Unconjugated bilirubin and acute schizophrenia: a probable correlation?

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Dear Editor,

Plenty of literature has been suggesting a possible relation between elevated unconjugated bilirubin (UCB) and schizophrenia, e.g. schizophrenic patients presented a positive correlation between bilirubin levels and higher scores on positive[1] and negative symptoms[2]. It has also been reported that schizophrenic individuals showed significantly higher UCB levels especially when acutely psychotic[3]. The objective of our study was to assess if high, yet within normal range UCB levels may represent a potential biomarker in the distinction among acute patients with schizophrenia, schizoaffective and bipolar disease.

First we searched in our clinical files for all the individuals tested for total and conjugated bilirubin in a three year hiatus. Secondly we checked their acute psychiatric admissions whenever an ICD10 psychiatric diagnosis of schizophrenia, schizoaffective or bipolar disorder was done. Individuals without known psychiatric diagnosis were our control group.

We were able to include 204 acute patients (50 with schizophrenia, 69 with schizoaffective disorder and 85 with bipolar disorder) and 55 healthy controls. Schizophrenia patients presented higher UCB mean values (0.39 mg/dL, SD 0.16 mg/dL), schizoaffective patients presented intermediate values for UCB mean values (0.36 mg/dL, SD 0.13 mg/dL), while bipolar patients presented lower values for UCB mean values (0.29 mg/dL, SD 0.13 mg/dL). We applied one sample Kolmogorov-Smirnov test to confirm normal distribution for age and UCB in the four groups. Then we applied one way ANOVA test to show a statistically significant difference ($p \leq 0.0001$) between the mean values of UCB. On the post-hoc Bonferroni multiple comparison test there was statistically significant difference between schizophrenic and bipolar patients ($p \leq 0.0001$) as well between schizoaffective and bipolar patients ($p \leq 0.01$). Both schizophrenic ($p \leq 0.0001$) and schizoaffective ($p \leq 0.01$) patients showed statistically significant difference when compared with controls. Regarding a plausible bias on these results we applied a univariate corrected ANOVA model with age and gender as covariates, and found no influence.

UCB mean levels are clearly higher in patients with acute psychotic episodes of the schizophrenia and schizoaffective spectrum, when compared with bipolar patients and healthy controls. Our results are similar to those already described by other groups[4,5] although all our patients were in normal range. The acute schizoaffective patients seem to have intermediate values between acute schizophrenic patients and acute bipolar patients, reinforcing the theory that schizoaffective disorder might be an intermediate clinical entity, somewhere in between the schizophrenic and the bipolar spectra. Yet, these findings cannot determine a causal relationship between higher level of UCB and psychosis. Indeed UCB level may be cause or consequence of a psychotic state. This is one of the highlights of our study that can be used for further investigations looking for a possible relation between UCB mean levels and psychosis severity. Thus we believe that UCB mean levels in normal range, deserves further investigation in psychotic patients.

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Delusional psychosis induced by dopamine agonists in the treatment of Parkinson's disease: four clinical cases

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Dear Editor,

Recent studies have shown a prevalence of psychosis in Parkinson's disease in 13.9% of patients[1], ranging up to 75% depending on the methodology and definition, as well as the population studied[2-4]. There is an association between the dose of antiparkinsonian medication and the presence or severity of induced psychotic symptoms. Dopamine agonists are combined with Levodopa to reduce the dose of antiparkinsonian medication and to improve dyskinesia and motor fluctuations related to its chronic administration. Pramipexole and Ropinirole are non-ergotic dopamine agonists, indicated among the signs and symptoms of idiopathic Parkinson's disease, either alone or combined with Levodopa. Pramipexole is used with a regular dose interval of 1.5-6 mg/day and it stimulates mainly the D_3 receptors of the frontal cortex, midbrain and limbic cortex, but has a lesser effect on the D_1, D_2 and D_4 receptors. Ropinirole is normally used at a dose of 2-8 mg/day (up to a maximum of 24 mg).

