappy most of the time. 5 6=looks miserable all the time. Extremely despondent
		MADRS #2 (Reported sadness) 2. _____ (Representing reports of depressed mood regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.) 0=Occasional sadness in keeping with the circumstances 1 2=Sad or low but brightens up without difficulty 3 4=Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances 5 6=Continuous or unvarying sadness, misery or despondency
GUILT FEELINGS / PESSIMISTIC THOUGHTS **Have you been feeling especially critical of yourself in the past week? Have you been feeling as if you've done things wrong or let others down? More than is normal for you?** IF YES: **What have your thoughts been? Have you felt guilty about things you've done or not done? Do you feel that the problems you are experiencing are a form of punishment? Do you believe you are being punished by being sick?**	**HAM-D #2 (Guilt feelings and Delusions)** 2. _____ 0=Absent 1=Self –reproach, feels as if she/he has let people down 2=Expresses guilt regarding past errors and misdeeds 3=Present illness is deserved punishment. Ruminations over past errors and sins 4=Severe self-reproach. Guilty delusions, e.g. is making other people ill. Deserves to die	**MADRS #9 (Pessimistic thoughts)** 9. _____ (Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.) 0=No pessimistic thoughts 1 2=Fluctuating ideas of failure, self-reproach, or selfdepreciation. 3 4=Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future 5 6=Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable

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The use of this hybrid tool was not very extended as there are no further publications on HMI properties or general use.

3.3. Carroll Depression Scale (CDS)

Modern psychometry in the assessment of depression started in the 60's with the publication of the Hamilton Depression Scale (Hamilton 1960, Hamilton 1967). Observer rated scales were developed and soon self-rated tools made their entrance in order to complement what the clinician was observing. Self-rated scales had several advantages as they were easy to administer, they save time to the clinician and they are easy to interpret.

As HAMD was the gold standard in the assessment of depression, the CDS was designed to mirror the HAMD and obtain scorings of the same 17 items initially designed by Hamilton in 1960. This would be the first time where a scale can be assessed by having clinician

ratings and subjective self-ratings from the patient (Carroll 1998). CDS total score ranges from 0 to 52, as the original HAMD17 and provide ratings from 0 to 2 and from 0 to 4 for the 17 items, matching the same scoring system as it is used in the HAMD17. The severity of depression is classified as follows, being remarkably similar to the cut-off ratings reported by several authors for HAMD17:

- No depression: 0-9
- Mild depression: 10-16
- Moderate depression: 17-24
- Severe depression: 25-35
- Extremely severe depression: >35

One of the major advantages of CDS is the simplicity of the answer for the patients. CDS has 52 sentences which are to be read by the patient and simply responded «YES» or «NO». This significantly reduces the response burden compared to other self-rated scales. The patients are not asked to make a deep assessment of the level of severity of their symptoms as they are in other self-rated scales (McCallum 1995, Toner 1988). In the Zung Self-Rating Depression Scale (Zung 1965) the patient is exposed to 20 items with 4 levels of severity each. This represents for the patient a total of 80 analysis and choices. Similar situation occurs with BDI where 21 items are presented to the patient some of them ranging from 0-4 levels of severity and some other ranging from 0-6. In total the patient has to make 94 analysis and choices (Beck 1961). CES-D is another example where the patient has to face 80 decision points (Radloff 1977).

This reduces the cognitive complexity of the CDS scale, which is extremely helpful in cases of severe depression or elderly population who might have difficulties to have a good concentration and go through the decision-making process.

Simplicity of the answer is also derived from the readability of the sentences which can be defined by the semantic difficulty and syntactic difficulty (Dale 1948). Computations to determine sentence length and word length were performed. The number of complete sentences is divided by the number of words to determine the average sentence length. Next, the number of «unfamiliar» words are counted. A word is considered unfamiliar if it does not appear in a list of 3.000 «familiar» words compiled by Edgar Dale (revised in 1983). Familiar words are known by 80% of children in the fourth grade. Consideration of the amount of familiar and unfamiliar words included increases in the accuracy of the reading level assessment. Use of the Dale-Chall procedure for the Carroll scale produces a North American grade 6 (i.e. students of 11 years of age) reading level. As such, the Carroll scale can confidently be administered in most of the adults.

CDS consists of 52 items, all of them to be answered YES or NO. The direction of a response indicative for of depression is YES for 40 statements and NO for 12 statements. Direction of response reliability was examined in a sample of 3.725 CDS ratings at the University of Michigan (Carroll 1981). The sum of statements for which the answer YES means depression correlated highly with the sum of NO statements. Also, the sum of the 12 NO statements correlated significantly with the Total score, this also being found for the sum of 42 YES statements. These results indicate the absence of a systematic bias introduced by varying the direction of the response.

CDS was also designed to be used in clinical trials and it has shown sensitivity to detect changes throughout the time due to a pharmacological treatment.

Carroll Scale can be used in patients from 17 years of age onwards. There is no upper limit for the age of administration.

CDS Technical Manual (Carroll 1998) provides clear instructions on how to administer the scale. Following must be considered:

- It is accepted that sentences are read outload to the patient and rater notes down the YES/NO answers from the patient.
- Clarifications might be provided to the subject if he requires so, however care must be taken for not providing explanations that could bias the response of the patient.
- If there are items with no response, these must be scored as «0»
- If there are items with both YES/NO responses circled, these must be scored as «1»
- No more than 10% of the sentences can be affected by incorrect answers (not marked; both YES/NO marked). Should there be more than 10% of sentences with incorrect answer, the entire scale becomes invalid.
- CDS might be administer on the phone as well, however this is considered a non-standard procedure and care must be taken when interpreting these results.

3.4. Beck Depression Inventory

The Beck Depression Inventory is a self-rated scale made up of 21 items assessing the severity of the already diagnosed depression. It is designed to be used in adults and adolescents aged 13 and older (Beck 1961).

The inventory was built using statements about depression expressed by psychiatric patients. Both more frequent and less frequent sentences were used for the inventory. For each item, sentences were organized in an increasing severity level order. Four sentences were used for each item, ranging from «0» (less severity) to «3» (more severity).

The first version of the BDI was designed to be read outload to the patient who had to select one of the 4 response options for each one of the items. The administration time was estimated from 10 to 15 minutes.

The spirit of the BDI was to capture depression as it is described in DSM. However, there were several deficiencies in this intention as some aspects like Psychomotor Agitation were not covered. Some other symptoms like Weight and Sleep were only reflected on its negative version, i.e. only when symptoms were decreasing.

This is why in 1979 the second version of the inventory (BDI-IA) was generated. New wording was used for some items and double negations were removed. In some cases, the number of response options was reduced so all 21 items were now having only 4 response options. However, this new version was not widely admitted as most of the investigators were still using the original version of BDI (Steer 1985).

In 1994 a second review of the BDI was initiated (BDI-II), this time with the purpose of having a better match with the DSM criteria for depression (Beck 1996). Four items were removed because they were mostly present in inpatient population: Weight Loss, Change of Corporal Image, Somatic Preoccupation. Working Difficulties was also eliminated. Instead, the following four items were added so the inventory was still embracing 21 items: Agitation, Worthlessness, Concentration Difficulties and Loss of Energy.

Additionally, items capturing Appetite and Sleep were re-designed in a way that now they capture the increase and the decrease of symptoms, matching therefore the DSM description. In the original BDI only decrease of Appetite and Sleep was collected.

It is noteworthy that Weight Loss was removed from BDI-II while it is a criterion for depression according to DSM. It should have been

modified as well to show the reverse version so both increase and decrease of weight would be captured.

Similarly, nothing was edited in the inventory to collect the Psychomotor Retardation thus only Psychomotor Agitation was considered. Again, DSM is considering both Retardation and Agitation as definers of depression however only Agitation is scored in BDI-II.

Other scales like HAMD29/SIGH-ADS capture both increase and decrease of symptoms for Weight/Appetite, Sleep and Agitation/ Retardation, being more aligned with DSM criteria.

BDI-II should take about 10 minutes to be completed. However, in patients with severe depression or obsessive component the administration can be longer. It is allowed that the rater reads outload the questionnaire, so the patient verbally makes his/her choices. Timeframe for symptoms reporting is the past 2 weeks, like the DSM criteria. Interviewer must carefully review the answers endorsed by the patient as some biases could occur. Some patients with severe depression tend to have dichotomous thought and answers can be extremely positive or negative, i.e. selecting always the first option or the fourth option. If a patient marks more than one answer, the most severe must be accounted for.

Cut Off scores are stablished as follows:

- Minimal Depression: 0-13
- Mild Depression: 14-19
- Moderate Depression: 20-28
- Severe Depression: 29-63

Factor Analysis was conducted in the resulting new BDI-II and two dimensions were identified.

Factor I: Anhedonia, Weeping, Agitation, Loss of Interest, Hesitation, Loss of Energy, Sleep Disturbance, Irritability, Appetite Changes, Concentration Difficulties, Fatigue, Loss of Interest in Sex. The highest saturations were on Fatigue and Sleep disturbance.

Factor II: Sadness, Pessimism, Feeling of Failure, Guilt, Feeling of Punishment, Self-Dissatisfaction, Self-Criticism, Suicidal Thoughts, Uselessness.

It was decided to label Factor I as «Somatic Affective Dimension» and Factor II as «Cognitive Dimension».

Of note is that the two factors were different depending on the study group (clinical sample and students sample were used in this study): the clinical sample showed somatic-affective and cognitive factors; whereas cognitive-affective and somatic factors were found for the students (Dozois 1998).

Several alternative factor structures have been proposed. Most of these alternatives include some combination of cognitive, somatic, and affective symptom factors. However, a considerable inconsistency is found in the item composition of factors across the proposed structures. Many items are included in different symptom domains across different models (Dere 2014).

BDI-II has shown a stable factor structure when used across different countries in Europe (Nuevo 2009). However, when comparing samples from countries as different as US and Sri Lanka, difficulties are found to adequately fit the two factors and even the three factors model. Total scores between these 2 different populations are comparable however different items are being endorsed by the different populations. Sri Lanka sample scored higher in somatic

symptoms whereas the US sample endorsed both somatic and cognitive symptoms (Jayawickreme 2017).

It must be noted that from the 21 items in BDI-II, only 6 items display somatic symptoms, that being less than a third of the explored symptoms. Care must be taken when using this inventory in multicultural populations where often depression symptomatology is expressed through the body. Somatizations are at risk to be minimized if using BDI-II which is mainly focused on psychologic symptomatology.

To finalize this section a comparison is made between BDI and the other scales under study in this project: HAMD and CDS.

- BDI-II and CDS have a correlation of r = +0.86
- HAMD and CDS have a correlation of r = + 0.71
- HAMD and BDI-II have a correlation of r = +0.60

The highest correlation belongs to both self-rated questionnaires which is somehow expected as both are patient self-completed questionnaires.

When comparing HAMD interview against self-rated questionnaires, the best correspondence belongs to CDS which is somehow expected because both tools follow the same structure. Correlation between HAMD and BDI is only moderate which can be explained not only because of the different structure but also because BDI is more focused in psychological symptoms whereas HAMD gives equal weight to both somatic and psychological symptoms. One can therefore conclude that CDS is a convenient alternative to the BDI, with the added value of a better correspondence with HAMD (Carroll 1981, 1998).

CHAPTER II:
Study 1 and Study 2

STUDY 1: CULTURAL DIFFERENCES IN THE ASSESSMENT OF DEPRESSION.

STUDY 2: CULTURAL DIFFERENCES IN THE EXPRESSION OF DEPRESSION.

INTRODUCTION TO STUDY 1 AND STUDY 2

When working in transcultural settings, being aware of the potential distinct expressions of depression from the patient is fundamental. Likewise, the way the assessor interprets patient's responses can be mediated as well by his/her own cultural background. Clinician needs to have robust cultural competences. Psychiatric interview is therefore a 2 ways interaction with two critical aspects which might vary depending on the cultural background:

- Clinician: How depression is assessed
- Patient: How depression is expressed

This doctoral project approaches both sides of the clinical interview with two differentiated studies:

- STUDY 1: Assessment of depression
- STUDY 2: Expression of depression

STUDY 1

In order to describe whether there are cultural differences in the assessment of depression, psychiatrists from different countries will assess the very same clinical interview, in a videotaped format, as part of the Rater Training program in a large multi-national clinical trial with MDD patients. The assessment tool will be the Hamilton Depression Scale, 17 items version.

STUDY 2

In order to describe whether there are cultural differences in the expression of depression, depressive patients attending to the Psychiatry Transcultural Unit of Hospital Vall d'Hebron will be assessed with the Hamilton Depression Scale, 17 items version. Most of these

patients reside in Barcelona but are originally from foreign countries.

These two studies will be of exploratory nature and their outcome will complement each other. With the STUDY 1 we will explore whether psychiatrists from different regions assess certain HAMD17 items in a different manner. With STUDY2 we will explore whether MDD patients from different geographies, express their depression in different patterns as described by HAMD17 items. We should be able to identify –or not– different symptoms patterns and see whether the claim that MDD in non-Western countries is manifested in a somatic way, is followed.

The edifying contribution of this research is that the same tool will be used in both studies, hence the potential impact of cultural differences in the HAMD17 will be investigated, from both perspectives: clinician and patient. Of note is that HAMD17 is well-known by its coverage of somatic symptoms, however, it is key to consider that psychologic symptoms are also well captured by many items of the scale.

Provided that HAMD17 is one of the gold standards as primary efficacy measure for international MDD clinical trials, information on how the scale behaves in transcultural settings is of significant importance. If some items are more sensitive than others to cultural differences, this should be taken in consideration when designing rater training programs in international clinical trials.

STUDY 1: CULTURAL DIFFERENCES IN THE ASSESSMENT OF DEPRESSION SYMPTOMS

AIM OF THIS RESEARCH WORK

Depression is an important health and social problem which can be found worldwide, regardless of the cultural background. Nevertheless, cultural context must be considered when assessing the clinical expression of depression.

From the clinical point of view, it is critical to consider such cultural differences when diagnosing MDD or assessing the severity of depression. The profile of the patient in health care settings has changed in western regions, due to immigrant groups arrived from non-western countries.

Other research areas like clinical trials are also affected by globalization. Countries where patients are recruited for clinical trials have expanded, especially to Asia. China, Japan and India are now usual participants in international studies.

In depression clinical trials, health authorities request a harmonization in the way depression is assessed throughout the study. Study results depend on the scores obtained by using depression scales (EMA 2013). Because of high number of countries often participate in clinical trials, a standardization in the way the scale is administered to the patients is needed. Harmonization in the way interviews are conducted by the raters is crucial.

Cultural differences cannot be erased, but we must do our best to minimize them as much as possible.

The EMA states that when the primary efficacy endpoint in a clinical trial is measured with a scale, it is essential to address factors like inter- and intra-rater reliability (EMA 2013).

- Inter-Rater Reliability: The property of yielding equivalent results when used by different raters on different occasions.
- Intra-Rater Reliability: The property of yielding equivalent results when used by the same rater on different occasions.

In order to document these parameters in clinical trials, raters must undergo a training program where they are asked to assess a recorded clinical interview using the primary efficacy scale of the associated clinical trial. This exercise can be requested several times during the life of the study.

The research work presented here is an analysis of the scores given to a recorded clinical interview using the HAMD-17 by raters from different countries. This exercise was done in the context of an international clinical trial.

The aim of this analysis is exploratory. It will be explored whether there are different ways of interpreting the symptoms shown in the recorded clinical interview. It will be analyzed whether the cultural differences have an impact on the way raters from different countries assess the same single patient.

METHODS AND MATERIALS

HAMD-17 data from 218 raters from the US, Belgium, Estonia, Finland, France, Germany, Greece, India, Malaysia, South Korea, Taiwan, Turkey, Morocco, and Tunisia were collected. Outliers were removed to have a homogeneous sample and fictitious trends are avoided. Outliers were defined as those raters whose Total scores were more than +/- 4 points away from the Total consensus OR whose item scores were more than 1 point away from the item consensus. This criterion was suggested by the author (Hamilton 1967) and it is

currently the standard criteria used in Clinical Trials for rater training programs (Muller 2003).

Figure 11. STUDY 1. Sample under study. Original and final sample size once outliers were removed.

	Original Sample size	Final sample size
Belgium	10	7
Estonia	8	8
Finland	7	6
France	6	6
Germany	16	15
Greece	8	4
India	22	12
Malaysia	8	6
Morocco	5	4
South Korea	13	8
Taiwan	12	8
Tunisia	6	4
Turkey	9	8
US	88	65
Total	**218**	**161**

Raters had been pre-qualified to rate the HAMD-17 in this trial based on minimum criteria established for prior training and experience.

Raters participated in a comprehensive, study-specific rater training and certification program that included didactic training on the HAMD-17, videotaped HAMD-17 practice rating and feedback, and a certification HAMD-17 interview rating.

Analyses of the certification HAMD-17 interview ratings were performed using SAS 8®. A series of ANOVAs were conducted on

each HAMD-17 item as well as the total score. In each analysis, HAMD-17 scores were the dependent variables, and Country, Continent or Western/Non-Western were the independent «region» variables. T-tests for individual comparisons within each model used LS Means. Statistical significance was set at the 5% level. No adjustments for multiple comparisons were made, as this was considered to be an exploratory analysis.

Descriptive statistics were also analyzed.

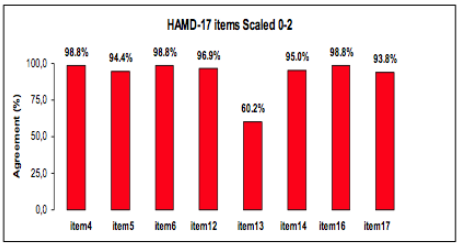
Figure 12. STUDY 1. Group distribution and sample size.

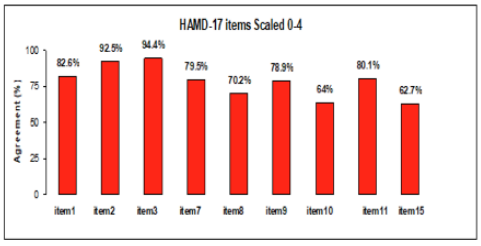
Western/ NonWestern	WESTERN (n = 111)		NON-WESTERN (n = 50)	
Continents	US (n = 65)	EUROPE (n = 46)	ASIA (n = 42)	AFRICA (n = 8)
Countries	US (n = 65)	Belgium (n=7) Estonia (n=8) Finland (n=6) France (n=6) Germany (n=15) Greece (n=4)	India (n=12) Malaysia (n=6) South Korea (n=8) Taiwan (n=8) Turkey (n=8)	Morocco (n=4) Tunisia (n=4)

RESULTS

Despite the culturally diverse backgrounds of raters, acceptable consistency was reached for all HAMD-17 items, with the exception of Somatic-General (Item 13), which showed a clear split in raters between a rating of «1» (39.8%) and rating of «2» (60.2 %).

Figure 13. STUDY 1. Agreement by raters





The individual ANOVA analyses (Figure 14) revealed significant main effects for region (Country, Continent or Western/Non-Western) for the same six HAMD-17 items: Insomnia-Early (Item 4), Agitation (Item 9), Anxiety-Psychic (Item 10), Somatic Symptoms-GI (Item 12), Somatic Symptoms-General (Item 13) and Insight (Item 17).

