

### Severe clozapine-induced agranulocytosis: successful treatment with G-CSF and rechallenge of clozapine plus D2 potentiation therapy (amisulpride)

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Dear Editor,

As is well known, clozapine, the antipsychotic of choice in treatment-resistant schizophrenia, has an incidence of agranulocytosis that is slightly less than 1%<sup>1-4</sup>, although there are marked epidemiological differences between populations. Higher incidences, associated with certain HLA genotypes, have been described in Scandinavian countries than in Southern European countries, including Spain.<sup>5</sup> Thus, during 5 years of follow-up of a cohort of 271 patients treated with clozapine in Spain, the incidence of benign leukopenia was only 1.3% and no cases of agranulocytosis were described.<sup>5</sup>

We present the case of a 46-year-old man diagnosed with treatment-resistant schizophrenia with a continuous course treated with 600 mg/day of clozapine and benzodiazepines for the last two decades, with reasonably satisfactory clinical control and not requiring hospitalisation during this period. As a result of a slight increase in the dose due to an acute exacerbation of the symptoms, he started to present a slow but progressive decrease in the WBC count, initially developing non-symptomatic leukopenia and granulocytopenia (leukocyte values of 2,500-3,500/mm<sup>3</sup> and neutrophils 500-1,000/mm<sup>3</sup>). It was decided that treatment with clozapine should be maintained and a risk-benefit assessment carried out. Closer haematological monitoring was instigated, with an exhaustive screening by Haematology for other non-pharmacological aetiologies of leukopenia, including a bone marrow biopsy. After 6 months the patient developed severe symptomatic agranulocytosis, with a leukocyte count of 1,400/mm<sup>3</sup> and neutrophil count of 20/mm<sup>3</sup>, fever of 39°C and impairment of his general condition, for which he was admitted immediately to Internal Medicine with a diagnosis of febrile neutropenia. While in hospital, the patient was monitored jointly by Internal Medicine, Haematology and Psychiatry. Clozapine treatment was

withdrawn, isolation precautions applied, and antibiotic therapy initiated with ciprofloxacin + amoxicillin (source of the fever: a superficial inguinal wound. Enterococcus Faecalis, Pseudomonas Aeruginosa and coagulase-negative Staphylococci were isolated in the exudate). The antibiotic treatment resolved the infection satisfactorily in 2 weeks and Psychiatry prescribed treatment with amisulpride 800 mg/day during hospitalisation. The haematologist initiated treatment with parenteral G-CSF (Granulocyte Colony-Stimulating Factor) at an initial dose of 150 mcg/day. After being discharged from hospital, the patient continued with this therapeutic regimen (800 mg/day of amisulpride + G-CSF at the above-described doses), with frequent check-ups by both departments. Upon discharge the patient presented partial recovery of bone marrow function, with a leukocyte count of 2390/mm<sup>3</sup> and a neutrophil count of 460/mm<sup>3</sup>.

Two months after he was discharged from hospital, when blood tests showed complete bone marrow recovery (leukocyte count of 4,500/mm<sup>3</sup> and neutrophils 2,450/mm<sup>3</sup>), an acute exacerbation of schizophrenic symptoms was observed in the psychiatric evaluation: reappearance of experiences of influence on corporeality, feelings and voluntary action, greater frequency and affective-behavioural impact of auditory pseudo-hallucinations, greater pressure from his chronic delusional system of sexual and mystic-religious themes, phenomena of transitivity and loss of ego boundaries, significant psychotic distress and insomnia. At that point it was decided that a clozapine-D2 augmentation strategy should be followed, with clozapine re-challenge and slowly titrating the dose up to 200 mg/day while maintaining the 800 mg/day of amisulpride. This combination has been endorsed by various studies.<sup>4,6,7</sup> After 6 weeks the psychotic symptoms were under control and only the chronic delusional issues and sensory processing disorders remained, both with much less pressure. The transitivity, influence phenomena and insomnia also disappeared, and the patient returned to his premorbid level of functioning. After a further 12 months of follow-up, the patient remained psychopathologically stable with bone marrow function and leukocyte and neutrophil counts within the normal range. He was receiving antipsychotic maintenance treatment with 200 mg/day of clozapine +800 mg/day of amisulpride and haematological treatment with 150 mcg/week of G-CSF.

