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Opening treatment windows for treatment-resistant schizophrenia: improving emotion regulation strategies using the Unified Protocol in a case study

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3 **Opening treatment windows for treatment-resistant schizophrenia: improving emotion**
4 **regulation strategies using the Unified Protocol in a case study**
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8 **ABSTRACT**
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11 Approximately 30%-50% of people with schizophrenia have treatment-resistant schizophrenia
12 (TRS). Currently available standard psychopharmacological and psychological treatments
13 have proven insufficient to achieve full recovery in these patients. Alternative psychological
14 interventions focused on improving emotion regulation, such as the Unified Protocol for
15 Transdiagnostic Treatment of Emotional Disorders (UP), could potentially improve treatment
16 outcomes in this difficult to treat population. The aim of the present case study is to
17 demonstrate how the UP can be adapted for the treatment of TRS. We decided to use UP to
18 treat this particular patient due to the presence of intense unpleasant emotions, aversive
19 reactions, and emotional avoidance strategies. After completing the full treatment protocol,
20 the patient showed significant decreases in scores on the Difficulties in Emotion Regulation
21 Scale (DERS), including total and emotional rejection, life interference, and emotional lack of
22 control. A significant reduction was also observed in anxiety (OASIS) and depressive
23 symptoms (ODSIS). The intervention had a positive impact on auditory hallucinations, with
24 decreased severity, less intense anxiety, and less interference in life. The treatment led to
25 greater control over voices and the patient reported feeling more confident in her relationship
26 with those voices. These results provide preliminary support for the use of UP for the
27 treatment of TRS.
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53 **KEYWORDS:** transdiagnostic, unified protocol, schizophrenia, treatment-resistant, emotion
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BIOGRAPHIES

Eva Grasa, PhD, coordinates the Psychotic Disorders Research Group at the Hospital de la Santa Creu i Sant Pau (Barcelona, Spain). Her research activity focuses on the evaluation and application of new therapeutic strategies in schizophrenia: metacognition in delusional patients, recovery in DBS patients, and digital solutions in treatment-resistant schizophrenia.

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Óscar Peris-Baquero, PhD student, is a Teaching and Research Staff Trainee in the Department of Psychology and Sociology (University of Zaragoza). His doctoral thesis is about the efficacy and acceptability of the Unified Protocol for transdiagnostic treatment of emotional disorders in group format in the Spanish public mental health system.

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Jorge Osma, PhD, is an Associate Professor at the University of Zaragoza (Spain). His research focuses on the prevention and treatment of emotional disorders using the Unified Protocol through cost-effective formats such as group therapy and digital health.

Opening treatment windows for treatment-resistant schizophrenia: Improving emotion regulation strategies by applying the Unified Protocol in a case study

1. Theoretical and Research Basis for Treatment

Schizophrenia is a severe mental health disorder affecting around 24 million people worldwide (WHO, 2022). Schizophrenia is usually a chronic condition associated with high disability levels (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). It is a highly complex condition, mainly due to the high risk of mental and physical health comorbidities. As a result, the care of these patients can impose a significant burden on informal caregivers and the health care system (Kennedy, 2014). Although the efficacy of antipsychotics in the treatment of schizophrenia has been demonstrated in randomized, double-blind, placebo-controlled clinical trials (Howes et al., 2017), first-line antipsychotics are only beneficial in around 50% of patients and thus the other 50% obtain scant benefit from this treatment (Kennedy, 2014; Nucifora et al, 2019). This lack of response (or an insufficient response) to pharmacological treatment is known as treatment-resistant schizophrenia (TRS), which is characterized by a poor response together with the persistence of delusions and hallucinations that distort reality and lead to behavioral alterations. In TRS, the therapeutic alternative of choice is clozapine, which has shown good results (Howes et al., 2017). Nevertheless, around 40% of patients with TRS do not respond to this drug either (Siskind et al, 2017). In fact, overall, only 13.5% of people with schizophrenia achieve recovery in clinical and social outcome (Jääskeläinen et al., 2013). In addition, the effect size in terms of a reduction in positive-negative symptoms and improvement in emotional well-being is small (Eack & Newhill, 2007).