Figure 14. STUDY 1. ANOVA analysis at different region levels

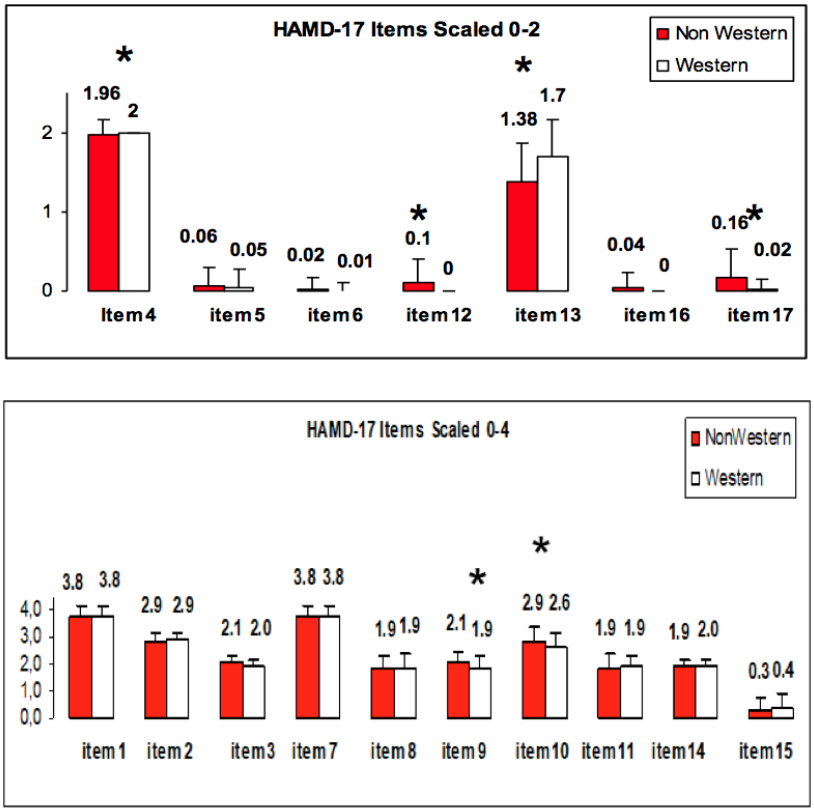
		Country		Continent		Western/Non-Western	
		F	**P value**	**F**	**P value**	**F**	**P value**
Item 1	Depress. Mood	1.88	0.0364*	5.37	0.0015*	0.10	0.7564
Item 2	Feelings Guilt	3.29	0.0002*	2.08	0.1048	0.68	0.4121
Item 3	Suicide	1.35	0.1887	4.54	0.0044*	10.14	0.0017*
Item 4	**Insomn. - Early**	**11.03**	**<0.0001***	**16.58**	**<0.0001***	**4.57**	**0.0341***
Item 5	Insom. - Middle	0.72	0.7407	1.68	0.1725	0.02	0.8801
Item 6	Insomnia - Late	0.44	0.9528	0.38	0.7654	0.34	0.5630
Item 7	Work Activities	1.03	0.4216	2.07	0.1059	0.27	0.6011
Item 8	Retardation	2.02	0.0226*	6.33	0.0004*	0.00	0.9572
Item 9	**Agitation**	**2.50**	**0.0041***	**8.92**	**<0.0001***	**8.92**	**0.0033***
It 10	**Anxie.-Psychic**	**3.31**	**0.0002***	**11.83**	**<0.0001***	**7.39**	**0.0073***
It 11	Anxie.-Somatic	0.87	0.5817	2.03	0.1116	0.63	0.4292
It 12	**Somatic – GI**	**2.25**	**0.0102***	**5.23**	**0.0018***	**12.18**	**0.0006***
It 13	**Somatic - Gral**	**5.00**	**<0.0001***	**12.51**	**<0.0001***	**16.32**	**<0.0001***
It 14	Genital Sympt.	1.19	0.2941	0.51	0.6731	0.16	0.6884
It 15	Hypochondriasis	2.16	0.0139*	1.93	0.1264	1.63	0.2029
It 16	Weight Loss	1.45	0.1413	1.93	0.1263	4.57	0.0341*
It 17	**Insight**	**4.16**	**<0.0001***	**7.58**	**<0.0001***	**12.72**	**0.005***
TOTAL		3.99	<0.0001*	7.65	<0.0001*	1.89	0.1707

To obtain larger sample sizes and facilitate the interpretation of results, the most general category (Western/Non-Western) was analyzed in further detail.

Agitation (Item 9), Anxiety-Psychic (Item 10), Somatic-GI (Item 12), and Insight (Item 17) were scored higher by Non-Western raters. Somewhat paradoxically, Somatic-General (Item 13) was rated lower in Non-Western countries. (Figure 14)

Although Insomnia-Early (Item 4) was statistically significant, only 2 raters (both in the Non-Western group) rated «1»; all other raters across both regions rated «2». Thus, this is likely to represent a data artifact rather than a true cultural difference.

Figure 15. STUDY 1. HAMD-17 ratings: Western Vs NonWestern



DISCUSSION

In this exploratory analysis, the data suggest that raters from different geographic regions and cultures can observe the same patient and provide consistently different ratings on certain HAMD-17 items. Differences in rater expectations, based on culturally-specific disease conceptualization and experience of «typical» patient presentations, may underlie these discrepancies in ratings.

Somatization of symptoms is one of the most described differences in the clinical expression of depression and anxiety between Western and Non-Western cultures, with Non-Western patients expressing greater somatic symptoms and fewer psychic symptoms. Differences in expectations between Western and Non-Western raters regarding somatic disease features may have contributed to differences we observed on more somatic HAMD-17 items (Somatic-General, Somatic-GI and Agitation).

In Non-Western countries, depression is often understood as a social or moral problem. Reluctance to consider psychological/biological/medical causes of depression could underlie differences in ratings among Western and Non-Western raters for the Insight item.

CONCLUSSIONS

There are several noteworthy limitations to the data obtained in this study:

ONE: Most importantly, all data and analysis results are based on ratings of a single videotaped interview. To make more definitive statements about potential cultural differences in rating the HAMD-17, ratings of additional patients expressing a range of symptom severity across the different HAMD-17 items will need to be considered. The current results are hypothesis-generating and will help inform studies of additional data sets to elucidate cultural influences.

TWO: The Group of raters analyzed in this study comes from Clinical Trials. This generates two considerations:

1. They might not be a good representation of the practicing psychiatrists at every country, as individuals participating in global clinical trials are more familiar with westernized concepts and scales more often used in western countries. Ideally, this analysis should be done on raters from the general clinical setting regardless of their involvement in clinical trials.
2. Raters were requested to have certain experience and educational background. This is one more reason why they are not representative of the general pool of psychiatrists in their respective countries.

THREE: A conservative criterion has been applied for removing outliers. Such removal could have ultimately masked some more potential differences.

Understanding and addressing cultural differences in symptom scale ratings is important to assuring data quality, especially as clinical trials are penetrating even more culturally diverse regions. At a minimum, the findings from this exploratory study suggest the types of items on the HAMD-17 and similar rating scales that may require additional focus in pre-trial rater training programs for international studies.

Although the rater training program did achieve consistent ratings across raters as a whole, some underlying culturally-specific trends were still detectable even with the coarse comparison of Western/ Non-Western. Identifying specific cultural factors affecting expression and perception of psychiatric symptoms and addressing them in rater training will become more important as trials include even more culturally diverse regions.

STUDY 2: CULTURAL DIFFERENCES IN THE EXPRESSION OF DEPRESSION SYMPTOMS

AIM OF THIS RESEARCH WORK

Major Depressive Disorder (MDD) currently affects 121 million people worldwide according to WHO. Economic, social and health impact of MDD is large, being the third cause of consultation at primary care level. Most of these consultations represent underdiagnosed MDD which are presented as a variety of different clinical symptoms (asthenia, complaints of somatic nature, etc.). On the other hand, nowadays migration phenomenon is particularly important, therefore cultural differences in psychiatry deserve special attention. Psychiatric classification systems have traditionally considered the transcultural factor (DSM, ICD, etc.). With regard MDD, the characterization of cultural differences on the expression of depression has been of interest since many years ago to. It has typically been considered that non-Western countries tend to offer a more somatic symptom profile, whereas in Western countries depressive symptoms would be more psychological-like. Non-Western societies are less exposed to the prevailing biomedical model in the West, bringing the social stigma about psychiatric illness in countries of non-Western tradition. This would facilitate the emergence of somatic symptoms above the psychological ones. Consequently, the level of insight in patients in these countries could be lower, having then consequences on the therapeutic approach for these patients, especially if they migrate to Western areas. Psychiatrists who exercise their practice in Western countries are exposed to different pattern of depressive symptoms. Western countries are recipients of migration flows from non-Western countries and this is reflected in the demography of patients seen in the healthcare system. It is vital that the mental health professionals adapt their diagnostic and therapeutic exercise to the different

profile shown by patients of non-Western origin. Factors such as the methodology in obtaining information (interview face-to-face or self-completed questionnaire by the patient) could have an impact in the nature of the obtained information. In this context, it is also critical to know how the psychometric scales reflect this cultural variability. The scales allow objectivation of the severity of clinical symptoms. Learning how to interpret a scale considering the transcultural factor is vital in the scenarios described above. In the case of MDD, classic scales for assessing depressive symptoms may be the HAMD, MADRS and BDI. In the sand of transcultural evaluation, it is considered more appropriate to use the HAMD due to higher somatic component, which apparently seems to be more frequent in non-Western origin patients. The MADRS would give less weight to the somatic aspect of depressive symptoms while BDI fully focuses on the cognitive aspect, in line with Beck's cognitive theory.

OBJECTIVES AND HIPOTHESIS

Objectives

- Objective 1: To characterize the influence of cultural differences in the depressive symptomatology assessed with the Hamilton Depression Scale.
- Objective 2: To explore if the face-to-face interview methodology is mediating the subject outcome, depending on the original culture of the subject.
- Objective 3: To detect if the cultural differences in the expression of depression are influenced by the acculturation level of the subject.

HYPOTHESIS

- Hypothesis 1: HAMD Somatic items will weigh more in non-Western patients.
- Hypothesis 2: HAMD interview symptoms pattern will better correlate with self-administered HAMD in patients of Western origin.
- Hypothesis 3: An Integration attitude (according to Berry model) in immigrant patients will lead to a symptoms pattern closer to local patients.

METHODS

Subjects

Patients meeting the following requirements will be recruited:

- Inclusion criteria
    - Presence of depressive type syndrome according to the clinical judgment of the evaluator
    - Presence of at least one of the symptoms of MDE
    - Able to understand the Spanish language in the context of a clinical interview
    - Man or woman; Age> 18 years and <65 years
- Exclusion criteria
    - Psychosis, mania or cognitive impairment

JUSTIFICATION FOR INCLUSION CRITERIA

In most of the consulted studies on cultural differences in depression, the study samples are highly heterogeneous, usually including students, general population, primary care patients, etc. The diagnosis of depression or even the presence of a depressive symptoms was not necessary to participate in the study.

If the object of study is the analysis of the variation of depressive symptoms in terms of cultural background, it would be necessary to ensure that the subjects actually display depressive symptoms. With the presence of depressive symptoms, the analysis will be focused on whether the pattern varies according to the cultural group. If a percentage of the sample does not have depressive disorder, that absence might mistakenly be attributed to their cultural group, leading to wrong conclusions.

On the other hand, imposing a classification system for determining the presence of a major depressive disorder could be in favor of the actually utilized classification system (Kleinman 1998). Some working groups have solved this problem by introducing an inclusion criterion compliance with one of the core symptoms of a depressive episode (Ryder 2008). This is the criterion to be followed in this project.

SAMPLE

JUSTIFICATION OF SAMPLE SIZE

As this exploratory study, there is no pre-determined sample size because there is not a pre-determined expected difference between groups in the targeted dependent variable. For this reason, it is not feasible to calculate a sample size associated with a given power.

Thus, the sample size of this study is based on recruiting capabilities depending on the size of the population attended in this hospital, as well as the orientation obtained from the Director of this PhD program.

The exploratory nature of this research needs to be acknowledged in order to comprehend how the sample has been built. This study sampling is not following a quantitative methodology based on already existing publications which can be used to predict differences that will lead to a powered sample size. Little is written about the systematic use of HAMD in cross-national communities (personal communication with Prof. Janet Williams) therefore it is difficult to anticipate where the differences in HAMD ratings would be found. There is extensive research discussing the MDD peculiarities in non-western population and how it is different from western patients. However, HAMD as assessment tool has seldom been used, despite being the gold

standard rating tool in international MDD clinical trials.

Several authors recognize sampling methodology as a weakness of the exploratory research. Purposeful sampling is often conducted, many times based in pragmatical criteria. Sample sizes tend to be small (Guetterman 2015, Palinkas 2015, Vasileiou 2018). Of note is a study of Mason who conducted a deep review of qualitative sample size in PhD dissertations and found a mean sample size of n=31. He reported that the most typical sample sizes were 10, 20, 30 and 40 (Mason 2010).

This project is not an interventional study but an exploratory research. The aim of the study is to discover potential cultural differences in the expression of depression in patients mostly attending the Transcultural Psychiatry Unit at Hospital Vall d'Hebron. Therefore, the study sample must mimic the country prevalence of patients' pool at the Unit. Only this will enable study outcome to be applicable to the Unit patient population, which is the clinical reality that clinicians are facing in their daily work. If we artificially give more or less representation to some countries, we will not be mirroring the clinical practice, therefore the extrapolation of the study outcome will be jeopardized.

As above described (see section 2.7 Pooling strategies) ICH guidelines also acknowledge that regional pooling could be a source of variability which needs to be mitigated. Care must be taken as too much mitigation (e.g. narrowing study population to small groups) may reduce the external validity of the study results in certain regions. EMA guidelines suggest following strategies to reduce the variability within a pooled group of subjects (EMA 1998, EMA 2017):

1. Disease definition
2. Standardized Protocol
3. Training of investigators

The three mitigation strategies have been applied to STUDY1 and STUDY2, supporting once again the use of regional pooling in this research project.

The idea of the present project is to have a better understanding of if/how the HAMD scale is affected when used in a cross-national population, but conclusive results will probably not be obtained due to the exploratory nature of the study. This research will be a medium to identify issues that can be the focus for future research.

MATERIALS

HAMILTON DEPRESSION SCALE (HAMD) - 17 items version

HAMD will be used to assess depressive symptoms. This scale will be administered in a face-to-face interview format, in Spanish language. HAMD has been selected for this study because of the weight it gives to the somatic symptoms. 17-item version is used because neither psychotic nor seasonal aspects will be explored.

JUSTIFICATION FOR THE USE OF HAMD

There are several psychometric scales to assess depressive symptoms: HAMD, MADRS, BDI, HAD; by listing the most common in clinical practice.

HAMD: It has been criticized because of the overrepresentation of anxiety (items 9 to 11) and the somatic component (items 4 to 6, item 13). However, for a study such as this where the somatic symptoms can be the differentiator between Western and non-Western patients; this scale provides a range of highly informative symptoms, from psychological (guilt, suicide, insight) to the most somatic (insomnia, somatic anxiety, somatic GI).

It must be noted, though, that HAMD is also designed to capture psychologic symptoms. Whereas there are certainly more items covering somatic symptoms, their total scoring equals the weight provided by the psychological symptoms. Therefore, one can affirm that HAMD is covering in equal terms both somatic and psychological symptoms.

Figure 16. STUDY 1. Somatic vs Psychological items in HAMD

Item 4	Insomnia Early	0-2
Item 5	Insomnia Middle	0-2
Item 6	Insomnia Late	0-2
Item 8	Retardation	0-4
Item 9	Agitation	0-4
Item 11	Anxiety Somatic	0-4
Item 12	Somatic GI	0-2
Item 13	Somatic General	0-2
Item 14	Genital Symptoms	0-2
Item 16	Weight loss	0-2
Sub-Total Somatic items		**0-26 (50%)**

Item 1	Depressed Mood	0-4
Item 2	Feelings of Guilt	0-4
Item 3	Suicide	0-4
Item 7	Work and activities	0-4
Item 10	Anxiety Psychic	0-4
Item 15	Hypochondriasis	0-4
Item 17	Insight	0-2
Sub-Total Psychologic items		**0-26 (50%)**

In addition, the HAMD can be extracted sub-scales that will be highly informative for the objectives of this study:

- Melancholy Sub-scale (items 1, 2,7,8,10 and 13)
- Anxiety Sub-scale (items 9,10 and 11)
- Insomnia Sub-scale (items 4.5 and 6)
- Vitality Sub-scale (items 1,7,8 and 14)

For the purpose of this study, 2 novel sub-scales will be used, depending on whether they capture somatic or psychologic symptoms. This classification of items has been tuned with personal communication with Dr. Janet Williams.

- SOMATIC ITEMS: items 4, 5, 6, 8, 9, 11, 12, 13, 14 and 16
- PSYCHOLOGIC: items 1, 2, 3, 7, 10, 15 and 17

MADRS: According to the literature, the advantage of the MADRS scale on the HAMD is its lower contamination of items assessing somatic aspects (Lobo 2002). Precisely for the present project this is a disadvantage, since the MADRS minimizes the weight of the somatic symptoms, which is one of the potential differentiators between the study groups.

BDI: Widely used in clinical practice, it focuses its assessment of depression in cognitive symptoms, which is in line with the Beck cognitive theory of depression (Bech 1988). This approach is ideal for patients of Western origin, where the cognitive profile of depression is supposed to be more often expressed than the somatic profile. However, in the frame of this project, the BDI could minimize somatic aspects of depression, which could be those that make the difference between Western and non-Western patients.

HAD: The Hospital Anxiety and Depression scale has proven to be a useful tool in detecting anxiety and depression in non-psychiatric hospital services disorders. While the scale may be useful for this project by the weight given to symptoms of anxiety (presumably more present in non-Western subjects) is not considered because most subjects in this study come from a psychiatric hospital service whereas this scale has been built to be used in non-psychiatric hospital setting.

HAMILTON DEPRESSION SCALE (HAMD) - SELF- ADMINISTERED VERSION (CDS Carroll Depression Scale).

If the subject can read Spanish, French or English, the self-administered version of the 17-item HAMD will be completed.

JUSTIFICATION FOR THE USE OF CDS - CARROLL DEPRESSION SCALE

There is a wide variety of self-administered scales to assess depression. Examples of the best-known tools are the BDI, IDS-SR, QIDS-SR or Zung (Bobes 2004).

The degree of overlap between the hetero-administered and self-completed scales has been questioned (Domken 1994, Prusoff 1972) so for achieving Objective 2 of this STUDY 2 we should utilize a self-administered scale.

In this sense, the best instrument would be the Carroll Depression Scale (CDS); a scale of 61 items reflecting one by one the 17 items of the HAMD. Thus, one can explore the equivalence not only in the overall severity of depression but also in the symptom pattern.

ACCULTURATION IN CONTEXT MEASURE (ACM) - self-administered

Lastly, each immigrant subject completed the ACM questionnaire to determine to which degree the patient is adapted to the host society. The subjects will be classified according to the two-dimensional model of Berry (Berry & Sam, 1997) where there are four possible categories: Integration, Assimilation, Separation / Segregation and Marginalization.

Thus, the possible variability arising from different degrees of adaptation of the immigrant population enrolled in this study will be monitored.

JUSTIFICATION FOR THE USE OF ACM (Acculturation in Context Measure)

There is no generally agreed scale for measuring acculturation. There are a variety of instruments that differ in their level of scrutiny. For example, ASA (Acculturation Attitude Scale) analyzes acculturation in

5 different domains of the subject's life through 20 items, while the CIS index (Cultural Integration-Separation index) takes only a question on the subject. Studies show that the formats to measure acculturation based in 2 or 4 questions can discriminate between more or less adaptive strategies on the subject (Arends-Tóth & Van de Vijver 2003, Van den Reek 1998).

Because the purpose of this study is the analysis of depressive symptoms and the subject already must go through a clinical interview and a self-administered questionnaire, it was considered that the acculturation measure should not be too long to avoid fatigue in the subject. The ACM consists of two questions posed to the subject for easy classification in the Berry model (Van de Vijver, Phalet, 2004). It has shown good validity (Phalet & Swyngedouw 2003).

For use in this study, it will be translated from the original English following the methodology of Spanish Translation and back translation by experts in psychology who are fluent Spanish and English languages.

PROCESS

Selection of subjects

Collaborating centers:

This project was presented to the health centers listed below. In all cases there is access to immigrant population with depressive pathology. Training was carried out to professionals who would manage the scales of this project, with the aim of standardizing data collection.

A- Psychiatry Service Hospital Vall d'Hebron. Transcultural Psychiatry Unit. Barcelona.

B- Centre d'Atenció Primària Lloret de Mar. Lloret de Mar.

NOTE IN RELATION TO STUDY1

The selection of collaborating centers and their raters is an improvement in regards STUDY1. A point of criticism from the previous study was that raters where somehow specialized in the use of the HAMD because all of them had previous experience in clinical trials. The ratings themselves for STUDY1 were obtained in the context of a clinical trial.

In STUDY2 the raters are clinicians not necessarily experienced in clinical trials whose knowledge on the HAMD and depression symptomatology is purely coming from their education and clinical practice. Therefore, the results obtained by this STUDY2 can be extrapolated to the general community of clinicians.

- Confirmation of Eligibility subject: Before proceeding with assessments, this form will be reviewed for each subject with the purpose of confirming that the subject is compliant with all the inclusion criteria and does not meet any of the exclusion criteria.
- Identity Form Subject: Subjects will be assigned an identifying code that appears on all administered tests. The only link between the code of the subject and its identity will be the identity of the subject form, which will remain on file at the medical facilities.

DATA COLLECTION

- First Evaluation: Hamilton Depression Scale 17 items version in interview format will be the first assessment. The necessary information will be collected to assess the 17 items of the scale. The interview will be conducted in Spanish.
- Second Evaluation: Acculturation in Context Measure (ACM). The subject will be instructed to fill this self-administered scale by himself/herself. Instructions will be standardized so that all subjects receive the same guidelines.
- Third Assessment: Hamilton Depression Scale - 17 items version- self-administered format. The subject will be instructed to fill this self-administered scale by himself/herself. Instructions will be standardized so that all subjects receive the same guidelines. The subject will fill the scale with privacy. Clinician will remain available to solve any potential question from the subject.

Although CDS Manual allows reading outload the items to the subject, this option was not used for this study as it was considered a Non-Standard administration procedure. The intention of the study was to leave the subject on its own to think his/her answers thoroughly without the pressure of the rater waiting for his/her answer in order to read the next item.

The sequence of evaluations will always be as follows:

- First Interview face-to-face using the HAMD
- Second: Acculturation in Context Measure (ACM)
- Third: self-administered HAMD

The two interviews about depression will be separated by the ACM questionnaire. Thus, the ACM will act in a certain way as a distracting task between the two tests of depression for the first responses to a lesser extent affect the responses of the second.