Common adverse symptoms to the treatment with dopamine agonists and Levodopa are hallucinations, especially visual ones. Pramipexole, in relation to placebo, has been proven to increase the risk of hallucinations (odds ratio 5.2)[5]. Other potential symptoms may include, although less frequently, delusions, compulsive gambling, increased libido and hypersexuality, among other psychopathologic symptoms and disorders of varying severity[6-9]. The so-called "Dopamine dysregulation syndrome" —DDS— (often associated with an impulsive consumption of dopaminergic agents) generally subsumes several of those clinical conditions, although the cholinergic and serotonergic systems are also implied within. Pramipexole-related psychosis is seldom reported, and it appears to be more frequent among patients suffering from Parkinson's disease than in those with depression.

This work aims to: 1. Signal the causal relation of dopaminergic agents and Levodopa, and more specifically of Pramipexole (Mirapexin®), with induced-psychosis in Parkinson's disease without dementia, due to the shortage of related cases described in specialized literature; and 2. Confirm the evolution of the psychiatric conditions and the effectiveness of the treatment.

Method

A description of a series of four clinical cases consecutively recruited within 19 months, between 2014 and 2016. These patients, suffering from Parkinson's disease, were admitted to the hospital and developed a delusional or hallucinatory-delusional induced syndrome following treatment with dopamine agonists.

All patients were assessed following the Clinician-Rated Dimensions of Psychosis Symptom Severity (CRDPSS) for DSM-5 upon admission, and the extended 35-point Spanish version of the Mini-Mental State Examination (MMSE) —MEC-35— during their hospital stay. Psychopharmacological treatment was discretionary and its effectiveness was assessed following the Clinical Global Impressions -Severity of Illness (CGI-SI) and Global Impressions -Global Improvement (CGI-GI) scales upon admission and discharge. Additionally, in February 2016, we conducted a search on PubMed with the keywords: "(Pramipexole or Levodopa or Ropinirole) and Psychosis", which resulted in 417 articles, only 4 of which mentioned specifically the link between Pramipexole and induced psychosis[6,7,9,10]. There were also very few works mentioning "Levodopa" or "Ropinirole" with "Psychosis" or "Psychotic" in their title.

Presentation of the patients

We analyzed a sample of four patients urgently admitted to hospital; three in the Psychiatry department, and one in neurology (Average=18.75 days; SD=3.49). Two of the patients were male and two female, all between 45-79 years of age, married, with children, not working at the time, and with good social and family support. All four patients were diagnosed with Parkinson's disease, which commenced between 16-1.5 years prior to the current admission date, without any other relevant disorders or psychiatric conditions. Treatment received for Parkinson's disease upon appearance of the psychiatric pathology consisted of: Patient #1: Pramipexole 2.1 mg/day (for 3 years approximately), Levodopa/Carbidopa 100/25 mg/day, and Entacapone 200 mg/day (specific and reversible inhibitor of catecho-O-methyltransferase —COMT—), Dipotassium Clorazepate 5 mg/day.

Patient #2: Pramipexole 1.05 mg/day (for a year), Diazepam 7.5 mg/day. Patient #3: Pramipexole 2.1 mg/day (for 1.5 years), Levodopa/Carbidopa 250/25 mg/day, Ropinirole 2 mg/day. Patient #4: Pramipexole 0.54 mg/day (for 7-8 years) and Levodopa/Carbidopa 400/100 mg/day. In addition, patients 2 and 3 had previously worn Rotigotine patches (also a dopaminergic antiparkinsonian drug), which was removed due to allergic reactions before the appearance of psychotic symptoms.