### Discussion

Severe clozapine-induced agranulocytosis is extremely rare in our community. The few cases described usually occur during the first 8 weeks of treatment, and it is extremely rare for it to occur with a slight increase in the clozapine dose (an additional 100 mg) after two decades of treatment,

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as was the case of our patient. In a Finnish cohort in follow-up for 25 years<sup>8</sup> in which 163 cases of agranulocytosis were described, less than 5% of the cases occurred after the 2<sup>nd</sup> year of treatment (late onset agranulocytosis), and only one case developed agranulocytosis after 20 years of treatment. This undesirable effect has repeatedly been related to genetic susceptibility involving certain HLA subtypes.<sup>3,9-12</sup> Thus, a recent pharmacogenomic study in the Japanese population related 50 cases of clozapine-induced agranulocytosis to HLA-B\*59.<sup>10</sup> Another similar study in the United States described an association with single amino acid changes in HLA-DQB1 (126Q) and HLA-B (158T)<sup>3</sup> and also studied the cost-effectiveness of HLA genotyping (approximately 700 US dollars); they concluded that the cost-effectiveness of systematic genotyping is questionable. Another similar paper<sup>11</sup> describes identical high-risk HLA subtypes, stating that the treatment and clinical management of agranulocytosis must be established on an individual basis. Lastly, Athanasiou et al.<sup>12</sup> also found a single nucleotide polymorphism in HLA-DQB1 (specifically 6,672G>C), which is associated with a 16.9-fold increased risk of developing clozapine-induced agranulocytosis.

As regards the clinical management of this serious side effect, an increasing number of papers endorse the efficacy of G-CSF (Granulocyte Colony-Stimulating Factor) as treatment<sup>13-17</sup> and even as preventive treatment in compensated patients with clozapine and low WBC counts.<sup>13,14,18</sup> In the latter case (benign asymptomatic neutropenia), combination with lithium may also be an alternative,<sup>19,20</sup> as there tends to be an increase in WBCs with lithium.

Subsequent clozapine re-challenge is a controversial issue, on which there is no agreement, and very few cases of re-challenge are described in the literature. Therapeutic management must be established on an individual basis, carrying out a benefit-risk assessment and monitoring in collaboration with Haematology. If re-challenge is undertaken, as in the case of our patient (very good previous response), very slow retitration of clozapine with maintenance treatment with G-CSF and close haematic monitoring may be successful, as can the use of D2 (amisulpride) augmentation strategies with a reasonable neurochemical basis,<sup>4,6,7</sup> which allow the dose of clozapine to be reduced. Haematology recommended that our patient should continue treatment with G-CSF at decreasing doses for 18 months until it was completely withdrawn, although complete bone marrow recovery took place in the 8<sup>th</sup> week. This is longer than the period reported in the systematic review by Lally et al. (average 7 days until recovery of bone marrow function).

Finally, by way of a conclusion, it should be stressed that the use of clozapine cannot be delayed due to rare ad-

verse reactions such as the case described, since the therapeutic benefit usually far outweighs the risks. In this regard, our group<sup>21</sup> has successfully used clozapine in treatment-resistant schizophrenic patients with severe leukopenia due to HIV (total count of 601 leukocytes/mm<sup>3</sup>), which is consistent with what other authors have reported.<sup>15</sup>

### ETHICS

We obtained the informed consent of patient and family for all diagnostic and therapeutic procedures, according with the World Medical Association ethics lines and Helsinki Declaration.

### CONFLICT OF INTERESTS

The present article has been designed for all authors without ethics, economics or other ones conflicts of interests. All authors have been a participation in the elaboration of the work, and they can take a complete public responsibility of it. S. Ruiz-Doblado had acted as speaker for Eli-Lilly, Janssen-Cilag, Astra-Zeneca, Otsuka Pharmaceuticals, Pfizer, Ammirall, Servier, Sanofi y Lundbeck; he had obtained copyright payments of Elsevier, acting also as consultant for Health-Care Advisory Board (Canadá) and Leadphysician (UK); and acting as referee for Rev Esp Salud Pub, C Med Psicosom, Psicosomática y Psiquiatría, BioMed Central, JEADV, Clin Drug Invest and Israel Science Foundation. B. Plasencia-García de Diego acts as speaker for Janssen-Cilag, Lundbeck, Sanofi, Pfizer and Servier. R. Perea-Pérez acts as speaker para Lundbeck. F. Jiménez-Gonzalo has not interest-disclosure.