NOTE IN RELATION TO STUDY1

One of the major criticism points in STUDY1 was the fact that clinical assessments were coming from the rating of one unique patient/ interview. In STUDY2 the approach is completely different as several different patients will be assessed. The identification of symptoms patterns will be more reliable as it will be extracted from a group of real patients.

This goes in line with the current tendency towards the use of Real Word Data (RWD) through Real World Evidence (RWE) studies. Whereas RWD might lack the robustness of Randomized Clinical Trials, they allow a more reliable extrapolation to the patients' population as the sample of study are real patients. RWD comes from the routine clinical practice as opposed to data collected within a clinical trial where study design controls variability in ways that are not totally representative of real-world care and outcomes (FDA 2018).

RESULTS

In this section the results of this study will be described, organized by the three exploratory objectives already defined in the study design. Before addressing the three objectives, a description of the study sample will be presented.

Description of study sample

A total of 80 subjects participated in the present study. The study sample consisted of 54 women and 26 men. The mean age was 41.2 and 44.5 years respectively.

Table Age and Gender of study sample

Sex	N	mean	sd	min	max
Female	54	41.2037	10.87212	22	64
Male	26	44.46154	8.682077	30	63
Total	80	42.2625	10.27193	22	64

In regards geographical classification strategy, same criteria as for STUDY 1 was followed: Three levels of geographic origin were defined: Western vs Non-Western; Regional (Amerindian vs Magreb vs Spain) and Country level.

Table 1. STUDY 2. Subjects' geographical origin

Western / Non Western	**WESTERN (n = 52)**			**NON WESTERN (n = 28)**	
Region	Amerindian (n = 23)	Spain (n = 22)	Other (n = 7)	Magreb (n = 21)	Other (n = 7)
Countries	Ecuador (n=6) Bolivia (n = 5) Perú (n = 5) Venezuela (n = 3) Honduras (n = 2) Colombia (n = 2)	-	Argentina (n=1) Bulgaria (n=1) Cuba (n=1) Rep Dominicana (n=3) UK (n=1)	Morocco (n=20) Argelia (n = 1)	Pakistan (n=2) India (n=2) Nigeria (n=1) Filipinas (n=1) Tailandia (n=1)

There were 28 subjects (35%) from Non-Western countries and 52 subjects (65%) from Western regions. They were aged in average 41.3 and 42.8 years respectively.

Table 2. STUDY 2 Age of Western and Non-Western groups

WesternNonW	N	mean	sd	min	max
Non Western	28	41.32143	7.211378	27	55
Western	52	42.76923	11.62589	22	64
Total	80	42.2625	10.27193	22	64

Non-Western group is composed of 12 females (42.9%) and 16 males (57.1%). Western group consist of 42 females (80.8%) and 10 males (19.2%).

Table 3. STUDY 2 Gender of Western and Non-Western groups

	Sex		
Western / NonW	**Female**	**Male**	**Total**
Non Western	12	16	28
Western	42	10	52
Total	54	26	80

In regards Regional groups (Amerindian, Magreb and Spain), subjects composing each group were 23, 21 and 22 individuals, having an average age of 40, 42.2 and 45.3 years respectively.

Table 4. STUDY 2 Age of Amerindian, Magreb and Spain groups

Region	N	mean	sd	min	max
Amerindian	23	40	9.371136	22	56
Magreb	21	42.19048	6.682956	30	55
Spain	22	45.27273	12.34497	27	64
Total	66	42.45455	9.876439	22	64

Amerindian group is composed of 22 females (95.7%) and 1 male (4.3%), Magreb group consists of 9 females (42.9%) and 12 males (57.1%) and Spain group is composed of 14 females (63.6%) and 8 males (36.4%).

Table 5. STUDY 2 Gender of Western and Non-Western groups

	Sex		
Region	**Female**	**Male**	**Total**
Ameridian	22	1	23
Magreb	9	12	21
Spain	14	8	22
Total	45	21	

No age/gender data is shown for Country level groups provided the small size of the groups.

As previously described 2 centers did participate in this study. Center 1 did have prominence in the recruitment of subjects as this was the physical location of this doctoral candidate and her Director.

Table 6. STUDY 2 Recruitment by Center

Center	Freq.	Percent
1	70	87.50
2	10	12.50
Total	80	100.00

Between both centers, a total of 12 raters did participate in the subject assessment activity. It must be noted that 2 of them did conduct most of the assessments. In consequence, the 2 main raters have been analyzed separately and the rest are grouped under «Other».

Table 7. STUDY 2 Recruitment by Rater (Individuals)

RATER	Freq.	Percent
1	4	5.00
2	19	23.75
3	3	3.75
4	1	1.25
5	1	1.25
6	1	1.25
7	40	50.00
8	6	7.50
9	1	1.25
10	2	2.50
11	1	1.25
12	1	1.25
Total	80	100.00

Table 8. STUDY 2 Recruitment by Rater (main raters and Other)

rater1	N
Rater 2	19
Rater 7	40
Other	21
Total	80

For all subjects (n=80), in all Centers (2) and by all Raters (12), HAMD assessment was conducted.

What follows is an analysis on HAMD outcomes depending on **Geographic origin, Center** and **Rater.** The aim of this study is to recruit patients with a certain degree of depression, independently of the just mentioned three factors. If degree of depression were different at any of these factors, such factor would be interfering in the final analysis of this work.

Western subjects scored a Total HAMD of 19.7 and Non-Western subjects scored a Total HAMD of 21.1. This is showing a moderate

severity level which is remarkably similar amongst both groups. No statistically significant difference is observed between both groups (p=0.2849).

Table 9. STUDY 2 Total HAMD scores for Western and Non-Western subjects

WesternNonW	N	mean	sd	min	max
Non Western	28	21.14286	6.484822	9	36
Western	52	19.73077	5.060866	8	32
Total	80	20.225	5.600576	8	36

Two-sample t test with equal variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
Non West	28	21.14286	1.225516	6.484822	18.62831	23.65741
Western	52	19.73077	.7018159	5.060866	18.32182	21.13972
combined	80	20.225	.6261635	5.600576	18.97865	21.47135
diff		1.412088	1.311474		-1.198855	4.023031

diff = mean(Non West) - mean(Western) t = 1.0767
Ho: diff = 0 degrees of freedom = 78

Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = 0.8575 Pr(|T| > |t|) = 0.2849 Pr(T > t) = 0.1425

Similarly, HAMD Total scorings were very similar amongst Amerindian, Magreb and Spain groups. Values were 20.0, 21.4 and 19.5 respectively and there were no statistically significant differences amongst them (p=0.4645).

Table 10. STUDY 2 Total HAMD scores for Amerindian, Magreb and Spain subjects

Region	N	mean	sd	min	max
Amerindian	23	19.95652	4.949548	8	28
Magreb	21	21.42857	5.599745	14	36
Spain	22	19.54545	5.05896	11	32
Total	66	20.28788	5.182115	8	36

Number of obs = 66 R-squared = 0.0240
Root MSE = 5.20005 Adj R-squared = -0.0069

Source	Partial SS	df	MS	F	Prob>F
Model	41.976379	2	20.988189	0.78	0.4645
Region1	41.976379	2	20.988189	0.78	0.4645
Residual	1703.5539	63	27.040538		
Total	1745.5303	65	26.854312		

Total HAMD scores assessed at Center 1 resulted in 20.6 whereas the scoring at Center 2 was 17.6. Again, moderate depression level is shown at both centers and the values are very similar, without statistically significant differences (p=0.1136).

Table 11. STUDY 2 Total HAMD scores for subjects recruited at Center 1 and Center 2

Two-sample t test with equal variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
1	70	20.6	.6243506	5.223692	19.35445	21.84555
2	10	17.6	2.395366	7.574812	12.18131	23.01869
combined	80	20.225	.6261635	5.600576	18.97865	21.47135
diff		3	1.874916		-.7326717	6.732672

diff = mean(1) - mean(2) t = 1.6001
Ho: diff = 0 degrees of freedom = 78

Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = 0.9432 Pr(|T| > |t|) = 0.1136 Pr(T > t) = 0.0568

As previously described, two raters conducted most of the assessment and several others did the rest. These others were grouped so comparisons could be made. As shown in the below Table, Total HAMD ratings were remarkably similar amongst them (19,1; 21,4 and 19,0). Once again, the severity levels were within the moderate ranges and very similar amongst themselves, without having statistically significant differences (p=0.1594).

Table 12. STUDY 2 Total HAMD scores by participating Raters

rater1	N	mean	sd
Rater 2	19	19.10526	3.828181
Rater 7	40	21.425	5.564943
Other	21	18.95238	6.6744
Total	80	20.225	5.600576

Number of obs = 80 R-squared = 0.0466
Root MSE = 5.53914 Adj R-squared = 0.0218

Source	Partial SS	df	MS	F	Prob>F
Model	115.43315	2	57.716573	1.88	0.1594
rater1	115.43315	2	57.716573	1.88	0.1594
Residual	2362.5169	77	30.682037		
Total	2477.95	79	31.366456		

Thu, one can assume that severity levels amongst **Geographical groups, Centers** and **Raters** were similar. Geographic group, center and rater did not influence the level of depression severity in the study subjects.

This is the starting point needed for this study. With a similar depression level, we will drill down to the sub-scales and even item-by-item in order to explore whether the nature of the depressive

symptoms follows different patterns in the different geographic groups.

What follows are the results belonging to the 3 objectives pursued by this study.

- **Objective 1:** To characterize the influence of cultural differences in the depressive symptomatology assessed with the Hamilton Depression Scale.
- **Hypothesis 1:** HAMD Somatic items will weigh more in non-Western patients.

As previously described, HAMD has several sub-scales established. Additionally, we have generated two new sub-scales gathering the somatic items and the psychologic items. The following is an analysis of all these sub-scales:

- HAMD6 (items 1, 2, 7, 8, 10 and 13)
- Anxiety Sub-scale (items 9,10 and 11)
- Insomnia Sub-scale (items 4, 5 and 6)
- Vitality Sub-scale (items 1,7,8 and 14)
- SOMATIC ITEMS (items 4, 5, 6, 8, 9, 11, 12, 13, 14 and 16)
- PSYCHOLOGIC ITEMS (items 1, 2, 3, 7, 10, 15 and 17)

Two levels of analysis will be used: Western vs Non-Wester and Regional level (Amerindian, Magreb, Spain groups). No lower level (i.e., countries) will be used because sample sizes are small and interpretation would be difficult (i.e. only applicable to that particular country).

HAMD 6

The HAMD 6 sub-scale did have similar scorings for Western and Non-Western groups (9.90 and 9.43 respectively). This minor difference between both groups was statistically non-significant ($p = 0.4630$).

Table 13. STUDY 2 HAMD6 values in Western and Non-Western groups

Two-sample t test with equal variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
Non West	28	9.428571	.6223963	3.293412	8.15152	10.70562
Western	52	9.903846	.3343795	2.411245	9.232551	10.57514
combined	80	9.7375	.3064413	2.740894	9.127544	10.34746
diff		-.4752747	.6443374		-1.758052	.8075026

diff = mean(Non West) - mean(Western) t = -0.7376
Ho: diff = 0 degrees of freedom = 78

Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = 0.2315 Pr(|T| > |t|) = 0.4630 Pr(T > t) = 0.7685

When Regional groups were compared (Ameridian, Magreb and Spain) there were no significant differences (p=0.9050) between HAMD6 scorings (9.83, 9.52 and 9.8 respectively).

Table 14. STUDY 2 HAMD6 values in Amerindian, Magreb and Spain groups

Region	Mean	SD	n
Amerindian	9,83	2,6	23
Magreb	9,52	2,7	21
Spain	9,8	2,2	22

Number of obs = 66 R-squared = 0.0032
Root MSE = 2.52547 Adj R-squared = -0.0285

Source	Partial SS	df	MS	F	Prob>F
Model	1.2757388	2	.63786938	0.10	0.9050
Region1	1.2757388	2	.63786938	0.10	0.9050
Residual	401.81517	63	6.3780186		
Total	403.09091	65	6.2013986		

HAMD Anxiety Sub-Scale

The HAMD Anxiety sub-scale did have similar scorings for Western and Non-Western groups (4.30 and 4.18 respectively). The minor difference between both groups was statistically non-significant (p = 0.7363).

Table 15. STUDY 2 HAMD Anxiety sub-scale values in Western and Non-Western groups

Two-sample t test with equal variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
Non West	28	4.178571	.3452381	1.826828	3.470201	4.886941
Western	52	4.307692	.210111	1.515132	3.885877	4.729508
combined	80	4.2625	.1811913	1.620625	3.901848	4.623152
diff		-.1291209	.382028		-.8896802	.6314384

diff = mean(Non West) - mean(Western) t = -0.3380
Ho: diff = 0 degrees of freedom = 78

Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = 0.3681 Pr(|T| > |t|) = 0.7363 Pr(T > t) = 0.6319

When Regional groups were compared (Ameridian, Magreb and Spain) there were no significant differences (p=0.9852) between Anxiety Sub-scale scorings (4.3, 4.4 and 4.4 respectively).

Table 16. STUDY 2 HAMD Anxiety sub-scale values in Amerindian, Magreb and Spain groups

Region	Mean	SD	n
Amerindian	4,3	1,6	23
Magreb	4,4	1,9	21
Spain	4,4	1,3	22

Number of obs = 66 R-squared = 0.0005
Root MSE = 1.63143 Adj R-squared = -0.0313

Source	Partial SS	df	MS	F	Prob>F
Model	.07914549	2	.03957275	0.01	0.9852
Region1	.07914549	2	.03957275	0.01	0.9852
Residual	167.67843	63	2.6615624		
Total	167.75758	65	2.5808858		

HAMD Sleep Sub-Scale

The HAMD Sleep sub-scale did have similar scorings for Western and Non-Western groups (3.59 and 3.57 respectively). The minor difference between both groups was statistically non-significant (p = 0.9478).

Table 17. STUDY 2 HAMD Sleep sub-scale values in Western and Non-Western groups

Two-sample t test with equal variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
Non West	28	3.571429	.3466719	1.834415	2.860117	4.282741
Western	52	3.596154	.2041419	1.472088	3.186322	4.005986
combined	80	3.5875	.178508	1.596624	3.232189	3.942811
diff		-.0247253	.3766355		-.774549	.7250984

diff = mean(Non West) - mean(Western) t = -0.0656
Ho: diff = 0 degrees of freedom = 78

Ha: diff < 0 Pr(T < t) = 0.4739
Ha: diff != 0 Pr(|T| > |t|) = 0.9478
Ha: diff > 0 Pr(T > t) = 0.5261

When Regional groups were compared (Ameridian, Magreb and Spain) there were no significant differences (p=0.7545) between Sleep Sub-scale scorings (3.5, 3.8 and 3.8 respectively).

Table 18. STUDY 2 HAMD Sleep sub-scale values in Amerindian, Magreb and Spain groups

Region	Mean	SD	n
Amerindian	3,5	1,5	23
Magreb	3,8	1,8	21
Spain	3,8	1,5	22

```
      Number of obs =        66    R-squared     =  0.0089
      Root MSE      =   1.62725    Adj R-squared = -0.0226
```

Source	Partial SS	df	MS	F	Prob>F
Model	1.4968003	2	.74840015	0.28	0.7547
Region1	1.4968003	2	.74840015	0.28	0.7547
Residual	166.82138	63	2.6479584		
Total	168.31818	65	2.5895105		

HAMD Vitality Sub-Scale

The HAMD Vitality sub-scale did have similar scorings for Western and Non-Western groups (6.5 and 6.64 respectively). The minor difference between both groups was statistically non-significant (p = 0.7676).

Table 19. STUDY 2 HAMD Vitality sub-scale values in Western and Non-Western groups

Two-sample t test with equal variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
Non West	28	6.642857	.4548803	2.407	5.70952	7.576194
Western	52	6.5	.2554091	1.841781	5.987245	7.012755
combined	80	6.55	.2284372	2.043204	6.095307	7.004693
diff		.1428571	.4817233		-.8161802	1.101895

diff = mean(Non West) - mean(Western) t = 0.2966
Ho: diff = 0 degrees of freedom = 78

Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = 0.6162 Pr(|T| > |t|) = 0.7676 Pr(T > t) = 0.3838

When Regional groups were compared (Ameridian, Magreb and Spain) there were no significant differences (p=0.8438) between Vitality Sub-scale scorings (6.4, 6.7 and 6.4 respectively).

Table 20. STUDY 2 HAMD Vitality sub-scale values in Amerindian, Magreb and Spain groups

Region	Mean	SD	n
Amerindian	6,4	2,2	23
Magreb	6,7	1,8	21
Spain	6,4	1,6	22

Number of obs = 66 R-squared = 0.0054
Root MSE = 1.89927 Adj R-squared = -0.0262

Source	Partial SS	df	MS	F	Prob>F
Model	1.2287785	2	.61438923	0.17	0.8438
Region1	1.2287785	2	.61438923	0.17	0.8438
Residual	227.25607	63	3.6072392		
Total	228.48485	65	3.5151515		

Psychologic vs Somatic items

As described in previous section, a novel classification of HAMD items was done depending on whether they assessed psychologic or somatic symptoms. Support was given by Prof. Janet Williams via personal communication with this doctoral student.

Psychologic items did not show statistically significant differences (p=0.8116) between Western and Non-Western groups (10.87 and 10.68 points respectively).

Table 21. STUDY 2 HAMD Psychologic item values in Western and Non-Western groups

Two-sample t test with equal variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
Non West	28	10.67857	.7647207	4.046522	9.109494	12.24765
Western	52	10.86538	.3998763	2.883549	10.0626	11.66817
combined	80	10.8	.3703402	3.312424	10.06286	11.53714
diff		-.1868132	.7811191		-1.741902	1.368276

diff = mean(Non West) - mean(Western) t = -0.2392
Ho: diff = 0 degrees of freedom = 78

Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = 0.4058 Pr(|T| > |t|) = 0.8116 Pr(T > t) = 0.5942

When comparing at regional level (Amerindian, Magreb and Spain) no statistically significant differences were shown (10.22, 10.62 and 11.27 points respectively; p = 0.5218).

Table 22. STUDY 2 HAMD Psychologic item values in Amerindian, Magreb and Spain groups

Summary for variables: item
by categories of: Region (Region)

Region	N	mean	sd
Amerindian	23	10.21739	2.696067
Magreb	21	10.61905	3.59828
Spain	22	11.27273	3.010803
Total	66	10.69697	3.093267

Number of obs = 66 R-squared = 0.0204
Root MSE = 3.10971 Adj R-squared = -0.0107

Source	Partial SS	df	MS	F	Prob>F
Model	12.710333	2	6.3551666	0.66	0.5218
Region1	12.710333	2	6.3551666	0.66	0.5218
Residual	609.22906	63	9.6703026		
Total	621.93939	65	9.5682984		

When analyzing the Somatic items of HAMD scale Western subjects showed a scoring of 8.83 whereas Non-Western subjects had a scoring of 10.46 points. Such difference was statistically significant (p=0.0380).

Table 23. STUDY 2 HAMD Somatic item values in Western and Non-Western groups

Two-sample t test with equal variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
Non West	28	10.46429	.5986805	3.16792	9.235895	11.69268
Western	52	8.826923	.4690425	3.382314	7.885281	9.768565
combined	80	9.4	.3780362	3.381259	8.647538	10.15246
diff		1.637363	.7757992		.0928652	3.18186

diff = mean(Non West) - mean(Western) t = 2.1105
Ho: diff = 0 degrees of freedom = 78

Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = 0.9810 Pr(|T| > |t|) = 0.0380 Pr(T > t) = 0.0190

Such statistically significant differences persisted when analysis was done at Regional level. Amerindian, Magreb and Spain groups had ratings of 9.74, 10.80 and 8.18 respectively (p = 0.0281).