Apart from pharmacotherapy, several different psychological interventions can be used to treat schizophrenia. Clinical guidelines recommend two psychological treatment modalities

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3 for schizophrenia (NICE, 2014; Working Group of the Clinical Practice Guideline for
4 Schizophrenia and Incipient Psychotic Disorder, 2009). The first of these is Cognitive
5 Behavioral Therapy in psychosis (CBTp; Morrison, 2017), whose objective is to reduce the
6 discomfort generated by positive symptoms. The second recommendation is Cognitive
7 Remediation Therapy (CRT; Wykes et al., 2011), whose aim is to improve cognitive
8 functions. Both of these psychological interventions have been shown to improve clinical
9 symptomatology and the cognitive processes associated with the development and
10 maintenance of the disease. Although these interventions can help to achieve clinical and
11 functional recovery, they do not appear to improve personal recovery (Bighelli et al., 2018;
12 Pankowski et al., 2016; Vita et al., 2021). This is an important point, as the personal recovery
13 process is considered critical to both emotional and psychological well-being in schizophrenia
14 (Schrank et al., 2014). Given that emotion regulation influences well-being (Fredrickson,
15 2000), interventions that target this facet could be beneficial in patients with schizophrenia.

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34 In this context, the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders
35 (UP; Barlow et al., 2017) could potentially reduce deficits in emotion regulation, which other
36 interventions for schizophrenia (i.e., CBT-p, CRT) do not directly target. The UP is an
37 evidence-based psychological treatment targeting shared dimensions associated with the
38 etiology and maintenance of emotional disorders, such as neuroticism, rumination, and
39 avoidance (Barlow et al., 2014). To date, three systematic reviews—two of which were meta-
40 analyses—have demonstrated the efficacy of UP in reducing anxiety and depressive
41 symptoms, and in improving the quality of life and functional status of patients with
42 emotional disorders (Carlucci et al. 2021; Cassiello-Robbins et al., 2020; Sakiris & Berle,
43 2019). In recent years, there has been a growing interest among clinicians and researchers to
44 investigate whether the UP could be adapted for the treatment of emotional disorders and/or
45 symptoms in people whose primary diagnosis is other than an emotional disorder, for
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3 example, borderline personality disorder (Sauer-Zavala et al., 2016) or bipolar disorder
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5 (Ellard et al., 2017). The preliminary results of those studies have been good. Based on the
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7 findings of those studies, we hypothesized that an intervention focused on improving emotion
8
9 regulation strategies in people with TRS could be clinically beneficial by reducing symptoms
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11 of anxiety, depression, and interference, while also improving quality of life. In the present
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13 study, we describe a patient diagnosed with TRS who received an adapted version of the UP.
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19 **2. Case Introduction**

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21 At the time of the UP intervention, Blossom (a pseudonym) was a 36-year-old woman who
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23 had completed primary education. She worked at a factory on the assembly line for eight
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25 years until her mental illness forced her to stop working. She was receiving a disability
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27 pension and was living with her boyfriend. She had good family support from her mother and
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29 sister (her father was deceased).
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35 **3. Presenting Complaints**

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37 The patient reported the presence of positive and negative symptoms of psychosis. She
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39 experienced auditory verbal hallucinations at least once a day, the content of which was
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41 always negative and unpleasant (“*you are bad*”, “*they’re going to fire you*”, “*be careful with*
42
43 *mobbing*”). As a consequence, she was largely isolated from society; her only relationships
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45 were with her family and boyfriend. She also suffered from anxiety and a fear of leaving
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47 home. Her symptoms also included apathy, and she had great difficulty engaging in daily
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49 routines including both low and high demand activities such as personal hygiene and cooking,
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51 respectively.
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56 **4. History**

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3 Blossom was admitted to the emergency unit six years ago for psychotic symptoms (delusion
4 of prejudice and auditory hallucinations) and received treatment at the outpatient unit. She
5 believed she was suffering from mobbing at work: *“My co-workers were always criticizing*
6 *each other”*; *“I felt that something bad was going to happen at work”*. She also presented
7 magical thinking with regard to her workmates: *“They began to make gestures at me; if they*
8 *touched something black, I touched something black”*, *“I began to follow them stealthily”*.
9
10 These thoughts turned into delusional interpretations: *“When I did something well, following*
11 *the instructions of one of my workmates, another one would come up behind him with a large*
12 *box that said Medallion, which I thought it was a medal for doing it well”*.