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### Possession Phenomena: a Case Report

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Dear Editor,

Cultural diversity and its influence in mental health is an increasingly relevant issue in our daily practice. Clinicians

increasingly treat patients from culturally, socially and linguistically different backgrounds, with diverse expressions of discomfort. Our patients' beliefs and culture affect their perception of mental illness, coping strategies and treatment seeking patterns<sup>1,2</sup>. A better understanding of these phenomena contributes in a better therapeutic alliance, more accurate diagnoses and increases treatment compliance<sup>3</sup>.

Abnormal spiritual experiences are common among the general population and most of them are not related to a psychotic disorder<sup>4</sup>. The 'Possession' phenomenon is considered the most prevalent culture-bound syndrome<sup>5</sup>, although this vision is not exempt from controversy either: some research suggests that it is a predominantly dissociative disorder, and not really culture-bound<sup>6</sup>. The term 'Possession' indicates that an individual has been invaded by an alien spirit or other paranormal force, which controls the person or at least significantly modifies his or her actions and identity to a greater or lesser extent. This manifests itself as an

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altered state of consciousness. It is accepted that a possession state must be considered pathological when it occurs involuntarily and/or causes significant discomfort for those suffering it or for their environment.

In DSM-IV (RT) possession and trance were classified under Appendix B – Research criteria for dissociative trance disorder<sup>7</sup>. This edition of the manual and in particular its classification of 'Culture-bound Syndromes' received many criticisms over its universalizing approach to the classification and diagnosis of mental disorders. In DSM-5 some changes were introduced, emphasizing that culturally appropriate possession states must be distinguished from dissociative identity disorder<sup>8</sup>. However, this binary view of possession remains excessively simplistic for many<sup>9</sup>.

Ritual elicitation of altered states of consciousness, particularly those associated with possession, is found in more than 450 societies around the world<sup>10</sup>. In Western countries is common among Pentecostalism, Catholic Charismatics, African American religions, Spiritualism and Spiritism cults<sup>11</sup>.

Hereby we present the case of a patient who presented a possession phenomenon as the main nosological entity.

### Case Report

The patient is a 41-year-old woman, born and raised in Bolivia, single and the mother of a 19-year old son. She was taken to the emergency department for a sudden onset alteration of the behavior including self and hetero-aggressive behavior of 12 hours of evolution. She reported having been possessed by the Holy Spirit and with great anguish announced the coming of the apocalypse. She had no relevant somatic or psychiatric history, nor reported recent or past toxic consumption.

The patient was born in a rural region of Bolivia. She recounted a happy childhood without significant trauma, becoming pregnant with his first and only son at 22, with whose father she has no relationship. At 27 she moved to Spain for work purposes. At the time of migration, the patient did not have any family or friends in Spain. Here she had worked as a saleswoman with good work performance, and had reunited with her son four years ago after he moved to live with her in Spain. She belonged to the Evangelical Christian cult and defined herself as a very religious and spiritual woman, with great participation in the evangelical community of her current place of living. Almost all of her social circle in Spain was made up of other people belonging to her church.

With regard to the current episode, the patient's son reported that the patient had abruptly woken up with fearful attitude, recounting having been possessed and announcing the imminent coming of the end of the world. She presented unmotivated crying and laughter outbursts as well as aggressive behaviors towards herself and her environment. The patient's son took her to the church where they regularly worshiped "to help her in her possession spell" [sic]. There, the evangelical pastor prayed together with several parishioners with the aim to help the patient's state. 8 hours later, in the absence of improvement, decided to transfer her to the emergency department.

Upon initial examination the patient was found to be conscious, partially connected to the environment, poorly collaborative. She obeyed simple orders in a fluctuating manner, interspersing a speech sparing with words with laughter and crying outbursts, as well as constant verbalizations of religious nature. She presented significant psychomotor agitation. Again, she referred to having been possessed by the Holy Spirit. Follow-up testing, including drug tests, were completely normal. Hospital admission was decided.

At the psychiatry ward the patient remained accompanied by her son and a close friend of hers, who was also a parishioner in her church. They both spent the following hours praying for her well-being. The patient presented a rapid improvement and mechanical contention could be removed within a few hours. She remained behaviorally adequate with only anxiolytic treatment. Two days later she was able to perform a full critique of the episode, recounting partial amnesia and spontaneously identifying a couple breakup as a possible trigger. At the time of discharge, she reported feeling "relieved" after the episode of possession, with marked improvement of the subdepressive symptoms she had presented after the breakup.