Table 24. STUDY 2 HAMD Somatic item values in Amerindian, Magreb and Spain groups

Summary for variables: item
by categories of: Region (Region)

Region	N	mean	sd	min	max
Amerindian	23	9.73913	3.519005	3	16
Magreb	21	10.80952	2.768015	7	16
Spain	22	8.181818	3.095871	3	14
Total	66	9.560606	3.286938	3	16

Number of obs = 66 R-squared = 0.1072
Root MSE = 3.1546 Adj R-squared = 0.0789

Source	Partial SS	df	MS	F	Prob>F
Model	75.311971	2	37.655985	3.78	0.0281
Region1	75.311971	2	37.655985	3.78	0.0281
Residual	626.94561	63	9.9515175		
Total	702.25758	65	10.803963		

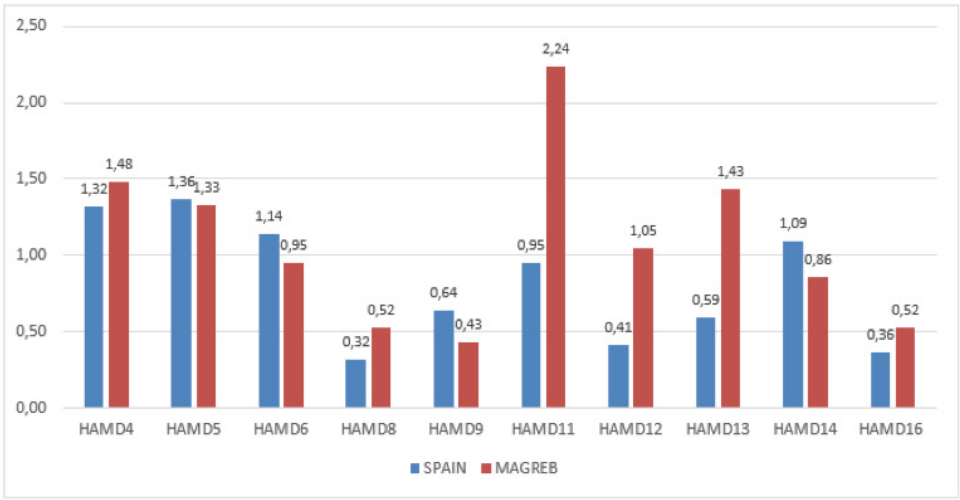
Provided the statistically significant differences between the Regional groups, successive pair comparisons were done in order to elucidate whether there was a pair showing more differences than other. Bonferroni correction was applied provided the conducted multiple comparisons within the sample. Despite the conservative effect of this correction, still one pair showed statistically significant differences, that being Magreb vs Spain pair. Thus, the Regional statistically significant differences were caused by differences between Spain and Magreb.

Table 25. STUDY 2 HAMD Somatic item values in Amerindian, Magreb and Spain groups- Pair analysis

	Contrast	Std. Err.	Bonferroni [95% Conf.	Interval]
Region1				
Amerindian vs Spain	1.557312	.9407531	-.7565491	3.871174
Magreb vs Spain	2.627706	.9624051	.2605895	4.994822
Magreb vs Amerindian	1.070393	.9521326	-1.271457	3.412244

If we examine item by item the Spain / Magreb pair, we can identify certain items which have more weight in the making of these statistically significant differences. While all these items have a somatic component, one may state that item 11 (Anxiety Somatic), item 12 (Somatic GI) and item 13 (Somatic General) are more prone to score much higher in Magreb subjects than in Spanish subjects.

Figure 17. STUDY 2. HAMD17-Somatic Items. Spain vs Magreb



Provided this is an exploratory study there have not been pre-specified expected differences neither the sample was powered to the standard 80%. However as significant differences have been found for the HAMD Somatic sub-scale, the sample power has been

calculated backwards, resulting in a sample power of 61% (Chow 2018, Julious 2010, Machin 1997, Zar 1984). It must be noted that with such low power, this sample has been able to find statistically significant differences between Western and Non-Western subjects for the Somatic Sub-Scale. This will be elaborated in the Discussion section.

Figure 18. STUDY 2. Power calculation for Somatic Sub-Scale in Western and Non-Western groups

Numeric Results for an Equal-Variance T-Test

δ = μ1 - μ2
Hypotheses: H0: δ = 0 vs. H1: δ ≠ 0

Power	N1	N2	N	μ1	μ2	δ	σ	Alpha
0,60968	28	52	80	10,5	8,8	1,7	3,2	0,05

Report Definitions
Power is the probability of rejecting a false null hypothesis.
N1 and N2 are the number of items sampled from each population.
N = N1 + N2 is the total sample size.
μ1 and μ2 are the assumed population means.
δ = μ1 - μ2 is the difference between population means at which power and sample size calculations are made.
σ is the assumed population standard deviation for each of the two groups.
Alpha is the probability of rejecting a true null hypothesis.

Summary Statements

Group sample sizes of 28 and 52 achieve 60,968% power to reject the null hypothesis of equal means when the population mean difference is μ1 - μ2 = 10,5 - 8,8 = 1,7 with a standard deviation for both groups of 3,2 and with a significance level (alpha) of 0,05 using a two-sided two-sample equal-variance t-test.

ITEM-BY-ITEM ANALYSIS

To finish this section an item-by-item analysis will be conducted in an exploratory manner. Three geographical levels will be used: Western vs Non-Western, Regional (Amerindian, Magreb and Spain) and Country level. As previously described the analysis at country level will be of poor value, however it has been included in order to mimic the analysis conducted in STUDY 1.

A series of ANOVA were conducted on each HAMD-17 item as well as the total score. In each analysis, HAMD-17 scores were the

dependent variables and Country, Region or Western/Non-Western were the independent «geographic» variables. Statistical significance was set at the 5% level. No adjustments for multiple comparisons were made, as this was considered to be an exploratory analysis (Jamovi 2021, Core Team 2020, Fox J 2020).

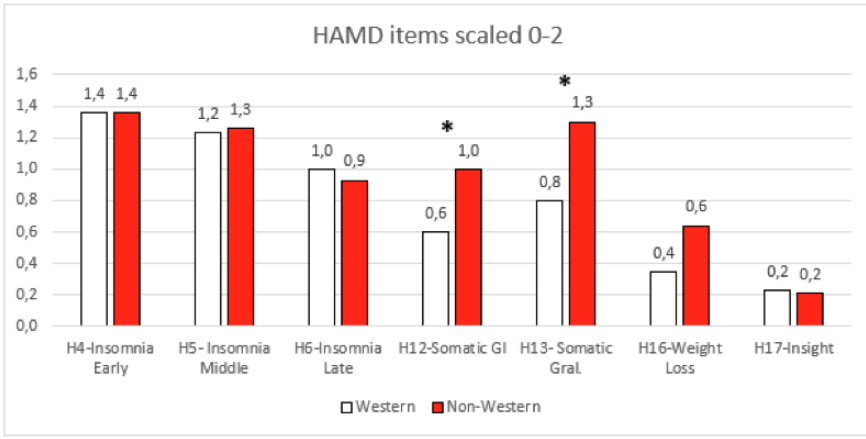
Table 26. STUDY 2 ANOVA analysis at different region levels

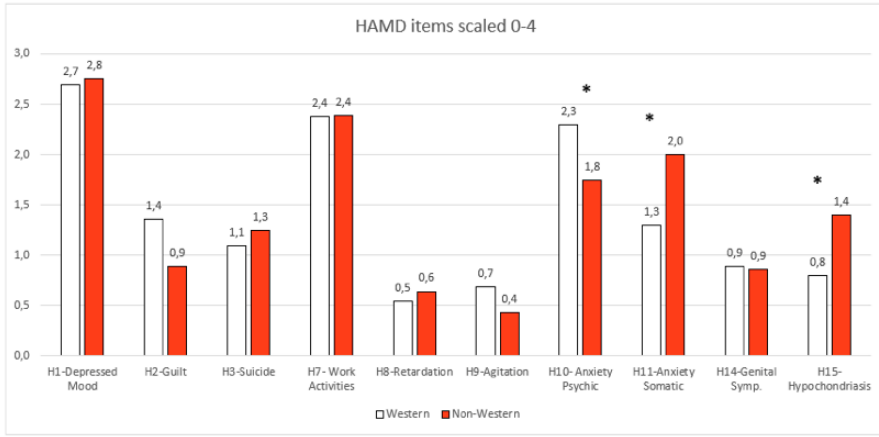
	COUNTRY		REGION		WESTERN / NON-WESTERN	
	F	p Value	F	p Value	F	p Value
H1	1,15	0,33	0,57	0,568	0,0839	0,773
H2	0,868	0,617	2,07	0,135	4,75	0,032*
H3	0,979	0,495	2,77	0,07*	0,276	0,601
H4	0,818	0,672	0,31	0,735	0,00264	0,959
H5	1	0,472	0,64	0,531	0,148	0,701
H6	1,12	0,358	0,622	0,54	0,145	0,704
H7	0,771	0,725	0,28	0,757	9,01	0,976
H8	1,45	0,143	1,37	0,261	0,313	0,577
H9	0,773	0,722	1,03	0,362	1,98	0,164
H10	1,75	0,049*	7,89	<0,001*	5,36	0,023*
H11	2,07	0,018*	9,66	<0,001*	9,31	0,003*
H12	1,25	0,075	4,81	0,011*	5,21	0,025*
H13	1,68	0,069	9,07	<0,001*	9,19	0,003*
H14	1,33	0,202	0,668	0,516	0,0196	0,889
H15	1,64	0,078	4,05	0,022*	6,09	0,016*
H16	1,1	0,373	0,435	0,649	3,27	0,074
H17	1,92	0,031*	2,89	0,063	0,0277	0,868
TOTAL	1,42	0,154	0,776	0,465	1,16	0,285

The individual ANOVA analyses revealed significant main effects for region (Country, Region or Wester-Non Western) for the same 2 items: Anxiety Psychic (item 10) and Anxiety Somatic (item 11). Interestingly, following items had significant effect at the 2 highest levels of geographical classification: Somatic GI (item 12), Somatic general (item 13) and Hypochondriasis (item 15).

To facilitate the interpretation of results, the most general category (Western/Non-Western) was analyzed in further detail.

Figure 19. STUDY 2. HAMD-17 Ratings: Western vs Non-Western



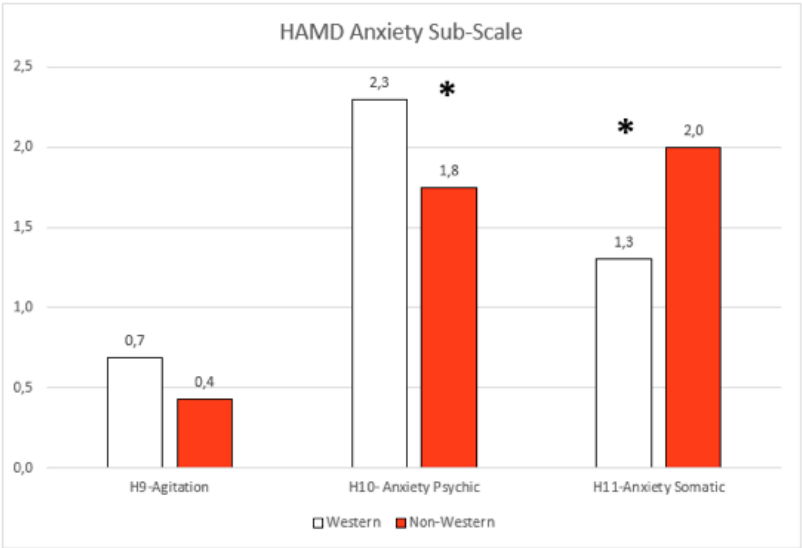


Following items are targeted as being influenced by the geographic origin of the subject: Anxiety Psychic (item 10), Anxiety Somatic (item 11), Somatic GI (item 12), Somatic general (item 13) and Hypochondriasis (item 15).

- Following items are scored higher in Non-Western subjects: Anxiety Somatic (item 11), Somatic GI (item 12), Somatic general (item 13) and Hypochondriasis (item 15).
- Following items are scored higher in Western subjects: Anxiety Psychic (item 10).

Interestingly, both Anxiety items are showing statistically significant differences, being the Psychic component higher in Western subjects and Somatic component higher in Non-Western subjects. If we look again in detail to the Anxiety Sub-Scale (which showed no significant differences as a sub-scale) we can see that such lack of difference is because Somatic and Psychologic components are compensating each other. As a result, the Sub-Scale will not vary, however the nature of the symptoms prevailing in each group are significantly different.

Figure 20. STUDY 2. Anxiety Sub-Scale: Western vs Non-Western



- **Objective 2:** To explore if the face-to-face interview methodology is mediating the subject outcome, depending on the original culture of the subject.
- **Hypothesis 2:** HAMD interview symptoms pattern will better correlate with self administered HAMD in patients of Western origin.

CDS RESPONSE RATE

From the total of 80 subjects participating in this study, 56 of them had the capacity to complete the CDS. From Western subjects, 75% completed CDS and from Non-Western subjects 60,7% completed the CDS.

When following the Regional classification of Amerindian, Magreb and Spain groups, the sample of CDS respondents is slightly reduced to 47 subjects. CDS was completed by 69,6% of Amerindian subjects, 57.1% of Magreb subjects and 86.4% of subjects from Spain.

Table 27. STUDY 2 Percentage of CDS respondents per geographic origin of the subject

	CDS respondents	% CDS respondents
Western	39	75,0%
Non-Western	17	60,7%
Amerindian	16	69,6%
Magreb	12	57,1%
Spain	19	86,4%

Following distribution in terms of age and gender was shown amongst CDS respondents:

Table 28. STUDY 2 Age and gender of CDS respondents per geographic origin of the subject

	Age average	Age SD	Male	Female
Western	43,5	10,9	10 (25,6%)	29 (74,4%)
Non-Western	40,7	7,2	8 (47,1%)	9 (52,9%)
Amerindian	40,7	8,5	1 (6,7%)	15 (93,8%)
Magreb	42,6	6,4	6 (50%)	6 (50%)
Spain	44,5	11,3	8 (42,1%)	11 (57,9%)

DEPRESSION SEVERITY

When comparing Western and Non-Western groups, they were shown to have the same depression severity level. Western had a CDS Total score of 28.18 and Non-Western had a CDS Total score of 28.24. All observations ranged from 15 to 35 points.

Table 29. Depression Severity Level in Western and Non-Western groups measured with CDS

Summary for variables: CDSSTOTAL
by categories of: WesternNonW (Western / NonW)

WesternNonW	N	mean	sd	min	max
Non Western	17	28.23529	3.683229	22	35
Western	39	28.17949	3.560542	15	35
Total	56	28.19643	3.564571	15	35

Comparison was done as well between Amerindian, Magreb and Spain groups. Still the same level of depression severity was identified in the three groups. Amerindian had a CDS Total of 29.19, Magreb had a CDS Total of 28.42 and Spain had a CDS Total of 27.63.

Table 29. STUDY 2 Depression Severity Level in Amerindian, Magreb and Spain groups measured with CDS

Summary for variables: CDSSTOTAL
by categories of: Region (Region)

Region	N	mean	sd	min	max
Amerindian	16	29.1875	1.600781	26	31
Magreb	12	28.41667	3.679386	23	35
Spain	19	27.63158	4.139384	15	35
Total	47	28.3617	3.351998	15	35

CORRELATION BETWEEN HAMD AND CDS

When correlating CDS Totals with the HAMD Totals for the 56 CDS respondents it was found a positive, moderate, and significant Concordance Correlation Coefficient (r = +0.450; p = 0.01).

Figure 21. STUDY 2. Concordance between CDS and HAMD

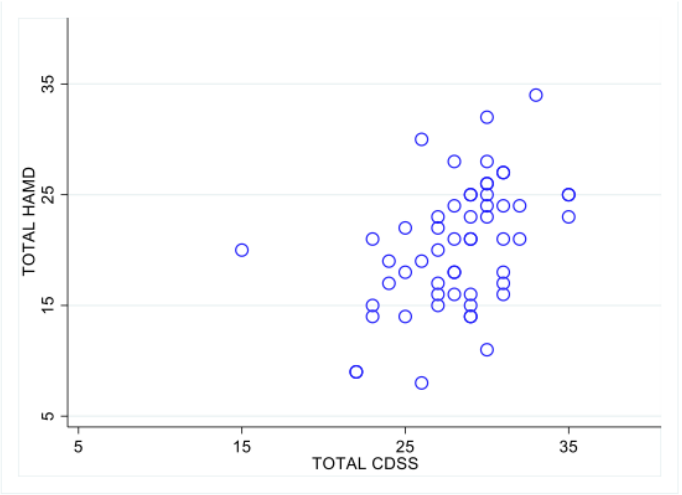


Table 30. STUDY 2 Concordance correlation between CDS Total and HAMD Total scores

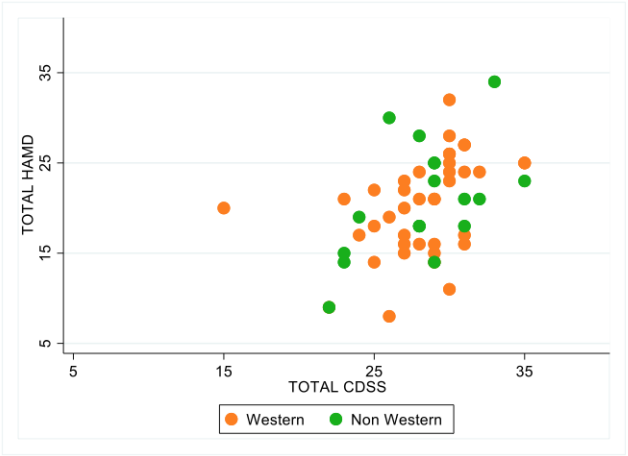
Concordance correlation coefficient (Lin, 1989, 2000):

rho_c	SE(rho_c)	Obs	[95% CI]		P	CI type
0.171	0.052	56	0.068	0.274	0.001	asymptotic
			0.067	0.272	0.001	z-transform

Pearson's r = 0.450 Pr(r = 0) = 0.001 C_b = rho_c/r = 0.380
Reduced major axis: Slope = 1.588 Intercept = -24.340

CDS and HAMD correlations were analyzed for both Western and Non-Western groups. Non-Western subjects had a correlation of r = +0.53 and Western patients had a correlation of r = +0.41. Both values had statistically significance.

Figure 22. STUDY 2. Correlations between CDS and HAMD Total Scores for Western and Non-Western groups



Non Western

Variable	Obs	Mean	Std. Err.	— Binomial Exact — [95% Conf.	Interval]
	17	.5294118	.1210578	.2781183	.7701673

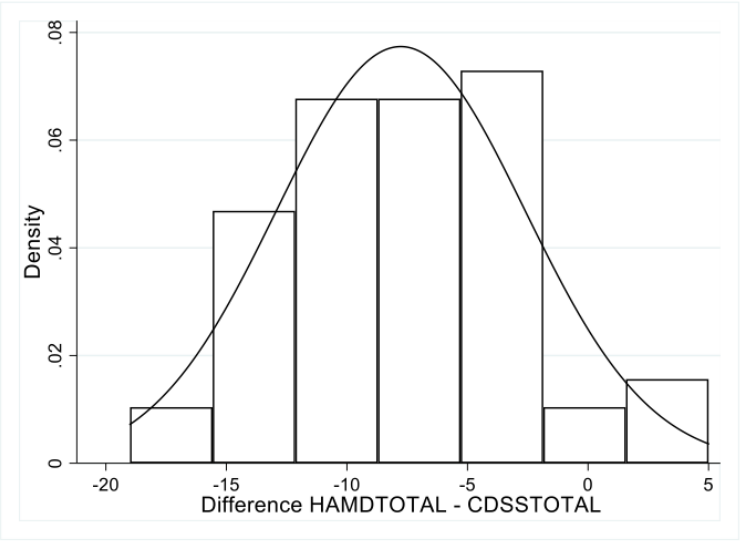
Western

Variable	Obs	Mean	Std. Err.	— Binomial Exact — [95% Conf.	Interval]
	39	.4102564	.0787639	.2556678	.5790013

CDS OVERSCORING

A tendency towards over-scoring CDS over HAMD was clearly observed. Differences between CDS and HAMD showed a normal distribution having the «zero» in the right extreme of the curve.

Figure 23. STUDY 2 Normal distribution of differences between HAMD total and CDS total scores

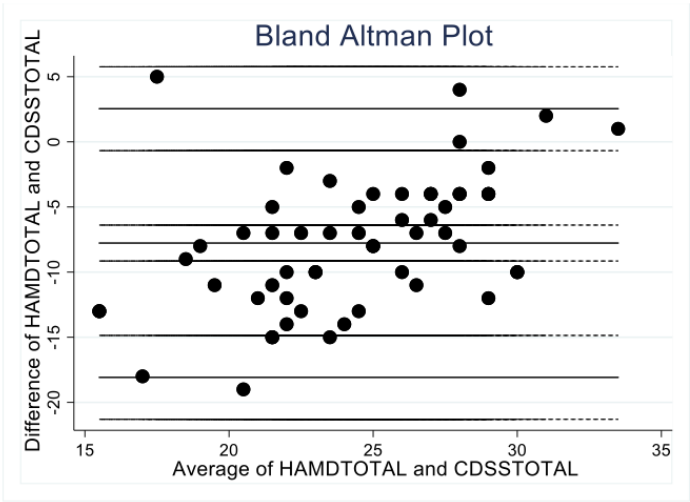


Shapiro-Wilk W test for normal data

Variable	Obs	W	V	z	Prob>z
Diff	56	0.99045	0.491	-1.527	0.93657

With Bland-Altman plot it can be evidenced how the CDS scoring consistently gives too high a result in comparison with HAMD; having most of the points below the zero line. This suggests that there is a systematic bias towards an over-rating of CDS against HAMD (Kalra 2017).