All patients presented sudden psychotic symptoms, synthesized with further data in Table 1. The severity of the

Table 1 **Patient Characteristics**

		Patients					
		Nº 1	Nº 2	Nº 3	Nº 4	M	DE
	Age (years)	58	65	45	79	61.75	12.28
	Gender	m	m	f	f		
	PD onset (years)	10	3	1,5	16	7.63	5.80
	Treatm. prior to PD	PL , L/C, EC	PL	PL , L/C, RL	PL, L/C		
	PD treatm. upon admission	L/C	-	PL, L/C	-		
	Psychosis onset (months)	4	2	5	1	3.00	1.58
	Hospital admission unit	Ps	Ps	Ne	Ps		
Upon Hospital admission	Auditory hallucinations	-	+	-	+		
	Visual hallucinations	+	+	-	-		
	Delusions	+	+	+	+		
	Escaping from home	+	+	+	-		
	Agitation	+	+	+	-		
	Sexual disinhibition	+	+	+	-		
	Alcohol use disorder	-	+	-	-		
	Compulsive gambling	-	+	-	-		
	Hist. of self-limited psychotic symptoms	-	-	+	+		
	Hist. of alcoholism	+	+	-	-		
	Hist. of compulsive gambling	+	+	-	-		
	Hist. of antiparkinsonian drug overuse	+	-	-	-		
	Final OLZP dose upon admission (mg)	5	20	-	15	13.33	6.24
	OLZP dose upon discharge (mg)	5	10	-	10	8.33	2.36
	OLZP removal upon discharge (months)	2	-	-	-		
	PD last treatm. upon discharge	L/C	L/C	PL	-		
	Psychosis evolution upon discharge	remissio	improvement	remissio	improvement		

Av.: average; EC: entacapone; f: female; Hist.: history; L/C: levodopa/carbidopa; m: male;Ne: neurology; OLZP: olanzapine; PD: Parkinson's Disease; PL: pramipexole; Psych. clin.: psychiatric clinic; Ps: psychiatry; RL: ropinirole; SD: standard deviation; Treatm.: treatment; +=yes; -=no

psychotic symptoms was measured upon admission to hospital following the CRDPSS, with scores of 14, 12, 11 and 11 respectively, (Average=12.2, SD=1.22; highest possible individual score=32). According to the MMSE, none of the patients presented clinically significant cognitive impairment, with scores >27.

Therapeutic intervention

See summary in Table 1. Patients 1, 2 and 4 were advised to discontinue treatment with Pramipexole. Patient 4 also stopped treatment with Levodopa/Carbidopa, but no changes were conducted for patients 1 and 3. It was not necessary to introduce other antiparkinsonian medication in any of the cases. Patients 1, 2 and 4 were advised to take 5-20 mg/day of Olanzapine during their hospital stay. Patient 3 did not require the addition of antipsychotic drugs. All patients presented a positive development upon hospital release, both with regards to Parkinson's disease, assessed by a neurologist, and to the psychotic symptoms. Patients 1 and 3 showed remission of psychosis, while 2 and 4 demonstrated clinically significant improvement. All four patients presented CGI-SI and CGI-GI values upon hospital admission and discharge of: 6-1; 6-2; 5-1 y 6-2, respectively. During follow-up visits after hospital discharge, eighteen months for patient #1 and three months for #4, none of them required a new hospitalization. Patient #1 was advised to discontinue treatment with Olanzapine at 2 months after being discharged, but continued the same treatment with antiparkinsonian drugs. #2 and 4 continued treatment with Olanzapine after being discharged, at a dose of 10 mg during their 15 and 3 follow-up months, respectively. Patient #2 continued to take Levodopa/Carbidopa on an outpatient basis, and #3 maintained only treatment with Pramipexole. Patient #4 was not introduced any antiparkinsonian medication. Patients 1 and 2 required antidepressants for a few months, which were initiated during or immediately after discharge, due to anxiety-depressive symptoms of subsequent remission.

Psychiatric differential diagnosis

Upon hospital admission, all patients presented severe delusional psychotic disorder or hallucinatory-delusional, induced by antiparkinsonian medication. The psychiatric diagnosis for all patients is coded as F19.56 (ICD-10, research criteria), F19.959 (ICD-10-CM, DSM-5) or 292.9 (ICD-9-CM). There is no concomitant "antiparkinsonian-use disorder" (which would be coded 304.90 by ICD-5 or F19.1 by ICD-10) because none of the patients showed addictive behaviors, such as lack of consumption control, upon hospital admission (although patient #1 did, one year earlier).