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Delusional symptoms were also common outside of work: *“When I was driving my car, I was*
followed by trucks with a V, which meant “everything was fine””; *“I left my family’s house to*
rent a flat because I followed these clues: I often saw moving trucks”. Regarding the auditory
hallucinations, she experienced hostile, critical and imperative voices: *“you are bad”*, *“don’t*
do that”, *“they’re going to fire you”*, *“be careful with mobbing”*.

Initially, the antipsychotics ziprasidone and paliperidone were prescribed. However, the
prescription was later switched to clozapine due to a lack of clinical response. After this
change in antipsychotic medication, she achieved complete remission of her symptoms, but
treatment had to be discontinued because she developed a severe, medication-related side
effect (neutropenia). Nevertheless, since her psychotic symptoms had fully remitted,
pharmacotherapy was not restarted and her psychiatrist recommended that she return to work.
Nine months later, she presented a second psychotic episode involving delusion of reference,
auditory hallucinations, disorganized behaviors, and thought blocking. She was admitted to
the inpatient unit where she received several different antipsychotics, but these only partially
improved her symptoms. She was then referred to a treatment program specifically designed

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3 for patients with TRS, which consisted of a specialized intervention involving both
4 pharmacological and psychological measures.
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10 **5. Assessment**

11 **Clinical Diagnosis**

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14 The diagnosis was made in accordance with the criteria established in the fifth edition of the
15 Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-5; APA, 2013).
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20 **Primary Measures**

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23 The Difficulties in Emotion Regulation Scale (DERS: Gratz & Roemer, 2004; Hervas &
24 Jodar, 2008) is a self-report measure designed to assess emotion regulation difficulties. The
25 DERS contains 28 items grouped into five dimensions of emotion regulation, as follows: lack
26 of emotional attention; emotional confusion; emotional rejection; life interference; and
27 emotional lack of control. The response options are given on a 5-point Likert scale ranging
28 from 1 (almost never) to 5 (almost always) to indicate the frequency of the behavior described
29 in each item. The higher the score, the greater the difficulty in the regulatory component
30 evaluated. The internal consistency of this scale in a sample of patients in Spain was $\alpha = 0.74$
31 (Hervas & Jodar, 2008).
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44 The 5-level EQ-5D visual analogue scale (EQ-5D-5L VAS: Herdman et al., 2011) is a self-
45 rated measure of health-related quality of life presented on a vertical visual analogue scale
46 ranging from 0 to 100. The higher the score, the greater the perceived health. Scores are
47 subclassified according to the number of points as follows: poor (0-40 points); fair (41- 53);
48 good (54- 76); very good (77- 80); and excellent (90-100).
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Longitudinal Assessment Measures

The Overall Anxiety Severity and Impairment Scale (OASIS: Norman et al., 2006; Osma et al., 2019) is a 5-item self-report measure evaluating the frequency, severity, avoidance, and interference of anxiety symptoms experienced in the past week. The items are rated on a 5-point Likert scale ranging from 0 (no anxiety in the past week or none) to 4 (constant anxiety or extreme/all the time). Higher scores indicate more severe anxiety. The internal consistency of the OASIS in a Spanish sample was $\alpha = 0.87$ (Osma et al., 2019).

The Overall Depression Severity and Impairment Scale (ODSIS: Bentley et al., 2014; Osma et al., 2019) is a 5-item self-report measure evaluating the frequency, severity, anhedonia, and interference of depressive symptoms experienced in the past week. The items are rated on a 5-point Likert scale ranging from 0 (no depression in the past week or none) to 4 (constant depression or extreme/all the time). Higher scores indicate greater severity. The internal consistency of the ODSIS was $\alpha = 0.94$ in a Spanish sample (Osma et al., 2019).

Secondary Measures

The Psychotic Symptom Rating Scale-Auditory Hallucinations (PSYRATS-AH: Haddock et al., 1999; González et al., 2003) is a semi-structured interview designed to provide a dimensional measure of hallucinatory experience over the past week. The scale contains 11 items grouped into three factors: physical, cognitive, and emotional. The items are rated on a 5-point Likert scale ranging from 0 to 5, with higher scores indicating greater severity of auditory hallucinations.