Figure 23. STUDY 2 Bland-Altman plot between CDS and HAMD Totals




```
Bland Altman Plot of HAMDTOTAL and CDSSTOTAL
- mean of difference between HAMDTOTAL and CDSSTOTAL is -7.7678571
- sd of difference between HAMDTOTAL and CDSSTOTAL is 5.1557243
- Limits of agreement (Reference Range for difference): -18.079306 to 2.5435915
- Mean difference:-7.7678571 (CI -9.1457825 to -6.3899317)
- Lower CI loa lower: -21.299673
- Upper CI loa lower: -14.858937
- Lower CI loa higher: -.67677647
- Upper CI loa higher: 5.7639594
```

To better understand the extent of the CDS overscoring, below is displayed a comparison between CDS and HAMD Total ratings. The magnitude of the difference of CDS over HAMD can be observed. CDS Total is scored as 28.20 whereas HAMD Total is scored as 20.23 amongst the whole sample (n=80), and 20.43 amongst the sample for CDS respondents only. Similar differences can be observed in the different geographical groups used during the present study.

Table 31. STUDY 2 Values of HAMD and CDS Total scores in the whole study sample (n=80)

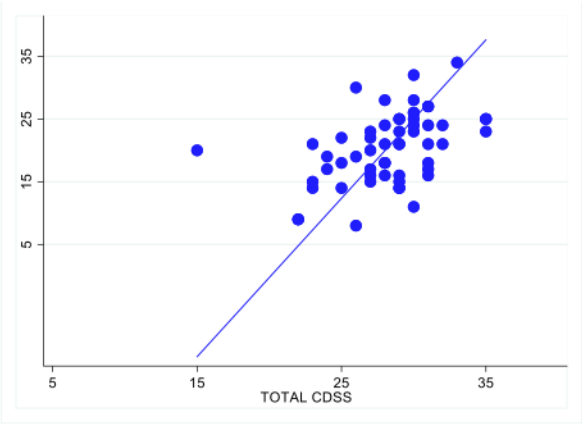
	HAMD *(n=80)*	CDS *(n=56)*	Difference CDS-HAMD
All groups	20,23	28,20	7,97
Western	19,73	28,18	8,45
Non-Western	21,14	28,24	7,10
Amerindian	19,96	29,19	9,23
Magreb	21,43	28,42	6,99
Spain	19,55	27,63	8,08

Table 32. STUDY 2 Values of HAMD and CDS Total scores in the sample of CDS respondents (n = 56)

	HAMD *(n=56)*	CDS *(n=56)*	Difference CDS-HAMD
All groups	20,43	28,20	7,77
Western	20,23	28,18	7,95
Non-Western	20,88	28,24	7,36
Amerindian	20,69	29,19	8,50
Magreb	20,42	28,42	8,00
Spain	20,05	27,63	7,58

Yet another technique to show a constant error is the Deeming Regression (NCSS) which is different from a linear regression where only one responsible variable is measured with error. With the Deeming Regression both variables are measured with error and is often used for looking for systematic differences between two measurement methods. Once again it is evidenced a clear trend towards over-rating CDS in a systematic manner.

Figure 24. STUDY 2 Deeming Regression CDS and HAMD Total scores



Deming regression — Number of obs = 56

	Mean	Std. Dev.		
HAMDTOTAL	20.429	5.6596	Variance ratio	= 1
CDSSTOTAL	28.196	3.5646	Root MSE	= 3.046221

	Coef.	Jackknife Std. Err.	t	P>|t|	[95% Conf.	Interval]
CDSSTOTAL	2.524854	.6688358	3.77	0.000	1.184477	3.86523
_cons	-50.76329	19.19541	-2.64	0.011	-89.23175	-12.29482

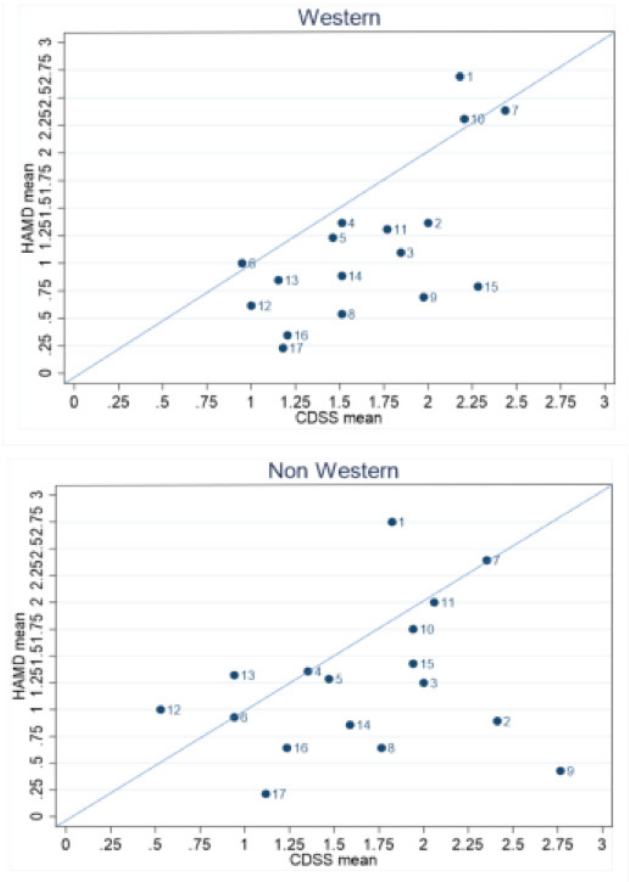
Note: One or more parameters could not be estimated in 24 jackknife replicates; standard-error estimates include only complete replications.

INDIVIDUAL ITEM ANALYSIS

Further analysis was conducted to elucidate if there were differences in individual item ratings depending on the geographic origin of the subjects.

In order to explore trends at item level the below plots are shown for both Western and Non-Western respondents.

Figure 25. STUDY 2 Individual Items score plots for Western and Non-Western groups



As a general trend the majority of the cases are located on the right side of the axis, indicating that CDS scorings are higher than HAMD ratings. This trend is shown in both Western and Non-Western groups showing that the overscoring effect for CDS does occur independently of the geographic origin of the patient. It seems though that the Western group has a more pronounced tendency towards CDS over rating.

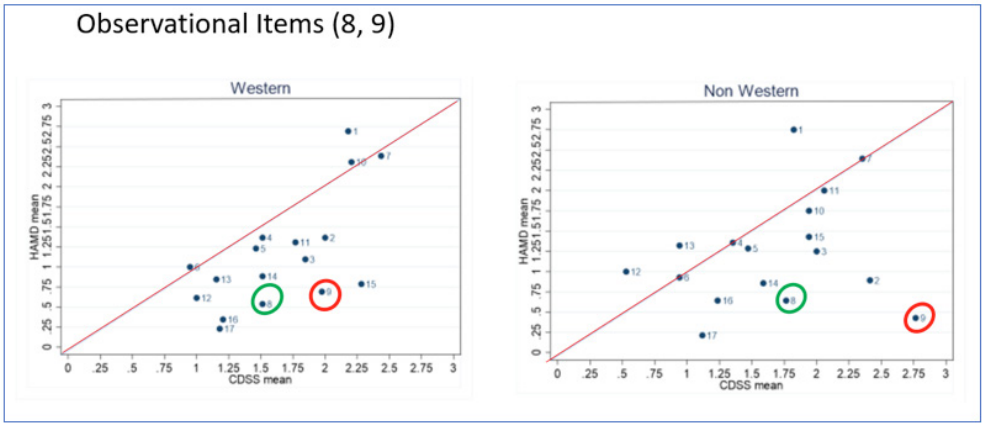
What follows is an item-by-item analysis for selected items that present different patterns between Western and Non-Western groups in the above displayed plots.

ITEM 8 and 9 – Retardation, Agitation (Observational items)

These items are defined as observational items by HAMD instructions. Therefore, HAMD will be rated on the basis of observation but CDS will only show the subjective impression of the patient.

For Non-Western group is noteworthy the much higher score to the Agitation item when responding the self-completed questionnaire. For Retardation, no substantial differences were observed.

Figure 26. STUDY 2 Item 8 (Retardation) and 9 (Agitation): HAMD vs CDS and Western vs Non-Western

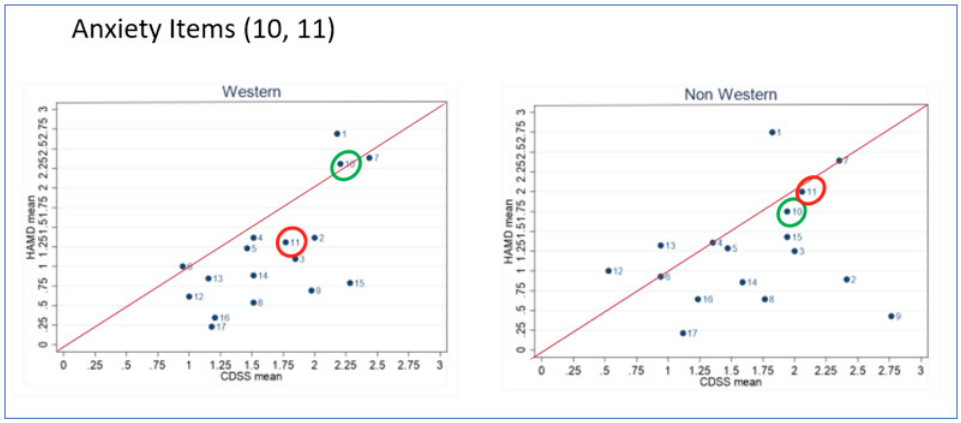


Anxiety Items: ITEM 10 (Psychic anxiety) and 11 (Somatic anxiety)

Psychic anxiety is one of the few items that is scored at similar intensities in both HAMD and CDS for both Western and Non-Western groups. Overall, the ratings are lower in Non-Western subjects than in Western group.

For Somatic anxiety the Non-Western group maintains the trend of scoring at same intensity on both HAMD and CDS. This is not happening in the Western group who scores higher in the CDS, following the general trend for all items. Overall, the ratings are lower in the Western subjects than in Non-Western group.

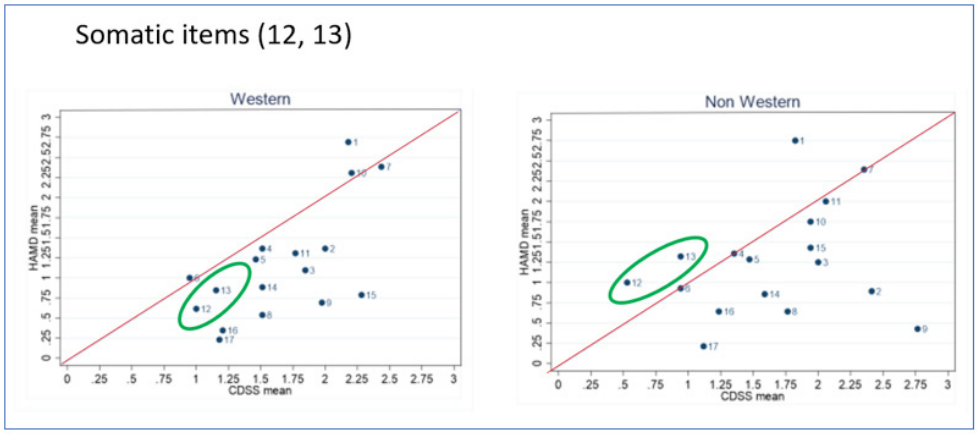
Figure 27. STUDY 2 Item 10 (Psychic Anxiety) and 11 (Somatic Anxiety): HAMD vs CDS and Western vs Non-Western



SOMATIC ITEMS: Item 12 (Somatic GI), Items 13 (Somatic Gral)

Both items are showing similar tendencies despite they assess different aspects of somatic symptoms. Interestingly the over-scoring phenomena does not happen for them in the Non-Western group where ratings where higher when assessed with the HAMD.

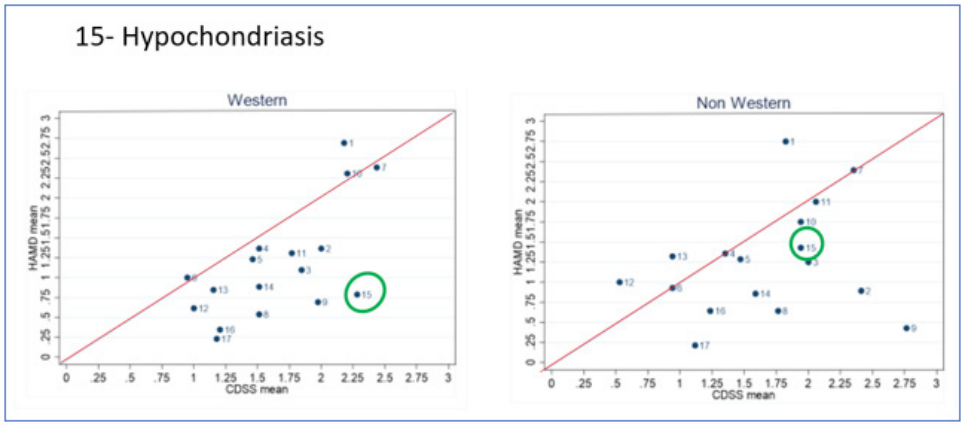
Figure 28. STUDY 2 Items 12 (Somatic GI) and 13 (Somatic Gral): HAMD vs CDS and Western vs Non-Western



ITEM 15- Hypochondriasis

The Non-Western subjects present similar ratings at both the interview and the self-completed questionnaire. However, the Western group clearly score this item higher in the CDS than in the HAMD interview.

Figure 29. STUDY 2 Item 15 Hypochondriasis: HAMD vs CDS and Western vs Non-Western

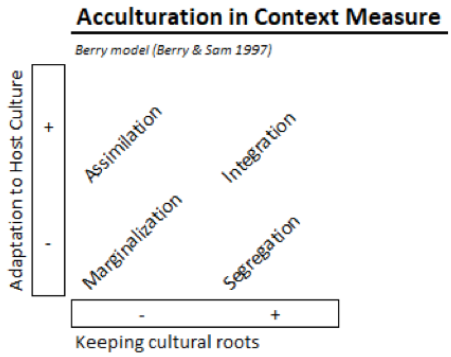


- **Objective 3:** To detect if the cultural differences in the expression of depression are influenced by the acculturation level of the subject.
- **Hypothesis 3:** An Integration attitude (according to Berry model) in immigrant patients will lead to a symptoms pattern closer to local patients.

Acculturation level has been analyzed in the immigrant population participating in this study. Immigrant population has been defined as subjects of non-Spanish origin. They were a total of 58 participants. From them, 47 subjects (81%) completed the ACM questionnaire. In regards gender, there were a 31.9% of males and 68.1% of females. There were no remarkable differences in the number of years living in Spain.

ACM respondents were classified According to the Berry model (Berry & Sam 1997).

Figure 30. STUDY 2 Berry Model for Acculturation



Importantly, their HAMD Totals were very similar between the 4 categories indicating that depression severity is not linked to the acculturation model the subject belongs to.

Likewise, depression level for immigrant patients (Total HAMD = 20,5) was comparable to depression level of Spain group (Total HAMD = 19,5) and the whole sample (Total HAMD = 20,2).

Table 33. STUDY 2 ACM respondents. Years in Spain and HAMD Totals

ACM Category	Respondents	%	Average Years in Spain	SD	HAMD Total
Assimilation	22	46,8%	13,09	8,77	22
Integration	16	34,0%	13,31	5,17	20,44
Marginalization	4	8,5%	10	7,87	20,25
Segregation	5	10,6%	10,6	6,23	19,4
Immigrant sample	47	100,0%	12,75	7,21	20,48

Table 34. STUDY 2 ACM respondents. Gender and Age

ACM Category	Respondents	%	Male	Female	Age
Assimilation	22	46,8%	8 (36,4%)	14 (63,6%)	44,6
Integration	16	34,0%	5 (31,3%)	11 (68,7%)	41,2
Marginalization	4	8,5%	1 (25%)	3 (75%)	42,5
Segregation	5	10,6%	1 (20%)	4 (80%)	35,4
Immigrant sample	47	100,0%	15 (31,9%)	32 (68,1%)	42,30

Therefore, it can be confirmed that immigrant patients are equally depressed independently of the acculturation group they belong to; and equally depressed when compared with the rest of the study sample.

With this starting point, trends amongst individual items will be explored depending on the Acculturation category. Spain group will act as a control.

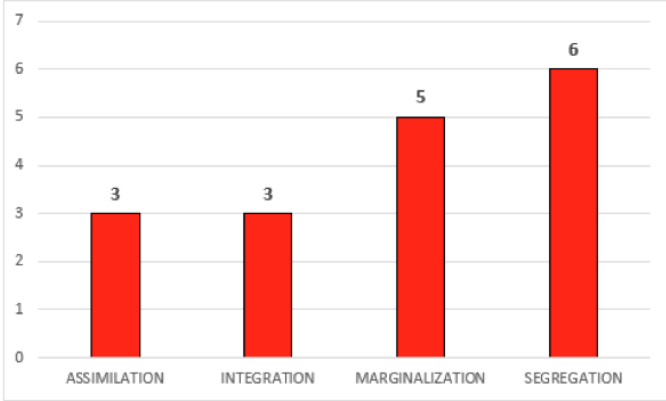
For all Acculturation groups, item-by-item comparisons were made against the Spanish group. The magnitude of the difference was calculated and the most differing group was selected for each item.

Table 35. STUDY 2Magnitude difference between Acculturation groups and Spain. Item by item analysis

ACM	HAMD1	HAMD2	HAMD3	HAMD4	HAMD5	HAMD6	HAMD7	HAMD8	HAMD9	HAMD10	HAMD11	HAMD12	HAMD13	HAMD14	HAMD15	HAMD16	HAMD17
ASSIMILATION	0,46	-0,13	-0,32	0,27	-0,04	-0,14	-0,18	0,36	0,04	-0,73	0,78	0,45	0,55	-0,04	0,68	0,41	0,13
INTEGRATION	0,16	0,04	-0,65	-0,13	-0,24	-0,27	0,15	0,49	-0,14	-1,01	0,86	0,53	0,72	-0,28	0,58	-0,05	0,20
MARGINALIZATION	-0,09	0,23	-0,34	0,18	-0,11	-0,39	-0,41	0,43	0,36	-0,82	0,55	0,59	0,16	-0,34	0,45	-0,11	0,45
SEGREGATION	0,21	0,13	-1,19	0,08	0,04	-0,34	-0,41	-0,12	-0,24	-1,22	1,85	0,19	0,81	-0,49	0,85	-0,36	0,15

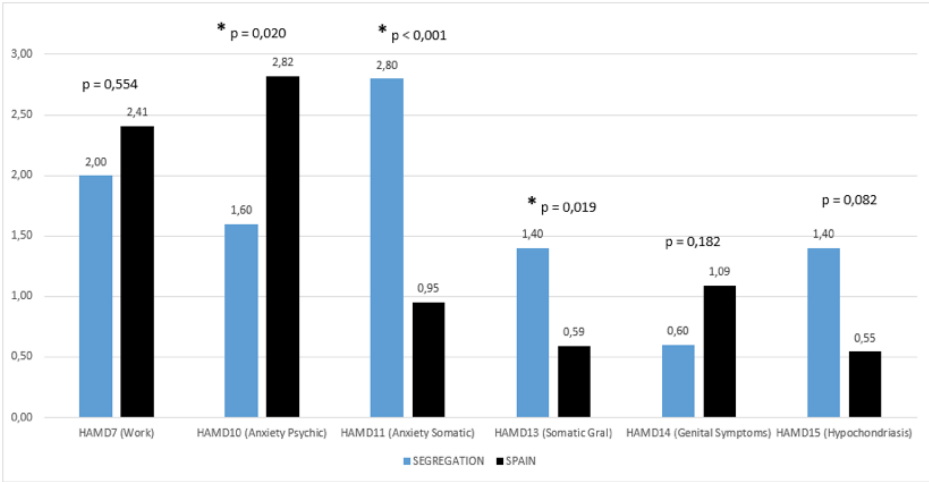
The next figure shows how many items with the widest difference each ACM category accrued. This indicates that Assimilation and Integration groups were more similar to Spain group whereas Marginalization and Segregation groups were more different from Spain, being the latter the most different.

Figure 31. STUDY 2 HAMD Items with widest differences with Spain per ACM category



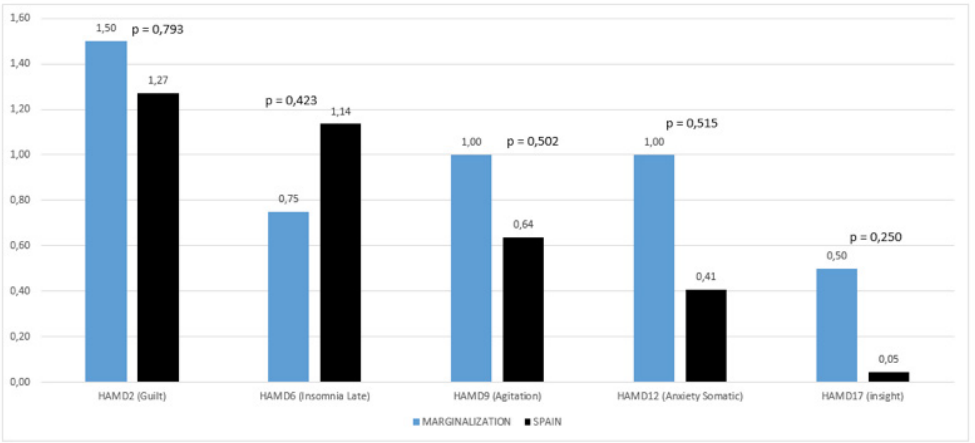
The ACM group that differs more substantially from the Spain group is Segregation. The impacted items are Item 7 (Work and activities), Item 10 (Anxiety psychic), Item 11 (Anxiety somatic), Item 13 (Somatic general), Item 14 (Genital symptoms) and Item 15 (Hypochondriasis). Statistically significant differences were reached for Item 10, Item 11 and Item 13.