Discussion

Our patients' psychopathologic symptoms (described above), appeared following treatment with Pramipexole combined with Levodopa or Ropinirole. It has been proven through positron emission tomography that Pramipexole diminishes cerebral blood flow in the bilateral frontal cortex, mainly in the right hemisphere[11]. Therefore, stimulation of receptors D_3 in the right frontal lobe could cause blood hypoperfusion and be the base for the development of psychotic symptoms similar to those that appear in injuries of the right frontal lobe[12]. This matches the findings of structural lesions in patients with delusions, mostly located in the right hemisphere[13].

Impulse control disorders are well-defined secondary effects to the treatment with dopaminergic antiparkinsonian drugs and Levodopa, and are generally easily detected in the clinical practice. However, psychotic episodes are a rarely-communicated complication and might not be taken into consideration during the usual clinical neurological interview. In general, interruption or reduction of treatment with antiparkinsonan drugs causes a complete reduction of the psychotic symptomatology, as occurred with patient #3. However, sometimes it is necessary to prescribe atypical antipsychotics, with fewer motor functions repercussions, although they may worsen them[14]. In the near future, the therapeutics of these psychoses could change, with new drugs like Pimavanserin, a selective inverse agonist of the 5HT2A receptor, which does not affect the dopaminergic, adrenergic or muscarinic functions. Pimavanserin has recently been approved by the U.S. Food and Drug Administration for treatment of Parkinson's disease-related psychoses[15].

Of the three patients who received antipsychotic drugs, none suffered associated dementia. All three were exclusively treated with Olanzapine, which was discretionally prescribed by two different psychiatrists, without prior agreement. Low doses of Clozapine are an effective treatment for those induced psychoses[16], but its use is limited due to risk of agranulocytosis. Olanzapine, however, shows similar receptorial affinity to Clozapine, with selective antipsychotic activity on mesolimbic functions, resulting in low levels of extrapyramidalism. According to its fact sheet and subsequent studies[17,18], and used at a dose of 2.5-15 mg/day, Olanzapine is not recommended for treatment of parkinsonian dopaminergic psychosis (with or without Parkinson's disease-related dementia) due to the possibility of it worsening parkinsonian symptoms and hallucinations. According to the authors[19], a 2.5 mg/day dose of Olanzapine has proven to be ineffective in the treatment of psychotic symptoms; however, in the revision of Durán et al.[20] Olanzapine did prove effective. Finally, a dose of about 120 mg/day of Quetiapine does not worsen motor parkinsonian symptoms, but it is barely effective with regards to the psychotic symp-

toms[21], and if increased to the usual antipsychotic dose of 300-450 mg/day, it could become excessively sedative to some patients. There is even more limited experience with the other atypical antipsychotics. Our patients were prescribed Olanzapine at a dose of 5-20 mg/day, higher than other authors[19], with effective results (either remission or significant clinical improvement) and high tolerability, even on the oldest patient. Assessing the repercussion of treatment with antipsychotic drugs on the patients' motor symptoms and signs was not among the objectives of this study; therefore, these factors have not been monitored. Nevertheless, most of our patients were prescribed less antiparkinsonian drugs in the follow-up visits after hospital discharge than during their hospitalization (except for patient 4, who did not receive any).

Our results support the causal link between Pramipexole and other dopamine agonists with induced psychosis in Parkinson's disease, as well as the positive response to Olanzapine at a ranging dose of 5-20 mg/day.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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Comorbidity of autism spectrum disorder and bipolar disorder

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Letter to the editor

Dear editor,

Patients with Autism Spectrum Disorder (ASD) may show aggressive behavior, irritability, or self-harm. Although these do not represent core symptoms of the disorder, they are associated with alarm and significant functional implications. These behaviors are often attributed to autism itself and consequently are not followed by specific therapeutic interventions, being conditioned by the lack of effective pharmacological approaches for ASD. In this context, it is important to consider that the emergence of behavioral changes in patients diagnosed with ASD may reflect the occurrence of other comorbid mental disorders whose early identification and treatment will be of great benefit to ASD patients[1].