The patient was diagnosed with Unspecified Dissociative Disorder [DSM-5 300.15]. The main differential diagnosis taken into account was a psychotic disorder, later ruled out in the absence of a structured delusion, the course of the episode and its complete resolution without neuroleptic treatment. The patient's son recounted having witnessed similar possession episodes among other members of their church, relating them to especially stressful situations.

Patient's evolution has been good, without requiring psychopharmacological treatment after discharge and having now resumed her everyday life.

### Discussion

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In some communities it is common to attribute unusual events or experiences (such as a state of anxiety or depression) to a state of possession. Beliefs about possession phenomena are frequent and should not be considered automatically as part of a psychotic disorder. This implied the need to exercise caution when establishing neuroleptic treatment, particularly in the medium and long term.

On the other hand, it is important to assert the baseline level of spirituality of the patient and his or her community, collecting a spiritual history<sup>12</sup>. There are instruments validated for this purpose, among which the FICA Questionnaire (*Faith, Importance, Community and Address*) stands out. It only takes 5 minutes to administer and it addresses four relevant domains regarding the relationship between spirituality and health<sup>13,14</sup>.

The approach to these symptoms should be as suited to the patient's culture as possible. In many cases ritual cures – along or in combination with conventional treatment – are effective. Current literature supports an integrated approach to culture and a greater education in cultural issues among staff<sup>1,3</sup>.

In conclusion, possession states are an entity described in most cultures and societies of the world. Most of them are not related with psychotic disorders. Before a state of possession, clinicians should consider all the biopsychosocial, cultural and spiritual aspects of the individual. A better understanding of cultural differences is crucial in mental health because of its relevance to the perception and significance of symptoms, the development of accurate diagnoses and the prescription of appropriate treatments.

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Pica: obsessive-compulsive spectrum disorder,  
recurrent depression or eating disorder?

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Dear Editor,

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2012)<sup>1</sup>, pica is a disorder characterized by the persistent ingestion of non-nutritive and non-food substances over a period of at least one month and not associated with an aversion to food. The eating behaviour is inappropriate to the developmental level of the individual and not as part of a culturally or socially normative practice<sup>2</sup>. If pica occurs in the context of another mental disorder, a separate diagnosis

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of pica should be made when the eating behavior is severe enough to require specific clinical attention.

Pica is frequently associated with intellectual disability; however, it has been described in individuals of all ages and in both sexes, in particular in children and pregnant women<sup>3</sup>. In some cultures, pica is considered normal and even a therapeutic behavior, not adjusting to the definition of DSM-5<sup>4</sup>.

It is more common in childhood, especially in children with nutritional deficits<sup>5</sup>, psychosocial stress, maternal deprivation and complex family problems<sup>6</sup>. In adults, pica is associated with pregnancy<sup>7</sup>, intellectual disability, psychotic disorders<sup>8</sup> and even recurrent depression and masked depression<sup>9</sup>. However, its exact prevalence in adults is unknown and there is no literature on pica as an individual entity.

Thus, a deeper study to classify this disorder correctly could contribute to greater understanding and therefore better approach to it.

### Case report

We present the case of a 43-year-old woman who was referred from primary care for mental health assessment because of a long-term evolution of eating wall plaster. She is of Latin American origins but has been living in Spain for more than 10 years.

As personal background, she was abandoned by her parents shortly after birth, being raised by her maternal grandmother. At the age of six, she went to live in a boarding school and began to eat pieces of wall plaster daily.

Her family psychiatric background is unknown. As medical history, she suffers from iron deficiency anemia which was being treated with iron at the time of her visit to our mental health center. From the age of 18 she has a tendency to iron deficiency anemia, remitting when treated with iron. She has never been to a mental health center.

On the first visit, she reported that she began eating wall plaster in childhood and since then has maintained the habit. Initially, she did it as an imitation of other girls from the boarding school where she lived, since they spent a lot of time alone without adult supervision. Later, she maintained this behavior because she felt pleasure and relief from anxiety or feelings of loneliness. Afterwards, she maintained this behavior daily both as a habit and as anxiolytic. In recent years, she eats plaster more compulsively, not being able to avoid doing so, which generates her feelings of shame and a lack of control. In fact, she hides this habit to her partner with whom she lives. In periods when

she has anemia the frequency of plaster eating increases. In addition, she has body image distortion, so she restricts her diet practically from her youth and does intense exercise daily.