Figure 32. STUDY 2 HAMD items with widest differences between Segregation and Spain groups



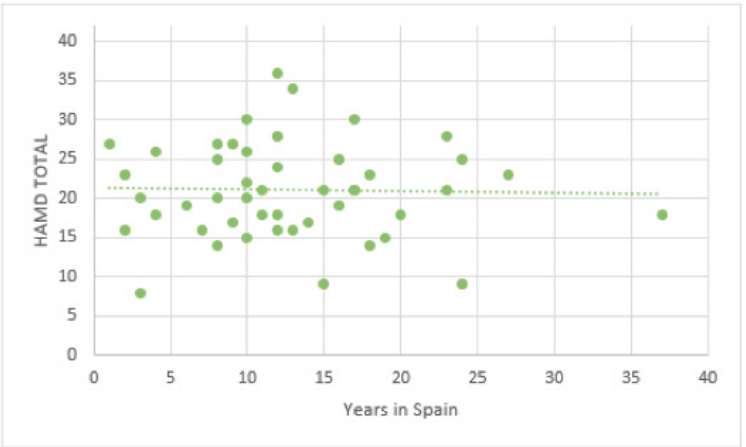
Same analysis was conducted for the Marginalization group who had 5 items accrued with widest differences, however none of the items resulted on statistically significant differences.

Figure 33. STUDY 2 HAMD items with widest differences between Marginalization and Spain groups



Pearson Correlation was run for the whole immigrant population between the years of residence in Spain and HAMD Total scoring. Such value resulted in a non-significant value (r = - 0.04)

Figure 34. STUDY 2 Correlation between years of residence in Spain and HAMD Total values



Same analysis was done within the four Acculturation groups, leading to values close to 0 with the exception of Marginalization group, who obtained -0.80. Still such value had not statistically significance.

Table 36. STUDY 2 Pearson correlation between years of residence in Spain and HAMD Total value

ACM category	Pearson correlation	p value
Assimilation	-0,01	0,955
Integration	0,04	0,871
Segregation	0,006	0,992
Marginalization	-0,803	0,197

DISCUSION

- **Objective 1:** To characterize the influence of cultural differences in the depressive symptomatology assessed with the Hamilton Depression Scale.
- **Hypothesis 1:** HAMD Somatic items will weigh more in non-Western patients.

The starting point for this project has been achieved, that being completing a sample of equally depressed multi-cultural patients.

When looking at the Sub-scales totals the same conclusion can be reached as there are no differences in their values depending on the geographic origin of the patient. One can say that sub-scales are not affected by the cultural factor.

This is especially important for HAMD6 sub-scale as it is often used as a surrogate of the Total HAMD17 evaluation (O'Sullivan 1997, Hooper 2000). In this study we can see that similar conclusions can be reached with HAMD17 and HAMD6 when evaluating a multi-cultural population.

Sub-Scales measuring vitality, Anxiety and Sleep disturbance also show similar levels of severity for all cultural groups. Some literature suggests that Anxiety and Sleep disturbance would be prone to be more visible in Non-Western patients, however this result has not emerged in the current study. It must be noted though that Anxiety sub-scale showed internal differences in the way its items were rated. Despite having equivalent total scores, the weight given to the individual items were different for Western and Non-Western subjects. Non-Western subjects had a higher somatic anxiety whereas Western subjects had a higher psychic anxiety.

Two novel sub-scales have been analyzed in this research work: Psychologic and Somatic items. The whole 17 items have been distributed amongst these 2 categories and results have been compared.

Psychologic sub-scale has shown similar results independently of the geographic origin of the patient. This is interesting as some authors sustain that Western patients would be prone to «psychologize» their symptoms in contrast of Non-Western patients who tend to the somatization of their depression symptoms (Ryder 2008, White 1982, Kirmayer 1984, Kirmayer 1998). In our multi-cultural sample psychologic items have not been rated higher by the Western patients, or lower by the Non-Western patients; all of them showed a similar symptoms pattern. It must be noted that Non-Western subjects have displayed psychological symptoms at the same level than Western subjects, thus confirming that if the interview digs deep enough, psychological symptoms are also present in Non-Western patients.

When analyzing the Somatic sub-scale, clearly Non-Western patients have scored higher than the Western patients. This would go in favour of the extensive literature supporting the somatization of depressive symptoms in Non-Western communities (Kirmayer 1984, Kirmayer 1998).

As previously described, this is an exploratory study therefore the sample is not powered to achieve a given pre-defined difference. However, provided that the Somatic sub-scale has shown statistically significant differences, the power has been calculated backwards achieving a value of 61%. It is noteworthy that with such low power value, significant differences have been found. This could mean that this sub-scale really behaves differently than the rest of items of the HAMD 17 scale.

To finish the analysis, a series of ANOVAS have been run to analyze potential differences at item level. Five items have been identified as behaving differently depending on the geographic origin of the patient: The already mentioned Item 11 (Anxiety somatic), Item 12 (Somatic GI) and Item 13 (Somatic General); but also Item 10 (Anxiety Psychic) and Item 15 (Hypochondriasis).

All these items were rated higher in Non-Western patients with the exception of Item 10 (Anxiety Psychic) which was rated higher by Western subjects. Again, the classical trend of Somatic items being rated higher by Non-Western patient is followed. Similarly, the Item 10 which has a psychological component has been rated higher by Western patients. It is noteworthy how Item 15 (Hypochondriasis) behaves. Despite being a psychological item (Hypochondriasis refers to thoughts, worries and preoccupations) it is substantially linked to somatic symptoms and it is ultimately rated higher by Non-Western subjects.

As a summary of Objective 1, the following discussion points can be considered:

- Classical HAMD Sub-Scales are not affected by cultural differences which is positive as some of them are used as surrogates of the Total HAMD17 scoring.

- Some somatic items (11- Anxiety somatic, 12-Somatic GI, 13-Somatic General) are scored significantly higher by Non-Western subjects.
- Psychological items (as a novel sub-scale) are rated with similar intensity by both Western and Non-Western subjects.
- Some psychological items (10-Anxiety Psychic) are scored higher by Western subjects.
- Interestingly, some psychological items (15-Hypochondriasis) are scored higher by Non-Western subjects.

- **Objective 2:** To explore if the face-to-face interview methodology is mediating the subject outcome, depending on the original culture of the subject.
- **Hypothesis 2:** HAMD interview symptoms pattern will better correlate with self-administered HAMD in patients of Western origin.

CDS RESPONSE RATE

From the total of 80 subjects participating in this study, 56 (70%) were able to correctly complete the CDS. The main reason for not completing the CDS were difficulties with reading / comprehending the CDS tool. Likewise, forms having more than 10% of irregular answers (missing or dual answers) were discarded, as indicated by the CDS Manual.

CDS has been especially designed to be a simple tool with low levels of semantic and syntactic difficulty (Dale 1948, Carroll 1981). However, in this study many subjects were simply not used to use self-completed documents and did not feel able to provide responses.

According to CDS Technical Manual (Carroll 1998) the sentences can be read outload to the subject and clarifications might be provided. However, when this option was attempted, subjects often needed clarifications in multiple items of the CDS. At the end, the

CDS administration was a sort of repetition of the HAMD interview where the administrator was describing what the CDS items mean and helping the subject to understand and find the best answer. Those cases were discarded as it was considered that the administrator had too much influence on the subject's responses.

The fatigue factor must be considered, as this study is designed in a way that CDS is the last test administered to the subject after the HAMD and the ACM. Should had the CDS been the only test used in the study, the response rate would have probably been higher.

It must be noted that the Spain / Amerindian groups showed the highest response rates. The fact of going through the study tests in their local language might have played a role in the fatigue aspect, being fresher than the others to complete the last test. Also, the effort of reading the 52 items of the test is less when using the own language.

Of note is that local language CDS forms were offered to the subjects. In any case, the linguistic fatigue was still present as the instructions and the whole session was conducted in Spanish language.

DEPRESSION SEVERITY. RELATION BETWEEN CDS AND HAMD

Although the CDS responses showed an ample range of total scorings (from 15 to 35) the mean values were remarkably similar amongst the groups, independently of the geographical subject's origin (means ranging from 27 to 29 points). The total average value was 28.2 points.

This means that all subject in this study had a Severe depression level as per CDS technical manual (Carroll 1998). This goes in line with the spirit of this study which aims to interview subjects with active depression, so different symptoms patterns can potentially be identified.

It must be noted that depression severity measured with CDS yielded higher scores than when measured with HAMD.

Amongst the 56 CDS respondents, HAMD total score was 20.4. Amongst the total of 80 participants in this study, HAMD total score was 20.2.

Therefore, the fact that CDS was completed or not did not relate to the level of depression of the subject. HAMD total ratings showed that all subjects were equally depressed independently of whether they completed CDS or not.

The severity showed by the CDS assessments is Severe depression (Carroll 1998) whereas HAMD assessment indicates Major depression (Bech 1996) or Moderate depression (Baer 2009, Zimmerman 2013). CDS assessment is 7.8 points higher than CDS ratings.

For the purpose of this study, either Moderate or Severe depression are valid as the aim is to explore subjects with active depression showing a variety of symptoms. This is true for both Moderate and Severe depression.

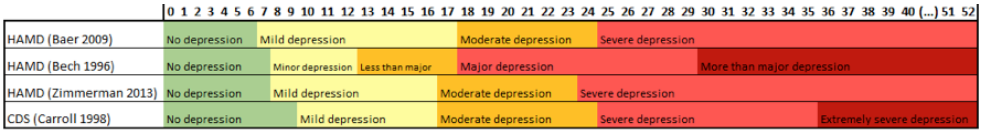
It is noteworthy the significant positive correlation between CDS and HAMD total ratings, showing that, despite distinct intensities, both scales are moving in the same direction. This significant correlation is present in both Western and Non-Western groups although the correlation is slightly stronger in the Western group. Nevertheless, the different intensity by which depression severity is captured must be further explored.

CDS OVERSCORING

According to the reviewed literature, CDS cut off values are aligned with HAMD severity categorization as the spirit of the CDS is to mimic the HAMD scale. In the below table it can be seen how CDS severity

levels match reasonably well with the different cut off scorings that have been defined for HAMD by different authors.

Table 39. STUDY 2 Severity cut off scores for HAMD and CDS



In the present study it has been evidenced that CDS was systematically scored higher than HAMD for all evaluated subjects independently of their geographic origin.

In the CDS technical manual (Carroll 1998) the author describes CDS as a tool to capture depression severity evolution across the time and he advices to administer the CDS two times before starting the evolution in order to have a more reliable baseline scoring. Otherwise, the author acknowledges that an inflation of CDS scores could take place.

The present study is a transversal analysis, i.e. no evolution is followed up thus CDS has been administered only once. Therefore, the inflation phenomena described by the author could have happened.

In the CDS technical manual there is an actual example of overrating of CDS over the HAMD across several weeks. Although this is reported only once in this manual, it must be taken in consideration as a potential explanation of the over ratings identified in the present study. In this example, a difference of 10 points in favour of CDS was evidenced in the baseline and it was not until week number 15-18 that the CDS and HAMD ratings became closer.

Figure 35. STUDY 2 HAMD and CDS ratings across time (CDS Technical Manual)

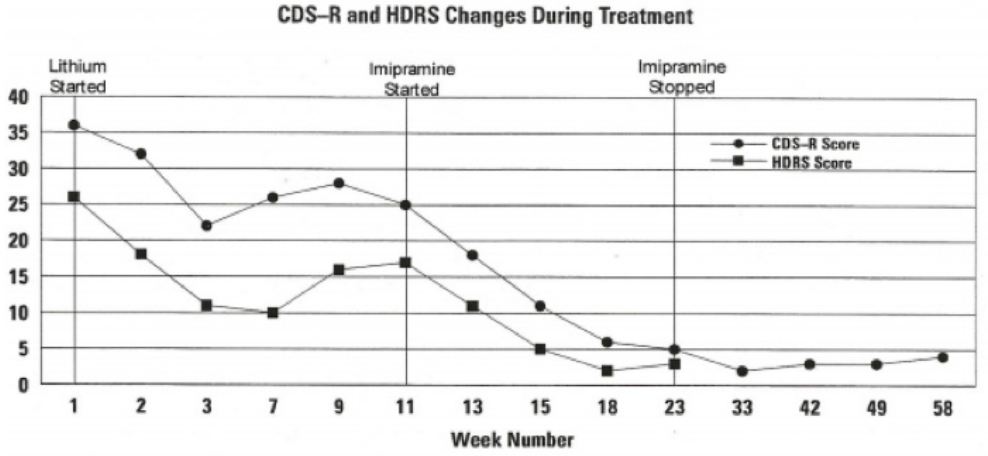


Figure extracted from the CDS Technical Manual (Carroll 1998)

Other studies with the CDS show that a systematic overreporting relative to clinical ratings could occur in depressed patients with comorbid Axis II personality disorders (Feinberg 1981). This was not taken in consideration in the current study when designing the exclusion criteria, therefore a certain non-controlled influence might have taken place.

Carroll acknowledges in his technical manual that in medical settings misleading high scores of the CDS can occur as a result of physical illness. As examples he lists sleep disturbance, poor concentration, or poor appetite. It must be noted that these symptoms are usually present in depression patients, especially if they are prone to somatization. Provided that patients enrolled in the present study had an active depression level, the somatization aspect could have played a role in over rating some items, as proposed by the CDS author.

Lastly, Carroll mentions in the technical manual that a non-significant negative correlation (r = -0.22) was found between years of education and scoring in CDS. It must be acknowledged that

education level was not captured in the present study. However, as a general trend, the education level of the patients was low-medium as an average. Thus, according to the above finding, a tendency towards higher scores in the CDS could have occurred. This is just an speculation as the reported trend was not significant.

Summarizing, the following can be established in regards the potential over rating of CDS in the present study:

1. Inflation phenomena could occur as a result of being administered only once.
2. Overrating of CDS could have happened if Axis II personality disorders were included in the study, which was not controlled.
3. Somatization aspect of depression can also lead to over rating of CDS.

Some studies suggest that self-rating tools might lead to an over-rating of depression symptoms when compared with clinician-rated tools specially in patients with non-endogenous depression (Feinberg 1981, Domken 1994). Some other researchers have found low correlations during acute phases but better correspondences during subsequent follow up (Prusoff 1972). Other studies found only moderate correlations (Carter 2010, Carroll 1973) whereas other authors found a good equivalence (Rush 2006) between self-rated and clinician-rated depression tools. Lastly, some studies suggest that self-rated and clinician-rated tools complement each other when assessing a depressed patient (Uher 2012).

It is obvious that there is not a clear consensus on the dynamics between self-rated and clinician-rated scales when assessing depressed patients. Stablishing correspondences between both methodologies is difficult because each scale (either self-completed or clinician-rated) is unique and might not be assessing exactly the same aspects of depression, thus the differences.

The added value of the present study is that both HAMD and CDS are meant to mirror themselves by using the same 17 items. However, still not clear correspondence has been identified.

That being said, one has to consider the possibility that for some reason patients minimized the severity of their depression during the clinical interview, which emerged in full while completing the self-reported tool. However, this would not follow a culturally specific pattern as the over rating phenomena has been observed equally between Western and Non-Western groups.

INDIVIDUAL ITEM ANALYSIS

ITEM 8 and 9 – Retardation, Agitation (Observational Items)

Both Western and Non-Western group show higher Agitation in the self-completed scale than during the interview. However, this difference is higher in the Non-Western group. This indicates that Non-Western subjects are perceiving themselves significantly more agitated than the clinician has rated. There are two potential interpretations for this:

a. Non-Western patients could have a tendency to show themselves more controlled in front of the clinician due to the social desirability they might feel in front of a doctor.
b. According to literature Non-Western subjects tend to express more somatic symptoms and Agitation could be one of them. Because of the reason above, the subject could try to hide Agitation during the interview however, this is how the patient feels as per the self-completed questionnaire (Visser 1989).

Of note is that this difference is not captured in the Retardation item. Both Western and Non-Western score higher in the self-completed questionnaire however this difference is of similar magnitude for both groups. Thus, the above-described explanation about social desirability would apply only to the Agitation aspect.

ANXIETY ITEMS – (Item 10- Anxiety Psychic and Item 11- Anxiety Somatic)

Psychic Anxiety is one of the few items that is rated very similarly by the clinician and by the subject for both groups. Notably, in the Western group the Psychic Anxiety is rated at higher intensity than it is in the Non-Western group (again, by both clinician and subject).

This would go in line with the abundant literature showing that Psychic symptoms are more expressed in Western patients. During the interview they talk more about their psychic symptomatology whereas Non-Western focus their explanations in the somatic aspects of anxiety. This is why Somatic Anxiety shows a higher intensity in the Non-Western group, again by both the clinician and patient.

Care must be taken with this interpretation. Whereas much literature claims that Non-Western subjects are more somatic; there could be the bias in the clinician who also score high the somatic symptoms because of the expectation that a Non-Western patient will show more somatic symptoms. The same mechanism could happen with the psychological symptoms: the rater could give more value to the psychological symptoms in Western patients as he has the expectation that they will be more prone to this kind of symptoms (Ryder 2008, White 1982, Kirmayer 1984, Kirmayer 1998).

ITEM 12 and 13 – Somatic items (GI and General)

These two items are built as independent items between themselves, however we have observed that both behave in a similar way, probably because the symptoms they are measuring are intrinsically connected. If a patient has important GI symptoms, that could impact in the Somatic General item as the patient is not feeling well from the somatic point of view.

Interestingly both items are rated higher by the clinician only for the Non-Western group. Of note is that these are of the few items that

are rated higher by the clinician. Two potential explanations can be extracted: The Non-Western subject is indeed showing more somatic symptoms, or the clinician is overrating the somatic symptoms because the expectation is that Non-Western patients will have more somatic symptomatology.

In regards Western group, both items are rated higher by the patient. Thus, the inverse trend is being observed. According to literature, Western patients are less prone to show somatic symptoms this could be why they score lower in the self-rated questionnaire (Ryder 2008, White 1982, Kirmayer 1984, Kirmayer 1998).

ITEM 15 – Hypochondriasis

Although hypochondriasis is based in somatic symptoms perception, it must be considered a psychological item because worry and rumination levels are assessed.

Western group has rated this item much higher in the self-completed questionnaire. Probably they have not talked a lot about their somatic symptoms preoccupations during the interview because they tend to express more psychological symptoms. However, in the inner self they feel a higher preoccupation than expressed during the interview.

This phenomenon is not happening in Non-Western patients. Whereas they also rate higher the self-completed questionnaire the difference with the clinician is not as big as in the Western group. The Non-Western patients have expressed their concerns about health during the interview as they are used to talk about their somatic symptoms with the clinician. Even a psychological item, Non-Western patients express it higher because is based in somatic symptoms.

As a summary of Objective 2, the following discussion points can be considered:

- Although designed to have an easy completion, execution rate for CDS has been low in this study population
- CDS and HAMD show a positive, moderate and significant correlation, that being slightly stronger in Non-Western group
- CDS systematically scores higher than HAMD for all study groups, with following exceptions:
  - Item 12 (Somatic GI) and Item 13 (Somatic general) is still higher in HAMD for Non-Western group
  - Item 10 (Psychic anxiety) scores at the same intensity for both CDS and HAMD for both subjects' groups

- **Objective 3:** To detect if the cultural differences in the expression of depression are influenced by the acculturation level of the subject.
- **Hypothesis 3:** An Integration attitude (according to Berry model) in immigrant patients will lead to a symptoms pattern closer to local patients.

Transculturality and immigration are intimately linked when compiling a cross-cultural study sample in centers located in the same country. Immigration is known to potentially have an impact on the psychological welfare of people (Achotegui 2006).

Immigration situation can be lived in different ways depending on how deep the subject adapt to the host culture and how much the subject maintains his own cultural roots (Berry & Sam 1997). This can obviously add noise in this study aiming to find cultural differences in the expression of depression, independently on the immigration effect. For this reason, Berry's model has been followed in an effort to control this factor.

In this study the severity of depression is not influenced by the Acculturation approach followed by the subject. All subjects had similar levels of depression in all four categories of the Berry model.

However, when the analysis drilled down to the item distribution of depression symptoms, different patterns have been found in some groups. Integration / Assimilation groups showed symptoms patterns closer to the Spanish group, who acted as a reference. In contrast, Marginalization / Segregation groups were more distant in terms of symptom's severity distribution when compared with Spanish group. Marginalization / Segregation groups have in common the rejection to the host culture which somehow would explain why their symptoms are different from their local counterparts. They are still using their own cultural features to express their depression. The same reverse explanation would apply to the Integration / Assimilation groups. As both accept the host culture, they also add on their behavior the local expressions of depression.