This paper presents the case of a 17-year-old patient diagnosed with Asperger Syndrome in childhood who developed Bipolar Disorder type I (BD) nine years later. The aim is to review the comorbidity of both disorders and discuss their relevance to making a differential diagnostic to guide treatment.

Clinical case

The patient required hospitalization so that disruptive behavior with aggressive episodes against people could be studied. These had been having serious repercussions in the family, social functions, and school in the preceding few weeks without a trigger being detected. Her emotional self-regulation problems significantly worsened in the preceding few months with irritability and a noticeable tendency to be extrapunitive. Her attitude was correct and cooperative during the inpatient assessment, she showed good personal grooming, dressing smartly, and made appropriate and syntonic visual contact. She was overalert. She emphasized precise speech, tachylalia, and was garrulous, talking with a high pitched and pedantic tone of voice, using language very rich in detail as well as scientific terms. Tachypsychia, her speech was difficult to interrupt with lax associations and a tendency to wander off the subject. She had remarkable emotional labiality, and was hyperthymic, dysphoric, and irritable at times. She expressed a feeling of well-being, felt she had improved her abilities, and that her self-concept had also improved, "*she felt that she was a popular girl at school last year, with many friends, very happy, with a different social status, she did not understand very well how it had happened*". She denied anxiety. She denied self-referential or delirious ideas, and sensoperceptual alterations. She described global insomnia and loss of structured meal times. She recognized a certain "lack of control", but she denied changes in behavior and aggressive behavior. The medical assessment showed a general analysis without remarkable alterations, her urine was negative for toxins, and there were no significant findings in the cranial magnetic resonance. The psychological assessment administered the Young Mania Rating Scale on which she scored 43, and her Global Assessment of Functioning Scale score was 35. Furthermore, the Wechsler Adult Intelligence Scale was administered (WAIS-III) with the following main results: Verbal Understanding 130, Perceptive Organization 100, Work Memory 105, Processing Speed 130. Global Intellectual Capacity was not interpretable.

The patient has no remarkable medical or toxicological medical history. She was an only child, born of a controlled pregnancy without complications. Correct psychomotor development with age. She was a calm girl, excelling in learning, showing pedantic, elaborate, prosodic, and adult language. She also has rigid behavior, with problems accepting changes to routine. She had problems being understood with peers, understanding the feelings of the others, and empathizing. She had a small circle of friends, preferring the company of adults. They report her interests have been restricted ever since first childhood. Previous academic results were good, she attended first grade at high school. Furthermore, they describe irregular dream patterns and disruptive behavior with aggression towards her parents from early childhood, which resulted in psychiatric examinations diagnosing Asperger Syndrome. The diagnosis of autism has remained until the time of writing, deficiencies in social communication persisting as well as repetitive behavior patterns and restricted interests according to DSM-5 criteria diagnoses. In addition, she presented episodes characterized by exacerbation of cognitive rigidity and disruptive behavior as well as greater irritability, a decrease in her habitual activities and greater keenness for restricted interests, compatible with depressive or mixed episodes that were spontaneously self-limiting or required referral for psychotherapeutic treatment.

Regarding family history of psychiatric disorders, there was a depressive disorder in a first degree relative and schizophrenia and an abuse disorder in a second degree relative. No report of a family history of bipolar disorder.

The inpatient confirmed persistent evolution of the mind with symptoms characteristic of mania, which oriented the diagnosis towards manic episodes without psychotic symptoms. The treatment was composed of antipsychotic and mood-stabilizing drugs, with good tolerance and gradual disappearance of affective symptoms until the state of euthymia was achieved. Notable cognitive rigidity, extrapunitive speech, and absence of introspection about aggressive episodes persisted. The discharge diagnosis was autism spectrum disorder (Asperger's syndrome) and bipolar disorder type I. The treatment was 30 mg per day aripiprazole and 1300 mg per day valproic acid (89.4 µg/mL valproatemia).

At the six-month follow-up she had maintained euthymia by sticking to her pharmacological treatment. However, the persistence of autistic difficulties in numerous areas was observed during the examinations, such as social comprehension

and interaction, interpersonal relationships, empathy, identification of her own feelings and the feelings of others, changes of routine, pedantic language, and restricted interests. These problems conditioned inappropriate emotional expressiveness and emotional management, entailing common misunderstandings and her adopting extrapunitive, confrontational, and victim attitudes as well as disruptive behavior as a response to frustrations that she still does not fully recognize.