The Beck Cognitive Insight Scale (BCIS: Beck et al., 2004; Gutiérrez-Zotes et al., 2012) is a self-report measure designed to assess cognitive insight capacity. This scale contains 15 items grouped into two factors: self-reflectiveness and self-certainty. Items are rated on a 4-point

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3 Likert scale ranging from 0 (do not agree at all) to 3 (agree completely). Higher score in self-
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5 reflectiveness indicate greater objectivity and lower score in self-certainty indicate mental
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7 flexibility in the interpretation of the experience. The internal consistency for self-
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9 reflectiveness was $\alpha = 0.59$ and for self-certainty was $\alpha = 0.62$ in the Spanish sample
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12 (Gutiérrez-Zotes et al., 2012).
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15 The Brief Core Schema Scales (BCSS: Fowler et al., 2006) is a 24-item self-report assessment
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17 of schemata concerning self and others in psychosis. The scales assess four dimensions of self
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19 and other evaluation: negative-self, positive-self, negative-other, positive-other. The items are
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21 rated on a 5-point Likert scale ranging from 0 (don't believe it) to 4 (believe it totally). Higher
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23 scores indicate higher endorsement of positive-negative beliefs to oneself and/or to others.
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26 All of the measures described above were administered pre- and post-treatment (at one year).
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29 30 31 **6. Case Conceptualization**

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33 To properly conceptualize this case, it is important to assess the three components of the
34
35 functional model of emotional disorders (Bullis et al., 2019), as follows: (a) presence of
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37 intense unpleasant emotions, (b) aversive reactions to these emotional experiences, and (c)
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39 emotional avoidance strategies.
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42 Blossom reported difficulties in managing several negative emotions, including fear, blame,
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44 sadness, and anger. Her fear was mainly related to having to leave her home (*"I am afraid*
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46 *that outside voices appear and make me feel bad, something happens"*). In terms of blame,
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48 she had negative thoughts about her social environment (*"when I was ill, I thought that my*
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50 *uncle had abused me; how could I believe that?"*) and low behavioral activation. She felt
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52 sadness related to her inability to achieve her daily goals (e.g., housework). She felt anger due
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54 to the presence of the voices and her lack of energy. As a consequence, she experienced
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56 cognitive aversive reactions, as exemplified in statements such as *"I'm fed up"* or *"What a*
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58 *disgusting life, sometimes I wish I was dead, but I'm not going to do anything to myself"*.
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3 In response to these negative reactions, she used several emotional avoidance strategies, as
4 follows: 1) explicit behavioral avoidance (situational/escape): not meeting with her friends,
5 not having her nephew at home, not contacting anyone via her mobile phone (WhatsApp), and
6 locking herself in the room; 2) subtle behavioral avoidance: covering herself with a blanket on
7 the sofa or closing her eyes to avoid following the signals; 3) cognitive avoidance: ruminating
8 on the past; 4) safety signs: having medications on hand; and 5) emotion trigger behaviors: for
9 example, when anger appeared she argued with the voices.
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20 **7. Course of Treatment and Assessment of Progress**

21 **Course of Treatment**

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23 The UP was specifically adapted to suit this particular case (Table 1). This treatment protocol
24 was administered over a twelve-month period, with a total of 33 sessions. During the first
25 eight months, these sessions were held in person on a weekly basis. During the final four
26 months, the in-person sessions were held every two weeks. The therapist followed the first
27 edition of the UP manual (Barlow et al., 2015); however, the order of the modules was
28 modified based on changes in the patient's clinical status and on changes in her specific needs
29 over time (Table 1). Due to the presence of cognitive deficits associated with schizophrenia,
30 we sent her an audio summary of each session to ensure that she understood the content.
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43 The treating therapist was a clinician (E.G.) with a PhD and more than 20 years of experience
44 in the assessment and treatment of patients with schizophrenia. The therapist received specific
45 training in the UP intervention and a certified supervisor (J.O.) reviewed her work during the
46 first phase of treatment.
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52 [insert Table 1]
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56 **Module 1. Setting goals and maintaining motivation.**