Following items showed statistically significant differences:

- Item 10 (Anxiety Psychic) is rated higher by Spanish subjects.
- Item 11 (Anxiety Somatic) is rated higher by Segregated subjects.
- Item 13 (Somatic General) is rated higher by Segregated subjects.

Interestingly, these 3 items had been already signaled as impacted by cultural differences when results of previous Objective have been discussed. Differences occurred in the same direction.

Years of residence in Spain was potentially another confounding factor, regardless of the Acculturation model followed by the subject. In this study no correlation has been found between years of residence and depression severity, thus precluding a protective factor of years of residence in front of depression.

Such correlation was sought within each Acculturation group, leading to the same conclusion with the exception of Marginalization group where a protective effect could potentially be observed. Nevertheless, this correlation was not significant.

It must be noted the small sample size of both Marginalization and Segregation groups which prevents the extrapolation of these results with a degree of certainty.

As a summary of Objective 3, the following discussion points can be considered:

- Years of residence in the host country does not necessarily act as a protection against depression severity.
- Immigrants subjects following Integration / Assimilation attitude will display a depressive symptoms pattern closer to the local subjects. Likewise, Marginalization / Segregation attitudes will differ the most from local counterparts.
- HAMD Items 10 (Anxiety psychic), 11 (Anxiety somatic) and 13 (Somatic general) might be more sensitive to the acculturation influence.

CONCLUSSIONS

The key findings of this research have two main applications in real life:

1. Enhancement of Rater Training programs in MDD International Clinical Trials
2. Emphasize the importance of cultural competencies when interviewing patients in clinical practice

1. Enhancement of Rater Training programs in MDD Multinational Clinical Trials

This research work shows that Western subjects could be prone to demonstrate more somatic symptoms when depressed, as already

published by numerous authors. This trend has been evidenced while using the HAMD-17 scale.

MDD multinational clinical trials often use HAMD-17 as primary efficacy endpoint measurement. It is therefore crucial to design robust rater training programs aiming to harmonize the way HAMD-17 is used across all participating countries. Only in this way cultural differences between countries will be minimized thus increasing the chances of the trial to reach its efficacy objectives.

In the current research, items belonging to the so-called «Somatic sub-scale» have shown higher variability when applied to a multi-cultural sample, some of them reaching statistically significance (Item11, Item12, Item13). Interestingly enough, some psychological items have also shown different behaviors depending on the origin of the subject (Item 10, Item 15). These items should deserve more attention when designing rater training programs provided they are more prone to vary when used in a multi-cultural sample. The application of similar exploratory systems (e.g. structured guidelines interviews) in all countries is crucial to reduce the variability due to culture, which could mask some true treatment effect.

In clinical trials where novel medications are tested, adverse events are of major importance. Those could be interfering with the depression symptoms expression, especially if they are of somatic nature. This is one more reason to stress the importance of proper rater training and educate the raters to differentiate between true depression expression and medical adverse event. Again, the so-called «somatic sub-scale» has been shown to have higher variability in this study conducted in real-world patients. The same occurs with the anxiety component of the scale. This could add noise to the HAMD-17 ratings in multinational clinical trials.

Some studies use the HAMD-6 as a surrogate of HAMD-17, thus minimizing the above referred potential somatic interferences. The

same approach could be taken with the so-called «Psychologic sub-scale» in this research which has shown a better stability in the way is rated between Western and Non-Western subjects. It would add further information about Suicide behaviour, Hypochondriasis and Insight (not present in HAMD6) and would totally remove the interference of somatic items.

As a conclusion, special care must be taken when designing rater training programs for the use of HAMD-17 and special emphasis needs to be done with the above-mentioned items.

2. Raise awareness on the importance of cultural competencies when interviewing patients in clinical practice

Administration of scales like the HAMD-17 in a clinical practice setting is not often done due to the lack of time from the clinicians. The use of self-rated scales could help this lack of time. This research study has explored whether the HAMD-17 self-administered version (CDS) would be affected by cultural differences.

The CDS has been found to correlate with HAMD-17 and did show similar results to those described with HAMD-17, in terms of Western and Non-Western subject's samples.

However, CDS was systematically over-scored by all subjects' groups. With only a few exceptions (Item 12, Item13, Item 10), all items were rated higher by subjects when completing the CDS than by the clinician when administering the HAMD-17.

This phenomenon could be understood as an over-rating of the CDS or an under-rating of the HAMD-17. Cultural competences play here a crucial factor. Social desirability from the patient could sometimes lead to lower intensity rates of depression in front of the assessor. The clinician must have the abilities to identify this bias and make the right questions during the interview, so the true intensity of the symptoms emerges. It is not only about interview skills but

also about avoiding preconceived notions about how a subject will express their symptoms when the patient has a different cultural background than the clinician.

Clinicians must be trained not only in interview skills but also in cultural competencies, so they are freed up from potential cultural biases.

When a clinician works with patients from different cultural backgrounds the migratory fact plays a role. Most of these culturally different patients did arrive to the host country after a not-always-easy journey. The way the patient has adapted to the host country might influence the expression of depression symptoms. This research study has shown that those patients who accept the host culture tend to express their depression with similar features than the patients native from the host country. On the contrary, immigrant patients who reject the host culture tend to differentiate their depression expression from their local counter partners.

Again, the clinician interview skills and cultural competence play a crucial role. The clinician needs to know the immigrant biography of the patient and get some knowledge on the attitude of the patient towards the host country and culture. This attitude might affect the manner on which depression is expressed and could be a confounding factor for the assessor.

To conclude this section study limitations are to be mentioned. This study is of exploratory nature and as such, no pre-defined country groups neither group sizes were set. Sample was built based in pragmatic criteria, following the real-world evidence methodology. Study sample was meant to mirror the clinical reality of the clinicians rather than being a controlled and pre-defined sample.

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ANNEXES

ANNEX 1 Hamilton Depression Scale – 17 items version form.
As provided by MAPI RESEARCH TRUST, copyright owner of Spanish translation of HAMD-17 scale.

ESCALA DE VALORACIÓN DE LA DEPRESIÓN DE HAMILTON: ESCALA DE 17 PREGUNTAS

INFORMACIÓN NO RECOGIDA ☐

MARQUE EL CÓDIGO NUMÉRICO que mejor describa al/a la paciente.

1. **ÁNIMO DEPRESIVO** (Tristeza, desesperanza, sentirse impotente, inútil)
   - ☐ 0 No presenta
   - ☐ 1 Sentimiento indicado solamente cuando se le pregunta
   - ☐ 2 Sentimiento comunicado verbalmente de forma espontánea
   - ☐ 3 Sentimiento comunicado no verbalmente, por ej. expresión facial, actitud, voz, tendencia a llorar
   - ☐ 4 Es casi el único sentimiento mostrado en comunicación espontánea verbal o no verbal

2. **SENTIMIENTOS DE CULPABILIDAD**
   - ☐ 0 No presenta
   - ☐ 1 Auto reproche, siente que ha fallado a los demás
   - ☐ 2 Ideas de culpabilidad o reflexiones sobre errores pasados o acciones impuras
   - ☐ 3 La enfermedad actual es un castigo; delirios de culpabilidad
   - ☐ 4 Oye voces acusativas o denunciantes y/o experimenta alucinaciones visuales amenazantes

3. **SUICIDIO**
   - ☐ 0 No presenta
   - ☐ 1 Siente que la vida no vale la pena vivirla
   - ☐ 2 Desearía estar muerto/a o tiene pensamientos de provocarse la muerte
   - ☐ 3 Tiene ideas o ademanes suicidas
   - ☐ 4 Intentos de suicidio (cualquier intento grave se puntúa 4)

4. **INSOMNIO TEMPRANO**
   - ☐ 0 Ninguna dificultad para quedarse dormido/a
   - ☐ 1 Se queja de dificultades ocasionales para quedarse dormido/a, por ejemplo, más de media hora
   - ☐ 2 Se queja de dificultades para quedarse dormido/a todas las noches

5. **INSOMNIO MEDIO**
   - ☐ 0 Ninguna dificultad
   - ☐ 1 Se queja de estar inquieto/a o alterado/a durante la noche
   - ☐ 2 Se despierta durante la noche – si se levanta de la cama (sin contar cuando va al baño) se puntúa 2

6. **INSOMNIO TARDÍO**
   - ☐ 0 Ninguna dificultad
   - ☐ 1 Se despierta temprano por la mañana pero se vuelve a dormir
   - ☐ 2 Incapaz de quedarse dormido/a de nuevo si se levanta de la cama

ESCALA DE VALORACIÓN DE LA DEPRESIÓN DE HAMILTON: ESCALA DE 17 PREGUNTAS

7. **TRABAJO Y ACTIVIDADES**

- ☐ 0 Ninguna dificultad
- ☐ 1 Pensamientos y sentimientos de incapacidad, fatiga o debilidad relacionados con las actividades, trabajos o aficiones
- ☐ 2 Pérdida de interès en actividades, aficiones o trabajo – por información directa del/de la paciente o indirecta mediante apatía, indecisión y vacilación (siente que tiene que forzarse para trabajar o hacer actividades)
- ☐ 3 Disminución del tiempo real empleado en actividades o disminución en la productividad. En el hospital, puntúe 3 si el/la paciente no dedica al menos tres horas al día a actividades
- ☐ 4 Dejó de trabajar debido a la enfermedad actual. En el hospital, puntúe 4 si el/la paciente no se dedica a ninguna actividad

8. **RETRASO:** Lentitud de pensamiento o de habla; disminución de la capacidad para concentrarse; disminución de la actividad motora

- ☐ 0 Pensamiento y habla normales
- ☐ 1 Ligero retraso durante la entrevista
- ☐ 2 Obvio retraso durante la entrevista
- ☐ 3 Dificultad durante la entrevista
- ☐ 4 Estupor completo

9. **AGITACIÓN**

- ☐ 0 Ninguna
- ☐ 1 Nerviosismo
- ☐ 2 Juega con las manos, pelo, etc.
- ☐ 3 Se mueve mucho, no puede quedarse quieto/a
- ☐ 4 Se retuerce las manos, se come las uñas, se tira del cabello, se muerde los labios

10. **ANSIEDAD (PSÍQUICA)**

- ☐ 0 Ninguna dificultad
- ☐ 1 Tensión e irritabilidad subjetivas
- ☐ 2 Se preocupa por cosas sin importancia
- ☐ 3 Actitud inquieta manifiesta en la cara o en el habla
- ☐ 4 Temores expresados sin tener que preguntar

11. **ANSIEDAD (SOMÀTICA):** Concomitantes fisiológicos de la ansiedad, tales como gastrointestinal: sequedad en la boca, gases, indigestión, diarrea, calambres, eructos; cardiovascular: palpitaciones del corazón, dolor de cabeza; respiratorio: hiperventilación, suspiros; frecuencia urinaria; sudor excesivo.

- ☐ 0 No presenta
- ☐ 1 Leve
- ☐ 2 Moderado
- ☐ 3 Grave
- ☐ 4 Incapacitante

12. **SÍNTOMAS SOMÀTICOS (GASTROINTESTINALES)**

- ☐ 0 Ninguno
- ☐ 1 Pérdida de apetito pero come sin que le inciten. Sensación de pesadez en el abdomen.
- ☐ 2 Dificultad para comer sin que el personal le incite. Precisa o pide laxantes, o medicación para ir de vientre o para los síntomas gastrointestinales

13. **SÍNTOMAS SOMÀTICOS GENERALES**

- ☐ 0 Ninguno
- ☐ 1 Pesadez en las extremidades, espalda o cabeza. Dolor de espalda, dolor de cabeza, dolor muscular. Pérdida de energía y fatiga
- ☐ 2 Cada síntoma bien definido puntúa 2

ESCALA DE VALORACIÓN DE LA DEPRESIÓN DE HAMILTON: ESCALA DE 17 PREGUNTAS

14. **SÍNTOMAS GENITALES:** tales como pérdida de libido, alteraciones menstruales

- ☐ 0 Ninguno
- ☐ 1 Leve
- ☐ 2 Grave

15. **HIPOCONDRÍA**

- ☐ 0 No presenta
- ☐ 1 Ensimismado/a (sobre su cuerpo)
- ☐ 2 Preocupación por la salud
- ☐ 3 Quejas frecuentes, pide ayuda, etc.
- ☐ 4 Delirios hipocondríacos

CAMBIO DE PESO REAL
(desde la última visita)

16. **PÉRDIDA DE PESO**

- ☐ 0 No ha habido pérdida de peso o NO ha sido debida a la enfermedad actual
- ☐ 1 Pérdida de peso probablemente debida a la enfermedad actual
- ☐ 2 Pérdida de peso evidente debida a la enfermedad actual

17. **CONCIENCIA**

- ☐ 0 Reconoce estar deprimido/a y enfermo/a
- ☐ 1 Reconoce la enfermedad pero atribuye la causa a la comida, el clima, el trabajo excesivo, el virus, la necesidad de descanso, etc.
- ☐ 2 Niega totalmente estar enfermo/a

(DNDE)

Puntuación Total de la Depresión 17-preguntas:_____

La puntuación debe ser mayor o igual a 18 para continuar en el estudio

Iniciales del evaluador _____ _____ _____
Nombre 1er. Apellido 2º Apellido

Referencia: M. Hamilton *J. Neurol. Neurosurg. Psychiat.*, 1960, 23, 56-62.

ANNEX 2. Hamilton Depression Scale – 17 items version.

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Author: Max Hamilton
Publication: Journal of Neurology, Neurosurgery and Psychiatry
Publisher: BMJ Publishing Group Ltd.
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Manjon, Marta <Marta.Manjontarrega@i3global.com>

Mon 12/12/2011 11:48 AM

Doctorat

To:'martamanjon@hotmail.com' <martamanjon@hotmail.com>;

1 attachments (89 KB)

hamd17spa#.doc;

From: Marie Dulac [mailto:mdulac@mapigroup.com]
Sent: lunes, 22 de junio de 2009 10:19
To: Manjon, Marta
Subject: RE: 13273_Spanish (Spain) scale request (HAMD)

Dear Marta

Many thanks for sending the written permission.

Please, find attached the Spanish version of the HAM-D.

I hope this helps.

Please, do not hesitate to contact me should you have any questions.

Best regards,

Marie

Marie DULAC TRIMOREAU
Information Unit Project Manager

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De : Manjon, Marta [mailto:Marta.Manjontarrega@i3research.com]
Envoyé : vendredi 19 juin 2009 13:43
À : Marie Dulac
Objet : RE: 13273_Spanish (Spain) scale request (HAMD)

Dear Marie,

I have contacted the BMJ Publishing Group and I have obtained the written permission, which I am attaching herein.

Is this what you needed for releasing the HAMD-17 in the Spanish for Spain version?

Thanks and best regards,
Marta

<< >>
From: Marie Dulac [mailto:mdulac@mapigroup.com]
Sent: lunes, 15 de junio de 2009 14:19
To: Manjon, Marta
Subject: RE: 13273_Spanish (Spain) scale request (HAMD, CSRS and ACM)

Dear Marta,

Many thanks for your message and for your interest in our services.

I am pleased to provide you with the needed information:
- Hamilton Depression Scale – 17 items
If you wish to use the HAM-D in your study, you first have to obtain a written permission from BMJ Publishing group. I first invite you to contact:
BMJ Publishing Group
Mrs Carol Torselli
BMA House Tavistock Square
London WC1H 9JR
UK
Phone: +44 (0) 207 383 6169
Fax: +44 (0) 171 383 6668
E-mail: ctorselli@bmjgroup.com

I am pleased to inform you that the HAM-D 17 is available in Spanish for Spain at MAPI Research Trust.
We may provide you with this version, but please note that we first have to receive BMJ's permission from you.

- Carroll Self-Rating Scale (CSRS)
We unfortunately have no information on this instrument, nor do we have a Spanish translation.
Are you referring to the Carroll Rating Scale for Depression (CDS)?
http://www.proqolid.org/instruments/carroll_rating_scale_for_depression_cds
If your answer is yes, I invite you to contact the translation department of MHS to obtain the Spanish translation: translation@mhs.com

- Acculturation in context measure (ACM)
We unfortunately have no information on this instrument, nor do we have a Spanish translation.

Please note that this information is provided to you free of charge as your request is related to an academic study. However, this information is usually subject to a specific budget for commercial companies.

I hope this helps.

Please, do not hesitate to contact me should you have any questions.

Best regards,

Marie

**** Please note that our office will be closed on Thursday June 18th (afternoon) and Friday June 19th. ****

Marie DULAC TRIMOREAU
Information Unit Project Manager

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ANNEX 3 Structured Interview Guide For The Hamilton Depression Scale (SIGH-D) – 17 item version Form.

SIGH-D form as provided by the original author Dr. Janet B.W. Williams

STRUCTURED INTERVIEW GUIDE
FOR THE HAMILTON DEPRESSION SCALE (SIGH-D) – 17 item version

Janet B.W. Williams, D.S.W.

INTERVIEWER

The first question for each item should be asked exactly as written. Often this question will elicit enough information about the severity and frequency of a symptom for you to rate the item with confidence. Follow-up questions are provided, however, for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information.

Time period. The interview questions indicate that the ratings should be based on the patient's condition in the past week.

Referent of "usual" or "normal" condition. Several of the interview questions in the HAM-D refer to the patient's usual or normal functioning. In some cases, such as when the patient has Dysthymia or Seasonal Affective Disorder, the referent should be to the last time they felt OK (i.e., not depressed or high) for at least a few weeks.

This instrument provides an interview guide for both the Hamilton Depression Scale (Hamilton, Max: A rating scale for depression. J Neurol Neurosurg Psychiat 23:56-61, 1960). The anchor point descriptions for both scales, with very minor modifications, have been taken from the ECDEU Assessment Manual (Guy, William, ECDEU Assessment Manual for Psychopharmacology, Revised 1976, DHEW Publication No. (ADM) 76-338). A reliability study of the SIGH-D (interview guide for the HAM-D alone) was published in the Archives of General Psychiatry (1988;45:742-747). Additional designators were added in parentheses to the anchor points by Kobak, Lipsitz and Williams to further standardize ratings.

For further information and permission to use or translate, contact Dr. Williams at jbw5@columbia.edu.

Revised 21 February 2007

STRUCTURED INTERVIEW GUIDE FOR THE HAMILTON DEPRESSION SCALE (SIGH-D)*

PT'S INITIALS: _____ **PT'S ID:** _____ **TIME BEGAN SIGH-D:** _____

INTERVIEWER: _____ **DATE: :** ___/___/____

OVERVIEW: **I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF WEEK)? IF OUTPATIENT: Have you been working? IF NOT: Why not?**	
What's your mood been like this past week (compared to when you feel OK)? Have you been feeling down or depressed? IF YES: Can you describe what this feeling has been like for you? How bad is the feeling? Does the feeling lift at all if something good happens? How are you feeling about the future? In the last week, how often have you felt (OWN EQUIVALENT)? Every day? All day? Have you been crying at all?	**DEPRESSED MOOD** (sadness, hopeless, helpless, worthless) 0 - absent 1 - indicated only on questioning *(occasional, mild depression)* 2 - spontaneously reported verbally *(persistent, mild to moderate depression)* 3 - communicated non-verbally, i.e., facial expression, posture, voice, tendency to weep *(persistent, moderate to severe depression)* 4 - VIRTUALLY ONLY those feeling states reported in spontaneous verbal and non-verbal communication *(persistent, very severe depression, with extreme hopelessness or tearfulness)*

IF SCORED 1-4 ABOVE, ASK: How long have you been feeling this way?