During mental state examination she was conscious and globally oriented, calm and approachable, her speech was fluid and without formal alterations, her mood was hypothythic with no major depressive or psychotic symptoms associated. She reported suffering moments of anxiety that fluctuated throughout the day depending on environment stressors, as well as rumination and compulsions of plaster intake as an anxiolytic measure. She presented obsessive personality traits, such as perfectionism, high self-demand or difficulty in speaking about her feelings, but she did not meet criteria of personality disorder since there were not rigid patterns of behavior, she was aware of these traits and did not had a repercussion in different areas of her personal or work life.

Complementary examinations (blood cell count, complete biochemical profile including iron and zinc levels, serologies, urinary sediment and urine drug screen) showed an iron deficiency anemia.

We started treating anemia with iron and fluoxetine was given at increasing doses up to 60 mg per day. Likewise, she was referred for psychology treatment. With iron treatment, serotonergic antidepressant and cognitive behavioral therapy through cognitive restructuring, psychoeducation, exposure and prevention of response and relaxation, she performed a progressive improvement. Our patient currently continues to eat wall plaster, although much less frequently and only at specific moments of stress. Her mood improved and she learnt the risks of this habit and acts accordingly. In addition, she has a balanced diet and regular but not excessive exercise.

### Discussion

Pica has been described for centuries<sup>10-12</sup> and one of the first cases was documented in the sixth century in a pregnant woman<sup>10</sup>. Since then, many cases of individuals who eat non-food substances such as soil, plaster, chalk, ice cubes, hair, cigarette butts, paper, cloth, etc. have been described<sup>10-13</sup>.

The etiology of pica is unknown, but a complex interaction between psychological and behavioral factors<sup>14</sup>, iron deficiency<sup>4,15,16</sup> and calcium deficiency<sup>3</sup> has been described.

In addition to the variety of substances that can be ingested, pica may be associated with very heterogeneous behaviors, such as compulsive behavior, oral self-stimulation

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or an emotional arousal. Many individuals with pica show a compulsive behavior that is usually described as a desire to eat the substance by its taste or consistency<sup>17</sup>.

The DSM 5 moved pica from "disorders with onset usually occurring in childhood or adolescence"<sup>18</sup> to "feeding and eating disorders"<sup>1</sup>. This change emphasizes the fact that the disorder may appear at all ages, including adulthood.

The literature suggests that the prevalence of pica varies widely in various social and clinical contexts and seems to be higher among selected populations that include pregnant women, children<sup>19,20</sup>, adults with iron deficiency<sup>21</sup> and institutionalized people<sup>22</sup>. However, the prevalence of pica disorder is unknown since published studies generally omit essential key data to establish the diagnosis, such as persistence of behavior, duration and relativity to local social norms.

In our case, the emotional deprivation suffered from the earliest stages of her development has probably contributed to the establishment of the anomalous behavior. The tendency of the patient to suffer from anemia added to the disorder. The intake of non-nutritive substances together with the food restriction that the patient voluntarily made could also worsen this tendency to anemia that, in turn, would worsen pica, in a worsening feedback loop.

On the other hand, the patient manifested an uncontrollable egodistonic desire or compulsion for the ingestion of plaster, especially in moments of great anxiety. This made her feel ashamed but calmed her anxiety. In this sense, pica could be included in obsessive-compulsive spectrum disorders. In fact, the improvement achieved with high doses of a serotonergic antidepressant would make us match the case to the response obtained in patients with obsessive-compulsive spectrum symptoms. Only a series of cases described pica as a disorder of impulse/compulsion control<sup>23</sup>. Stress can induce a dysfunction in the serotonin system<sup>24</sup> and an analogous alteration has been described in obsessive-compulsive spectrum disorder<sup>25</sup>. Possibly, a similar dysfunction developed in this patient during periods of stress and changed to impulse/obsession symptoms later. Thus, stress can induce pica in some adults and such behaviors may have impulsive/compulsive characteristics. Therefore, proper stress management can help relieve the symptoms of pica.

In conclusion, more studies are warranted to establish the exact prevalence of pica in different populations and to clarify its best etiological and taxonomic approach in order to offer a more effective treatment.

### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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### PostCOVID Mental Health

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Dear Editor,

The SARS-CoV2 (COVID-19) pandemic is a current challenge for the healthcare systems of the world. In just a few months, COVID-19 has spread in more than 200 countries and has supposed a huge adjustment effort for the health systems as never seen before. An important part of the stress generated on the healthcare organizations has been due to the peaks or waves of care needs for patients infected with SARS-CoV2. Many countries seem to be holding back the first wave, although several waves of care needs, with differential characteristics, are anticipated.

From a descriptive point of view, there are several classifications of the healthcare needs derived from COVID-19, through which the consequences of the pandemic could be studied or analyzed<sup>1</sup>. However, we are going to try to have a look down from above, in order to understand what can happen in relation to this pandemic and health, and particularly to mental health needs, for which we will contemplate the following scenario.

#### First wave. Initial impact of the COVID-19 pandemic

This first wave is linked to the pandemic itself. In a few weeks, COVID-19 has put in check the health systems' capacity throughout the world, with almost 3 million people infected, more than 200,000 deaths and 850,000 patients recovered (data as of the time of writing, published by the Spanish Ministry of Health)<sup>2</sup>. A very important fact to take into account, is that it has occurred in a limited space of time, which has been a unique stress test for the health sys-

tems across the world, which have had to adjust in a record time, in order to absorb all demand and meet the needs of the population. These systems have had to channel, especially in those regions most affected, a very important part of their health resources to face the pandemic, even by creating new specific structures such as IFEMA in Madrid<sup>3</sup>. Mental health needs have focused on the reorganization of care for patients under treatment and, particularly, on continuity care programs, focusing on a telematic assistance model. On the other hand, psychiatric hospitalization resources have had to be reorganized in general hospitals, while liaison psychiatry programs have been launched for the care of both health professionals under high stress load, as well as patients affected by COVID-19 and their families<sup>4</sup>. This has forced to defer, non-urgent mental health care in a second stage. Due to the consequences of this first wave, some authors have focused on the possible neglect of these patients<sup>5</sup>.

#### Second wave. Non-COVID related general health issues

The second wave has to do with to the health care needs of the general population for reasons other than COVID-19, which begin to appear after the withdrawal of the first wave. We have been unable to find conclusive data in the literature on the real impact this type of phenomenon has on health care needs in general terms, except for those related to the reduction of traffic accidents, work accidents or other communicable diseases. The rest of the health needs are still present, although confined. The attention of the first wave has forced to cancel many non-urgent procedures and to reschedule surgeries. But after a time of confinement, as the general perception that the first wave begins to withdraw arises, other health needs tend to reappear. In fact, these needs never disappeared, but remained hidden instead<sup>6</sup>. This is one of the many tests of social consciousness that emerge in these times of crisis, where there is a certain renunciation of the individual needs in favour of collective needs. No reference is made to new needs, but to those that were prior to the start of the pandemic and that have been deferred over time. A hidden challenge remains on how we can help patients who avoid seeking help for their ailments for fear of the SARS-CoV-2 infection.



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Added to all of the above, there are needs related to chronic conditions and the temporary withdrawal of continuity care programs, mostly patients who, during this time, have lowered their self-care protocols, often limited by the confinement circumstances. Finally, it should be borne in mind that chronic pathology tends to be linked to age<sup>7</sup> and current circumstances have caused higher levels of isolation on the elderly to prevent their infection, with the consequent potential increase in other health risks, such as a sedentary lifestyle<sup>8</sup>, which is known to be a risk factor associated with poorer health status.

### Third wave. Mental Health Problems

This last wave is the most specific of mental health problems. It is a longitudinal and cumulative wave. First of all, we are expecting the needs of patients affected by SARS-CoV-2 who have been treated by hospital liaison teams as a result of the first wave. Secondly, the needs of the second wave, which include the follow-up visits and decompensations of patients with previous chronic mental disorders, as well as the needs of the patients who were already waiting for an appointment to be attended. Even more, we cannot forget the support and assistance to the needs of health professionals immersed in stressful situations.