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3 The first sessions of the UP are considered essential to work on developing therapeutic
4 alliance, one of the main drivers of motivation and change in patients with schizophrenia. In
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6 this case, the patient also needed help to normalize her psychotic experiences, giving her
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8 space to explain her personal and clinical history. In this regard, certain evaluation
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10 instruments (such as the PSYRATS scale) proved highly valuable.
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14 During the intervention, we identified several possible precipitating factors (i.e., substance
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16 abuse, high expressed emotion in the family, stressors such as the death of the grandmother
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18 and/or work problems) and symptom maintainers (social isolation, not sharing worries) as
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20 well as protective factors of well-being (extroverted, socially skilled). Identification of these
21
22 factors allowed us to take advantage of Blossom's own experiences to introduce UP and give
23
24 her examples of her ability to improve her condition. The information shared through the
25
26 assessment and case formulation helped Blossom to identify her main goals and to determine
27
28 the intermediate steps that would be necessary to achieve those goals. We agreed on the
29
30 following: (1) improving personal care; (2) getting together with family and friends; (3)
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32 performing certain daily tasks; and (4) participating in activities outside of the home (e.g.,
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34 volunteering).
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42 **Module 2. Understanding emotions.**

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44 This module is especially important for people with schizophrenia. In a clinical context, it is
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46 unusual to approach emotions from a self-knowledge perspective; similarly, it is not common
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48 to ask patients to observe and reflect on emotions. With Blossom, we identified her usual
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50 emotions through the use of images. Alterations in short-term memory and executive
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52 function, together with the habitual presence of voices during the treatment sessions, made it
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54 necessary to resort to information channels other than language such as new technologies.
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56 More specifically, we sent an audio summary of the sessions to her after each session. We
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3 also suggested that she verbally record her experiences using her mobile phone and the
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5 different tasks to be performed in therapy. In this way, we were able to get the patient to
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7 perform her homework assignments.
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10 She listed four common emotions: sadness (*“when I get up, when I see that I don't do what I*
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12 *wanted to do”*), anxiety (*“before going out or when I do something, I am afraid of voices*
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14 *appearing”*), anger (*“because of the presence of the voices”, “because I felt powerless to do*
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16 *things”*), and tiredness (*“it's the most annoying thing”, “I feel I have no energy, I can't do*
17
18 *anything”*). We introduced the concept of how to record these emotions using the Antecedent-
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20 Response-Consequences (ARC), with a special focus on the short- and long-term
21
22 consequences of her emotional responses.
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28 **Module 3. Mindful emotion awareness.**

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30 Our clinical experience in treating patients with affective and anxiety disorders has shown us
31
32 that patients with schizophrenia seem to relate to their emotional experiences in a similar way.
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34 Feeling bad is experienced as a state to be ashamed of; it is synonymous with weakness and a
35
36 source of anger and guilt. Primary and secondary emotions merge and the patient
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38 maladaptively copes with the emotional burden through self-medication or isolation. Blossom
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40 experienced anxiety as a primary emotion and guilt and shame as secondary emotions. She
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42 presented a constant pattern of ruminating about her past experience at work (*“everything that*
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44 *happened was my fault, I didn't want to be fired and I behaved badly”*), which ended up
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46 affecting other areas in her life. Several factors—the presence of intrusive thoughts, together
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48 with the phenomenon of thought-action fusion (*“I realized that I was looking at my nephew's*
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50 *butt”, “thoughts came to me as if I were going to abuse him”, “the voices told me to be*
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52 *careful”, “I was afraid of hurting him”*) and the associated guilt—all contributed to her
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54 tendency to turn to avoidance and suppression as coping strategies (*“I prefer not to be alone*
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3 *with my nephew*”, “*when I see someone and they remind me of my father, or my ex, I force*
4 *myself not to think; I don't want to have bad thoughts about the way they behaved and be*
5 *bad*”). At the end, a dysfunctional self-perception pattern had been generated which was
6 based on past negative assessments (“*I’m bad*”, “*I deserve what happens to me*”) and future
7 actions (“*I should clean my house, but I’m tired*”, “*I should be with people, but I have no*
8 *conversation*”). This pattern confirmed her personal disability believes (“*I’m a bad friend*”,
9 “*I’m useless*”). To help the patient decenter from her emotional experiences (including voices)
10 and to learn how to observe these experiences in order to break the vicious circle of
11 interaction between sensations, thoughts and behaviors, we trained her in three exercises: 1)
12 informal mindfulness tasks (washing, showering), 2) anchoring through breathing, and 3)
13 emotional induction with songs associated with powerful aversive and rewarding emotions.
14 During the informal practice, we observed that other elements (apart from the voices) in her
15 daily life may have played a role in her discomfort. For example, she noticed that the emotion
16 of tiredness generated thoughts of “*stop, lie down*”, which led her to interrupt the tasks she
17 was doing; as a result, this became a source of discomfort.
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40 **Module 5. Countering emotional behaviors**