NOTES:

SIGH-D Feb 07

How have you been spending your time this past week (when not at work)? Have you felt interested in doing (THOSE THINGS), or do you feel you have to push yourself to do them? How much less interested in these things have you been this past week compared to when you're not depressed? How hard to do you have to push yourself to do them? Have you stopped doing anything you used to do? (What about hobbies?) IF YES: Why? About how many hours a day do you spend doing things that interest you? Is there anything you look forward to? IF WORKING (IN OR OUT OF THE HOME): Have you been able to get as much (work) done as you usually do? How much less productive or efficient are you compared to before you were depressed?	**WORK AND ACTIVITIES** 0 - no difficulty 1 - thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies *(mild reduction in interest or pleasure; no clear impairment in functioning)* 2 - loss of interest in activity, hobbies or work - by direct report of the patient or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities *(clear reduction in interest, pleasure or functioning)* 3 - decrease in actual time spent in activities or decrease in productivity. In hosp., pt. spends less than 3 hrs./day in activities (hospital job or hobbies) exclusive of ward chores (*profound reduction in interest, pleasure, or functioning)* 4 - stopped working bec. of present illness. In hospital, no activities except ward chores, or fails to perform ward chores unassisted (*unable to work or fulfill primary role because of illness, and total loss of interest)*
Now let's talk about your sleep. What were your usual hours of going to sleep and waking up, before this began? **When have you been falling asleep and waking up over the past week?**	
Have you had any trouble falling asleep at the beginning of the night? (Right after you go to bed, how long has it been taking you to fall asleep?) How many nights this week have you had trouble falling asleep? Have you changed the time at which you try to get to sleep since you've been depressed?	**INSOMNIA EARLY (INITIAL INSOMNIA)** 0 - no difficulty falling asleep 1 - complains of occasional difficulty falling asleep *(i.e., more than 1/2 hour, 2-3 nights)* 2 - complains of nightly difficulty falling asleep *(i.e., more than ½ hour, 4 or more nights)*

SIGH-D Feb 07

During the past week, have you been waking up in the middle of the night? IF YES: Do you get out of bed? What do you do? (Only go to the bathroom?) When you get back in bed, are you able to fall right back asleep? How long does it take you to fall back asleep? Do you wake up more than once during the night? (If yes: How long does it take for you to fall back to sleep each time?) Have you felt your sleeping has been restless or disturbed some nights? How many nights this week have you had that kind of trouble?	**INSOMNIA MIDDLE** 0 - no difficulty 1 - complains of being restless and disturbed during the night (*or occasional difficulty, i.e., 2-3 nights, more than ½ hr)* 2 - waking during the night - any getting out of bed (except to void) (*often, i.e., 4 or more nights of difficulty, more than ½ hr)*
What time have you been waking up in the morning for the last time, this past week? IF EARLY: Is that with an alarm clock, or do you just wake up yourself? What time do you usually wake up (that is, when you feel well)? How many mornings this past week have you awakened early?	**INSOMNIA LATE (TERMINAL INSOMNIA)** 0 - no difficulty 1 - waking in early hours of morning but goes back to sleep *(occasional, i.e., 2-3 nights difficulty)* 2 - unable to fall asleep again if gets out of bed *(often, i.e., 4 or more nights difficulty)*
Sometimes, along with depression or anxiety, people might lose interest in sex. This week, how has your interest in sex been? (I'm not asking about actual sexual activity, but about your interest in sex.) Has there been any change in your interest in sex (from when you were feeling OK)? IF YES: How much less interest do you have compared to when you're not depressed? (Is it a little less or a lot less?)	**GENITAL SYMPTOMS** (such as loss of libido, menstrual disturbances) 0 - absent 1 - mild (*somewhat less interest than usual)* 2 - severe (*a lot less interest than usual)*
How has your appetite been this past week? (What about compared to your usual appetite?) IF LESS: How much less than usual? Have you had to force yourself to eat? Have other people had to urge you to eat? (Have you skipped meals?)	**SOMATIC SYMPTOMS GASTROINTESTINAL** 0 - none 1 - loss of appetite but eating without encouragement (*appetite somewhat less than usual)* 2 - difficulty eating without urging (or *appetite significantly less than usual)*

SIGH-D Feb 07

Have you lost any weight since this (DEPRESSION) began? IF YES: Did you lose any weight this last week? (Was it because of feeling depressed or down?) How much did you lose? IF NOT SURE: Do you think your clothes are any looser on you? AT FOLLOW-UP: Have you gained any of the weight back? IF YES: How much? **NOTE: RATE 1 TO 3 ONLY IF PATIENT LOST WEIGHT AND HAS NOT BEGUN TO GAIN IT BACK.**	**LOSS OF WEIGHT (Rate either A or B)** A. When rating by history: 0 - no weight loss 1 - probable weight loss due to current depression 2 - definite (according to patient) weight loss due to depression 3 - not assessed B. On weekly ratings by ward staff, when actual weight changes are measured: 0 - less than 1 lb. loss in week 1 - more than 1 lb. loss in week 2 - more than 2 lb. loss in week 3 - not assessed **NOTE: AVOID CODING "3" IF POSSIBLE**
How has your energy been this past week? IF LOW ENERGY: Have you felt tired? (How much of the time? How bad has it been?) This week, have you had any aches or pains? (What about backaches or muscle aches?) (How much of the time? How bad has it been?) Have you felt any heaviness in your limbs, back, or head?	**SOMATIC SYMPTOMS GENERAL** 0 - none 1 - heaviness in limbs, back, or head. Backaches, muscle aches. Loss of energy and fatiguability. *(somewhat less energy than usual; mild, intermittent loss of energy or muscle aches/heaviness)* 2 - any clear-cut symptoms *(persistent, significant loss of energy or muscle aches/heaviness)*

SIGH-D Feb 07

Have you been putting yourself down this past week, feeling you've done things wrong, or let others down? IF YES: What have your thoughts been? Have you been feeling guilty about anything that you've done or not done? IF YES: What have your thoughts been? What about things that happened a long time ago? (if unknown) How often have you thought about this the past week? Have you thought that you've brought (THIS DEPRESSION) on yourself in some way? (Have you been hearing voices or seeing visions in the last week? IF YES: Tell me about them.)	**FEELINGS OF GUILT** 0 - absent 1 - self-reproach, feels he has let people down 2 - ideas of guilt or rumination over past errors or sinful deeds *(feelings of guilt, remorse or shame)* 3 - present illness is a punishment. Delusions of guilt (*severe, pervasive feelings of guilt*) 4 - hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
This past week, have you had thoughts that life is not worth living? IF YES: What about thinking you'd be better off dead? Have you had thoughts of hurting or killing yourself? IF YES: What have you thought about? Have you actually done anything to hurt yourself?	**SUICIDE** 0 - absent 1 - feels life is not worth living 2 - wishes he were dead or any thoughts of possible death to self 3 - suicidal ideas of gesture 4 - attempts at suicide
Have you been feeling especially tense this past week? IF YES: Is this more than is normal for you? Have you been unusually argumentative or impatient? Have you been worrying a lot about little things, things you don't ordinarily worry about? IF YES: Like what, for example? How often have you felt this way the past week? Has this caused you any problems or difficulties? IF YES: Like what, for example?	**ANXIETY PSYCHIC** 0 - no difficulty 1 - subjective tension and irritability *(mild, occasional)* 2 - worrying about minor matters (*moderate, causes some distress)* 3 - apprehensive attitude apparent in face or speech (*severe; significant impairment in functioning due to anxiety)* 4 - fears expressed without questioning (*symptoms incapacitating)*

SIGH-D Feb 07

Tell me if you've had any of the following physical symptoms in the past week. (READ LIST) FOR EACH SX ACKNOWLEDGED AS PRESENT: How much has (THE SX) been bothering you this past week? (How bad has it gotten? How much of the time, or how often, have you had it? Did (the symptom) interfere at all with your functioning or your usual activities?) NOTE: DO NOT RATE SXS THAT ARE CLEARLY RELATED TO A DOCUMENTED PHYSICAL CONDITION.	**ANXIETY SOMATIC** (physiologic concomitants of anxiety, such as GI - dry mouth, gas, indigestion, diarrhea, stomach cramps, belching CV - heart palpitations, headaches Resp - hyperventilating, sighing Urinary frequency Sweating): 0 - not present 1 - mild *(symptom(s) present only infrequently, no impairment, minimal distress)* 2 - moderate (*symptom(s) more persistent, or some interference with usual activities, moderate distress)* 3 - severe *(significant impairment in functioning)* 4 - incapacitating
In the last week, how much have your thoughts been focused on your physical health or how your body is working (compared to your normal thinking)? (Have you worried a lot about being or becoming physically ill? Have you really been preoccupied with this?) Have you worried a lot that you had a specific medical illness? Do you complain much about how you feel physically? Have you seen a doctor about these problems? What did the doctor say?	**HYPOCHONDRIASIS** 0 - not present 1 - self-absorption (bodily) (*some inappropriate worry about his/her health OR slightly concerned despite reassurance)* 2 - preoccupation with health *(often has excessive worries about his/her health OR definitely concerned has specific illness despite medical reassurance)* 3 - frequent complaints, requests for help, etc. *(is certain there is a physical problem which the doctors cannot confirm; exaggerated or unrealistic concerns about body and physical health)* 4 - hypochondriacal delusions
RATING BASED ON OBSERVATION DURING INTERVIEW	**INSIGHT** 0 - acknowledges being depressed and ill OR not currently depressed 1 - acknowledges illness but attributes cause to bad food, overwork, virus, need for rest, etc. 2 - denies being ill at all

SIGH-D Feb 07

RATING BASED ON OBSERVATION DURING INTERVIEW	**AGITATION** 0 - none 1 - fidgetiness (*slight agitation or mild restlessness*) 2 - playing with hands, hair, etc. (*moderate to marked restlessness or agitation*) 3 - moving about, can't sit still (*cannot remain seated*) 4 - hand-wringing, nail biting, hair-pulling, biting of lips (*interview cannot be conducted; severe agitation*)

RATING BASED ON OBSERVATION DURING INTERVIEW	**RETARDATION** (slowness of thought and speech; impaired ability to concentrate; decreased motor activity) 0 - normal speech and thought 1 - slight retardation at interview (*mild psychomotor retardation*) 2 - obvious retardation at interview (*moderate; some difficulty with interview, noticeable pauses and slowness of thought*) 3 - interview difficult (*severe psychomotor retardation; very long pauses*) 4 - complete stupor (*extreme retardation; interview barely possible*)

TIME ENDED SIGH-D:	_____
TOTAL HAM-D-17 SCORE:	_____

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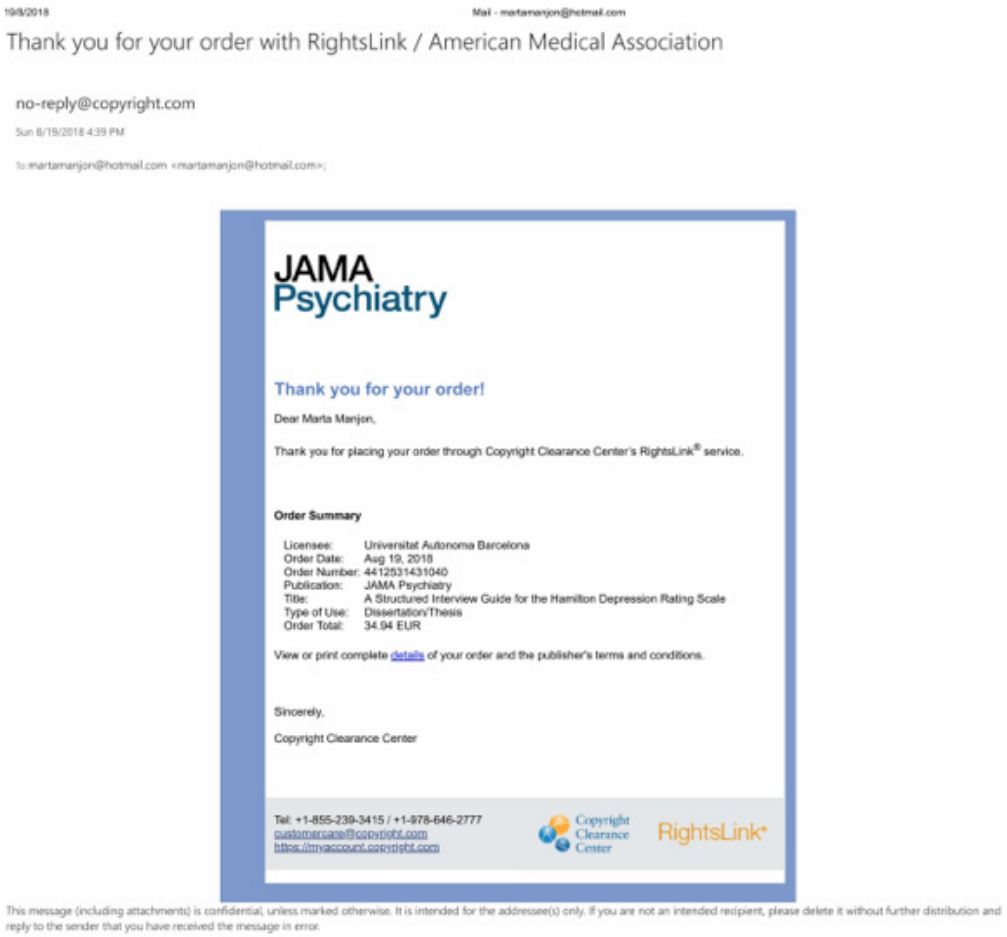

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ANNEX 5 Permission to use Carroll Depression Scale form

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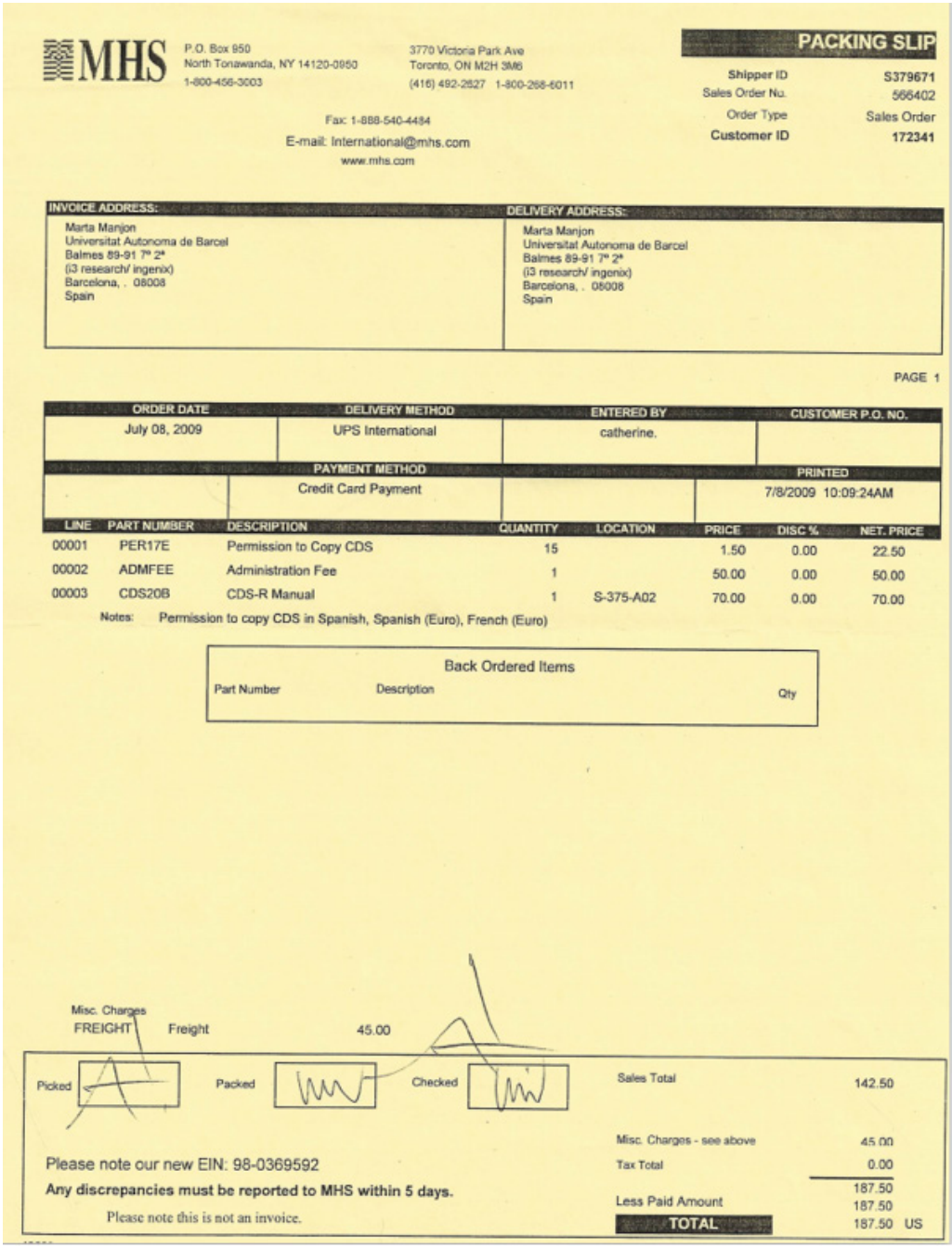

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ANNEX 6 Carroll Depression Scale as provided by the copyright owner (MHS)

CARROLL DEPRESSION SCALES (CDS)
Bernard Carroll, M.B., Ph.D.

Nombre:
Sexo:
Fecha de nacimiento (mes/día/año):
Fecha actual (mes/día/año):

Instrucciones: Conteste a todos los enunciados a continuación marcando con un círculo "sí" o "no" según cómo se ha sentido en los ÚLTIMOS POCOS DÍAS.

1. Me siento con la misma energía que siempre.
2. Estoy perdiendo peso.
3. He dejado muchas cosas y actividades que me interesaban.
4. Desde el inicio de mi enfermedad he perdido por completo el interés por el sexo.
5. Me preocupo de forma especial sobre cómo está funcionando mi cuerpo.
6. Tiene que ser evidente que estoy trastornado y agitado.
7. Todavía soy capaz de sacar hacia delante el trabajo que se espera de mí.
8. Tardo más de una hora en quedarme dormido.
9. Me puedo concentrar con facilidad cuando leo papeles.
10. No tengo descanso y soy inquieto.
11. Me despierto por la mañana mucho más temprano de lo que sería necesario.
12. La mejor solución para mí sería morirme.
13. Tengo muchos problemas con sentimientos de mareo y apenas perceptibles.
14. Mi interés sexual es igual que antes de enfermar.
15. Se me está castigando por algo malo en mi pasado.
16. Soy un desgraciado o muchas veces tengo ganas de llorar.
17. Muchas veces quisiera estar muerto.
18. Tengo problemas de indigestión.
19. Muchas veces me despierto en medio de la noche.
20. Me siento despreciable y me avergüenzo de mí mismo.
21. Estoy tan ralentizado que necesito ayuda para tomar baño y vestirme.
22. Tardo más de lo habitual hasta que me quede dormido por la noche.
23. Durante una gran parte del tiempo tengo mucho miedo pero no sé por qué
24. Las cosas de mi vida de las que me arrepiento me molestan.
25. Lo que hago me produce placer y satisfacción.
26. Todo lo que necesito es un buen descanso para ponerme perfectamente bien de nuevo.
27. Mi sueño es sin reposo y agitado.
28. Mi mente es tan rápida y está tan alerta como siempre.
29. Siento que vale la pena vivir la vida.
30. Mi voz es sin brío y apagada.
31. Me siento irritable o nervioso.
32. Me siento animado.

---

33. Mi corazón bate a veces más rápido de lo habitual.
34. Creo que mi caso no tiene esperanza.
35. Por las mañanas me despierto antes de mi hora habitual.
36. Sigo disfrutando de la comida igual que habitualmente.
37. Tengo que estar dando vueltas durante la mayor parte del tiempo.
38. Estoy aterrizado y próximo al pánico.
39. Mi cuerpo es malo y está podrido por dentro.
40. He enfermado por el mal tiempo que hemos tenido.
41. Mis manos tiemblan tanto que la gente lo nota fácilmente.
42. Me sigue gustando salir y reunirme con gente.
43. Creo que aparento estar tranquilo por fuera.
44. Creo que soy tan buena persona como cualquiera.
45. Mi problema es el resultado de una enfermedad interna seria.
46. He estado pensando en matarme a mí mismo.
47. Últimamente me cuesta hacer cosas.
48. El futuro me deparará sólo miseria.
49. Me preocupo muchísimo por mis síntomas corporales.
50. Me tengo que forzar para comer por lo menos un poco.
51. Gran parte del tiempo estoy agotado/a.
52. Puede afirmar que he perdido mucho peso.
53. Estoy de ánimo decaído incluso cuando me pasan cosas buenas.
54. Este sentimiento es como si alguien muy cercano ha mí hubiera muerto.
55. Por las mañanas es cuando me siento peor.
56. Mi ánimo siempre se levante mucho cuando pasa algo bueno.
57. Mi apetito actual es más de lo que yo realmente quiero.
58. Puedo afirmar que ha ganado mucho peso.
59. Duermo más de lo que realmente quiero la mayoría de los días.
60. Me siento como si estuviera arrastrando un peso y hubiera perdido toda la energía física.
61. He sufrido mucho a lo largo de mi vida porque no se me acepta.

ANNEX 7 Acculturation in Context Measure

This is the Source Data form designed for this study, based on Berry Model and Van de Vijver & Phalet interpretation.

Nombre del Evaluador:_____

Fecha de Evaluación:_____

N° Sujeto

ACCULTURATION IN CONTEXT MEASURE (ACM)
(Van de Vijver & Phalet, 2004)

Pregunta 1: Piensa que (nacionalidad del sujeto *e.g los.marroquíes*) **en España debe mantener su cultura** (cultura del sujeto *e.g. marroquí*)**?**

(4) Completamente

(3) En la mayoría de los casos

(2) Sólo en parte

(1) En ningún caso

Pregunta 2: Piensa que (nacionalidad del sujeto *e.g los.marroquíes*) **en España debe adaptarse a la cultura española?**

(4) Completamente

(3) En la mayoría de los casos

(2) Sólo en parte

(1) En ningún caso

Pregunta 3: ¿Cuántos años lleva viviendo en España? ____ **Años**