In view of the above, we have to include the foreseeable or at least potential new healthcare demands as a consequence of the pandemic, confinement and stress. Thus, we already know the results of the first specific studies on the consequences of COVID-19. Using the Impact of Event Scale (IES), in a population of 263 residents in the Liaoning province of China, 7.6% of the population suffered a high psychological impact<sup>9</sup>. Wang et al<sup>10</sup> estimate up to 29% of the moderate or severe impact related to anxiety symptoms and up to 17% of the depressive symptoms in the confined population. The first data in Italy<sup>11</sup> show a 19.4% moderate psychological impact and 18.6% a severe psychological impact due to stress related to confinement, showing a greater impact in the youngest (under 37) and in women.

From the literature review of previous situations with similar characteristics, such as natural disasters or attacks, certain conclusions can be drawn, with some caution. Between 11% and 38% of the exposed population presents adjustment disorders, depression or substance use disorders, with special relevance in the most vulnerable population or with a history of previous psychiatric disorders, which represent 40% of the sample<sup>12</sup>. In a review of more than 150 studies<sup>13</sup> on one of the most studied traumatic events, such as the attacks of 9/11, found an increase in the rates of post-traumatic stress disorder (between 4 and 11%) with an increased risk related with several factors: with previous psychopathology, nearby life events such as recent immigra-

tion, female sex, and the increase in hours watching related events in the media.

Regarding the consequences of confinement, at least 3 studies have found a correlation between the duration of the confinement and worse mental health and, specifically, with the presence of symptoms of post-traumatic stress, avoidance behaviours or irritability<sup>14</sup>. Economic uncertainty is another relevant factor that should be taken into account, as it increases the risk of psychological problems after a quarantine<sup>15</sup>. In the specific case of the child-youth population<sup>13</sup>, the most relevant symptoms are those related to anxiety and, specifically, to agoraphobia and separation anxiety.

After the pandemic and the confinement, it is expected that there will be a significant impact on the mental health of the general population. Without psychologizing everyday life, nor pathologizing the normal secondary reactions to stress, a space should be opened for debate, planning and anticipation of these foreseeable needs.

In this sense, we have learned from other catastrophes<sup>16</sup> that we must promote certain attitudes and, as far as possible, enhance a feeling both of security and calm, emphasizing the effectiveness of personal and community resources; promote social connectivity as a support mechanism; make visible the hope of a quick and complete recovery, offering real and verifiable information on health resources; and offer accessible healthcare resources, while ensuring that participation is voluntary<sup>14</sup>.

The psychosocial impact of COVID-19 may be particularly relevant in the following groups of people:

1. Those who have been infected with COVID-19.
2. Those who have had a sick close family member.
3. Those who have lost a family member during this pandemic.
4. People who were previously vulnerable to psychosocial stressors.
5. Health professionals who have been exposed in the first line of work.

Furthermore, we also have to include patients with previous psychopathology and those who were already being under mental health care. Finally, it should be noted that some authors<sup>17</sup> generalize the risk to the general population due to mere exposure to the media and the consequences of confinement.

### CONCLUSIONS

With the SARS-CoV-2 pandemic we have entered the field of the unknown, for never before in recent history have

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we faced such an event, with such a long confinement and with a foreseeable socioeconomic impact. We must try to anticipate the consequences on the mental health of the general population, avoiding, of course, pathologizing normal emotional reactions, even if they are painful. It seems clear that we should pay more attention to specific populations, especially those with a potential increased risk, such as people infected with COVID-19, those who have lost a family member or health professionals who have been in the first line of care, but it is foreseeable to expect an increased demand for mental health care also in other groups.

In an illustrative, but not limiting way, the symptoms related to stress in health personnel, the more or less complicated bereavements that have occurred these days, the needs of a general population under the stress of confinement, the pandemic and its socioeconomic consequences appear. All of this would add up to the prior mental health needs of the population and could pose a great challenge for mental health care worldwide.

From a conceptual perspective, WHO defines health as the balance between physical, social and psychological well-being. There is no doubt that the deployment of health care resources to approach COVID-19 is being memorable. We are beginning to acknowledge how governments around the world are moving towards meeting social needs. But, from this biopsychosocial perspective of health, the need arises to be able to foresee this third wave of needs for the population, that is, for the care of their mental health.

Just like any other public health problem, we must emphasize on prevention. During the last weeks, primary prevention actions have been launched, such as initiatives to promote self-care which aim to minimize the impact of confinement. Now is the time to activate secondary prevention measures, aimed at identifying populations at risk, and allowing effective interventions to be implemented, before having to work on tertiary prevention.

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