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42 The patient was instructed to use the ARC worksheet, which allowed us to identify specific
43 situations of distress and avoidance (Table 2) in order to assess alternatives.
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47 [insert Table 2]

48
49 Blossom realized that she needed to find a way to handle these situations of discomfort
50 differently. Consequently, she gradually began to use the mindfulness tools that worked so
51 well in dealing with intrusive thoughts while doing chores around the house. The emotional
52 avoidance behaviors that she routinely turned to in order to curb her tendency to “follow the
53 signs” (e.g., pulling the blanket up or closing her eyes), actually made her more focused on
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3 the voices, thus increasing her discomfort. She realized that she could not turn to medication
4 every time this happened. She did not want to be dependent on medications to deal with
5 anxiety, and she needed to stop "hiding" from the signs because this simply ended up
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10 perpetuating the same situation.
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12 13 **Module 7. Emotion exposures**

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15 In this module, Blossom was exposed to situations associated with anxiety. We worked with
16 her to define an exposure hierarchy in which the situations were ranked in order (low,
17 medium and high) in terms of the level of distress and avoidance that they caused. For
18 instance, low distress situations included performing (without interruption) a household chore
19 on a daily basis or communicating with friends every week by messenger (WhatsApp).
20 Medium distress situations included meeting once a week with her mother or sister and
21 deciding, in advance, how much time she would spend with them (increasing the exposure
22 time gradually). High distress situations included looking at her partner while he was playing
23 with his mobile phone without "following the signs" or staying with her nephew (being alone
24 with him at home, increasing the time gradually). In all of these exposures, she was told to
25 apply the emotion regulation strategies she had learned and practiced in Module 3. For
26 example, the exposure to daily chores while she was practicing mindfulness helped her to
27 observe the emotion of tiredness, to let go the thoughts of "stop" and to continue with the
28 tasks.
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48 **Module 4. Cognitive flexibility**

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50 In patients with schizophrenia, it is often hard to identify thought distortions due to the high
51 conviction and the low flexibility that these patients have in the beliefs associated with the
52 voices and delusions. For this reason, we decided to modify the order in which the UP
53 modules were presented. Consequently, we first presented and practiced mindfulness and
54 anchoring, and then proceeded to exposure to unpleasant emotions. Exposure could help to
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3 increase a person's sense of self-efficacy while weakening the strength of their distorted
4 beliefs. After Blossom was exposed to discomfort and then reached a certain level of
5 achievement, we observed that she was more receptive to considering the possibility of re-
6 evaluating her beliefs. The data obtained from the process of emotion exposure gave us
7 enough material to show Blossom her main errors in thinking and how anticipation does not
8 always match reality. In her case, the type of thoughts that predominated her thinking were as
9 follows: catastrophizing, perfectionism, overgeneralization, and a tendency to jump to
10 conclusions. The patient was instructed to use the cognitive flexibility worksheet to help
11 identify distorted thoughts. Based on this, we taught her how to observe and describe reality
12 and to realize that she did not need to stay with her first interpretation of a given situation, but
13 could consider alternative explanations.
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30 [insert Table 3]
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33 **Module 6. Understanding and confronting physical sensations.**

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36 Module 6 was the last to be performed because we expected that it would be the most difficult
37 module for the patient. We also modified the content of this module in order to focus on
38 understanding and confronting the voices. The rationale behind this change was as follows.
39
40 First, although patients with schizophrenia are able to pay attention to emotions, they often
41 have problems with clarity (i.e., localizing emotions in the body) (Torregrossa et al., 2019).
42 Blossom found it difficult to identify the part of the body associated with the emotion.
43
44 Second, according to the cognitive model of schizophrenia, voices are similar to physical
45 sensations in panic disorder (Morrison, 1998). Thus, we decided to induce hallucinatory
46 experiences through behavioral experiments. Then we reviewed the evidence for and against
47 possible alternative explanations for the hallucinations' origin with the patient.
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[insert Table 4]

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3 For Blossom, the voices were the signal that something bad was going to happen or that she
4 was behaving badly. Through the experiments, Blossom started to think and behave
5 differently with the voices. For example, she stopped talking to and obeying the voices'
6 orders; instead, she started to believe that "*they speak more subtly to me*", "*they resemble my*
7 *thoughts*", "*they are kinder*" and "*they give me advice*". We suggested that she establish a
8 relationship with the voices, similar to the relationships she had with people close to her. We
9 explained that even people close to her are not always right, can be contradictory, and we do
10 not always pay attention to them.
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24 **Module 8. Moving up from here.**