Discussion

Studies carried out in recent years confirm the existence of strong psychiatric comorbidity in ASD[2]. A recent review of the case in question stated that the average prevalence of comorbidity with BD is 7%, with variations of 2% to 31%[3-8], which suggests that BD is one of the psychiatric comorbidities most commonly associated with autism.

BD manifests in patients with ASD earlier than in the general population, mania occurs with increased irritability, aggressive behavior, and symptoms of grandiosity. On the whole, the comorbidity of both disorders involves a psychopathological state of great severity and functional impact, which reinforces the importance of early diagnosis[9-12]. There are factors that hinder this differential diagnosis[13]. Firstly, the emerging symptoms tend to be attributed to ASD without other comorbid disorders being considered. Symptoms are often masked and confused with the characteristic symptoms of autism. Furthermore, it frequently manifests subtly, without well-defined symptoms being expressed until later, when affective symptoms appear. In addition, the autistic patient's reduced capacity for abstract thought and their poor communication skills, mood swings, and changes in emotions or feelings contribute to this difficulty[14].

Several studies have shown a high prevalence of affective disorders in relatives of ASD patients, postulating a direct association between the presence of this background and comorbility with BD[3-5,15]. Family genetic studies have suggested a shared genetic vulnerability between the bipolar and autistic spectrum, supported by how highly heritable both disorders are[11].

Possible clinical indicators of comorbidity between BD and ASD have been listed. First, there is the deterioration of the patient's overall functioning, and a worsening of autism symptoms or behavioral problems already present such as aggression, which become more intense, varied, or disruptive. Then there is the appearance of heterogeneous affective symptoms such as the tendency to become impassioned when speaking about things of interest, things that irritate, to be hyperactive, use expressive speech, or suffer sleep disorders. Note that depressive phases can condition a significant reduction in usual activities. Finally, the presence of Bipolar Disorder or another affective disorder in medical history of first degree relatives should be recalled[1,16-18].

The problems diagnosing this comorbidity often mean many cases are not treated correctly, and make the evolution worse. The few studies in literature about the treatment of comorbid BD and ASD have found that pharmacological treatment improves the clinical picture and the overall functioning of the subject with this comorbidity[1,2]. Previous studies have explained that mood stabilizers (especially lithium but also valproic acid) can be effective and safe in treating mania in ASD patients[19-22]. More recent studies also confirm the good tolerance of and clinical response to atypical antipsychotics[23,24]. Finally, note that the evaluation of the result of treatment should separate BD clinical improvement from nuclear autism symptoms[25].

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Preliminary versions of the chapter on mental disorders of the ICD-11

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Dear Editor,

The approval of the 11th edition of the International Classification of Diseases (ICD-11) by the World General Assembly is scheduled at the moment in May 2018.

The following sections will be included in the chapter: neurodevelopmental disorders; schizophrenia and other primary psychotic disorders; mood disorders; anxiety and fear-related disorders; obsessive-compulsive and related disorders; disorders specifically associated with stress; dissociative disorders; bodily distress disorders; feeding and eating disorders; elimination disorders; disorders due to substance use; impulse control disorders; disruptive behaviour and dissocial disorders; personality disorders; paraphilic disorders; factitious disorders; neurocognitive disorders; and mental and behavioural disorders due to disorders or diseases classified in other chapters of the system.

Conditions related to sexual health and sleep-wake disorders will appear in chapters of the classification different from the one on mental disorders. This has been decided in order to address the criticism to the ICD-10 concerning the problematic distinction between "organic" and "non-organic" sexual dysfunctions (covered in the ICD-10, respectively, in the chapters on diseases of the genitourinary system and on mental and behavioural disorders) and between "organic" and "non-organic" sleep disorders (covered in that system, respectively, in the chapters on diseases of the nervous system and on mental and behavioural disorders).