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26 In this module, we reviewed all of the work done with Blossom up to that point, including her
27 level of achievement with regard to the four objectives established at the start of treatment.
28 Based on this review, we decided that we needed to continue working on objectives 2 (getting
29 together with family and friends) and 4 (activities outside home) in order to continue making
30 progress in therapy and towards recovery.
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39 **Assessment of Progress**

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41 In terms of adherence to the 12-month intervention, the patient missed five sessions (out of a
42 total of 33). The reasons she gave for missing these sessions were that the "*voices told me not*
43 *to go to the visit*" and "*I was tired*". We observed that she tended to be more tired when both
44 the intramuscular injection and the UP visit were scheduled during the same week. As a
45 result, we decided to stop performing both visits on the same day, which resolved the
46 problem.
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55 To determine whether the pre- to post-intervention changes were significant, we calculated
56 the reliable change index except for the scales EQ-5D-5L VAS, PSYRATS, and BCSS. Data
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3 on the internal consistency of these measures were not available. The results of the pre- and
4
5 post-intervention questionnaires are summarized in Table 5.
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8 [Insert Table 5]
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10 As Table 5 shows, scores on Total and Emotional rejection, Life interference, and Emotional
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12 lack of control factors in DERS decreased significantly after intervention. The EQ-5D-5L
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14 VAS score (personal well-being) improved from fair to very good. Changes in the PSYRATS
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16 showed a decrease in severity of auditory hallucinations. Although the frequency of the
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18 hallucinations remained unchanged (occurring at least once a day), with a longer duration (the
19
20 hallucinations remained unchanged (occurring at least once a day), with a longer duration (the
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22 voices could last for hours), we did observe a decrease over time in terms of volume (the
23
24 hallucinations became quieter than her own voice), intensity of anxiety (from extreme to low),
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26 interference in life (from moderate to minimal impact), and control over voices (from
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28 “occasionally” to “most of the time”). On the BCSS, pre-post intervention changes were
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30 observed in negative-self score, with a decrease in the number of negative beliefs and in the
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32 associated intensity.
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35 Finally, OASIS and ODSIS scores decreased significantly after completion of the UP. Figure
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37 1 shows the evolution of the OASIS and ODSIS scores over the course of the full
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39 intervention. At the start of the intervention, she scored 16 points (out of a maximum of 20)
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41 on both questionnaires. On the ODSIS, her scores progressively decreased from 16 to < 10
42
43 points, the cut-off point established for the Spanish clinical population (people with emotional
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45 disorder diagnosis; Osma et al., 2019), until finally falling to 0 points in most of the sessions.
46
47 The increase observed in session 27 (score=13) was due to the anniversary of her father’s
48
49 death. On the OASIS, the scores declined below 10, but only later in the therapeutic process,
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51 with more peaks compared to ODSIS due to the influence of the psychotic symptomatology
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53 on anxiety. It is notable that the OASIS scores first started to fall below the cut-off point when
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55 Module 3 (Mindful Emotion Awareness) was presented. The increases observed in OASIS
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3 scores in sessions 11 (score=14) and 20 (score=11) were due to the emotional impact of the
4
5 voices.
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9 [insert Figure 1]
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11 At the end of the full intervention, we asked the patient to qualitatively evaluate the
12 intervention. Her feedback was positive. The patient affirmed that she felt more confident in
13 her relationship with the voices, stating that *“now, the anxiety caused by the voices has*
14 *decreased”*, *“I have more control over them”*, and *“voices interfere less in my daily life”*.
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23 **8. Complicating Factors**

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25 Notwithstanding the important advances in Blossom’s condition, some issues remained. For
26 example, in cases when the voices remained in her mind for a long period of time, she
27 continued to return to her previous anxiety-related patterns (e.g., staying in her bedroom or
28 taking medication to feel better). The sessions with the therapist helped her to understand the
29 importance of decentering from the voices, independently of their negative content and/or
30 persistence. Another unresolved issue was her delusional belief that other people could read
31 her mind. She continued to feel vulnerable and presented deficits in communicating with
32 other people. Her belief in this idea was almost inflexible and hindered her capacity to contact
33 people outside of her close circle. In fact, this symptom blocked the progress of objective #4
34 (doing activities, such as volunteering, outside of the home).
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50 **9. Access and Barriers to Care**