Sexual dysfunctions are currently proposed to be subdivided in the ICD-11 into four main groups[1-3]: sexual desire and arousal dysfunctions; orgasmic dysfunctions; ejaculatory dysfunctions; and other specified sexual dysfunctions. ICD-10 gender identity disorders will be reconceptualized as "gender incongruence", and also included in the chapter on sexual health. An explicit recommendation has been made to delete the ICD-10 categories related to sexual orientation from the ICD-11.

The final version of the ICD-11 clinical descriptions and diagnostic guidelines will contain, for each disorder[4]: a) a short definition (100-125 words); b) inclusion and exclusion

terms; c) a description of those characteristics that a clinician could expect to find in all cases of the disorder ("essential features"); d) information about "boundary with normality" (i.e., the differentiation between that given disorder and some "normal" conditions); e) guidance about the differential diagnosis with other disorders; f) a list of codable qualifiers and subtypes; g) a description of the typical course of the disorder; h) a list of clinically relevant conditions frequently associated with the disorder ("associated clinical presentations"); i) culture-related characteristics; j) a description of how the disorder may appear differently at various developmental stages, including childhood, adolescence and old age; l) gender-related characteristics.

For all the above-mentioned sections of the chapter on mental disorders, a draft of the clinical descriptions and diagnostic guidelines has been produced by the corresponding Working Groups[5]. A shortened draft of the guidelines has been developed for each disorder in order to be used in ICD-11 field studies. This draft includes a short definition, a description of the essential features, information about the boundary with other disorders and with normality, and a description of the most common associated features. Qualifiers or subtypes are also provided for some of the conditions[6]. This shortened version is currently available for schizophrenia and other primary psychotic disorders, mood disorders, anxiety and fear-related disorders, disorders specifically associated with stress, and feeding and eating disorders. For all the other sections of the classification, a brief general definition and in some cases a description of the individual disorders can be found on the ICD-11 beta platform[7].

All these products should not be considered as definitive[4], and the World Health Organization (WHO) welcomes comments and suggestions from the field. In order to collect them, the WHO has created an Internet platform called GCP.Network, to which all the members of the Global Clinical Practice Network can have access. This Network is open to all mental health or primary care professionals who are authorized to provide services to people with mental disorders in their countries. At present, the Network consists of more than 12,500 mental health and primary care professionals from almost 150 countries, of whom more than half are psychiatrists (please visit the website http://gcp.network to register in any of nine languages, including Spanish)[6].

Internet-based and clinic-based field studies of the draft of the ICD-11 clinical descriptions and diagnostic guidelines are now ongoing[8,9]. Internet-based field studies are based on a case vignette methodology and aim to explore clinical decision-making concerning the proposed ICD-11 guidelines; they are being conducted through the Global Clinical Practice Network. Clinic-based field trials are intended to assess the reliability and utility of the proposed ICD-11 guidelines in ordinary clinical settings, and are being carried out through the WHO Network of International Field Study Centres.

This is the first time that the clinical utility of a psychiatric classification is being explored systematically. It is to be noted that clinical utility has been identified as a primary aim of the previous versions of the ICD as well as of the DSM-III and its successors, and has been repeatedly regarded as the highest priority in diagnostic systems[10-13].

In all sections of the ICD-11 draft, it is usually avoided to use, in the description of the essential features of the various mental disorders, the precise thresholds concerning number and duration of symptoms which appear in the DSM-III and its successors. Indeed, the aim of the guidelines is to reflect the way psychiatrists ordinary make diagnoses in clinical practice, i.e., by the exercise of clinical judgment.

At the moment, the possibility is being considered of an interaction between the process of revision of the ICD and the development of the Research Domain Criteria (RDoC) project by the US National Institute of Mental Health[14,15]. In fact, the main objectives of the two projects (respectively, improving the clinical utility of psychiatric diagnoses and exploring in an innovative way the etiopathogenetic underpinnings of mental disorder) can be considered complementary, and an effort can be made to narrow the current gap between the RDoC domains and the phenomena that psychiatrists encounter in their clinical practice, especially in the field of psychoses.

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