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52 There is a clear need to explore and develop novel therapeutic approaches for the treatment of
53 TRS due to the fragmentation of current interventions (Mohr et al., 2018). In addition, most
54 community programs for schizophrenia patients focus primarily on first episodes or negative
55 symptomatology. As a result, patients with persistent positive symptoms usually do not
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3 participate in such programs and are thus practically excluded from current intervention
4 streams. In this regard, the UP offers several interesting advantages that could help to address
5 these issues. First, the main focus of UP is on targeting the key problems of the disorder while
6 also allowing the therapist to work on the comorbid affective symptoms (Abdullah et al.,
7 2020). A second advantage of UP is its flexible, modular design (Sauer-Zavala et al., 2019),
8 which allows for a highly customized intervention. This means that the time spent on learning
9 a specific skill can be extended or reduced depending on the patient's particular
10 characteristics.
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21 22 23 24 **10. Follow-Up**

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26 There was no follow-up in this clinical case.
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31 32 **11. Treatment Implications of the Case**

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34 The case report described here, which involved the application of the UP in
35 schizophrenia, emphasizes the affective dimension, an important factor in the recovery
36 process of patients with schizophrenia (Best et al., 2020). Interventions targeting
37 emotional experiences in TRS can help patients learn to distance themselves from those
38 emotions, to manage their situation through more adaptive strategies, and to obtain a
39 greater sense of self-efficacy and confidence in their ability to achieve their aims. These
40 changes can positively influence personal recovery by increasing the degree of
41 perceived autonomy while simultaneously reducing the feeling of being permanently
42 sick and disabled. In the present case, the application of UP to manage Blossom's
43 psychotic symptoms—specifically in how she experienced these symptoms—allowed her to
44 begin to live in closer accordance with her personal values. Of the four objectives established
45 at the beginning of therapy, the patient felt that she had fully achieved two of these objectives
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(improved personal care and cleanliness; carrying out daily tasks), while also largely meeting a third objective (getting together with family and friends).

The patient's therapeutic compliance was high. As her ability to cope with the voices improved, these voices increasingly lost their capacity to influence her behavior, thus enabling her to attend most of the scheduled sessions at the hospital, despite the voices.

Even though the nature of the hallucinations remains unchanged (frequent, negative, a source of anxiety), it is interesting to observe how the patient—after completing the various UP modules—learned to transform her relationship with these hallucinations, by becoming more assertive and learning to ignore the orders given by the voices. Importantly, this transformation resulted in an increase in her perceived quality of life. In addition, the skills learned through the UP (focusing on skills through awareness, emotion exposure), allowed Blossom to better manage her emotions, especially through greater acceptance, regulation, and non-interference in functioning. However, she still has difficulty understanding and differentiating between emotions. Nonetheless, as she has decentered from distress, she has increased her sense of self-efficacy and her self-concept. Similarly, her previously-held strong beliefs and thoughts (such as *"I am worthless, weak, vulnerable"*) have weakened.

At the cognitive level, we were unable to improve the self-certainty component of cognitive insight, and thus the patient's certainty about erroneous ideas has not decreased. Our proposed approach to managing the content of the voices was similar to that used to handle intrusive thoughts. However, we encountered certain difficulties in this area, mainly due to the origin of the phenomenon. People can quickly identify intrusive thoughts as a mental product, with an easily recognizable origin, but in schizophrenia this was less clear. Blossom did not clearly understand that the voices were originated in her mind, due to the disease. Her doubts about the origin gave the voices power over her. Although the UP intervention has enabled her to relate to the voices in a more adaptive way, she still presents a firm belief in

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3 delusional ideas associated with hallucinations, despite the evidence against this belief. The
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5 time spent during the sessions on discussing and treating “errors in thinking” is probably
6
7 insufficient to generate significant changes in persistent delusional symptoms in patients with
8
9 TRS. This finding suggests that, once all of the UP modules have been completed, repeating
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11 Module 4 (Cognitive Flexibility) during the follow-up could help to further consolidate
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13 patients’ capacities in this area.
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17 To our knowledge, this is the first time that the UP has been applied to a person with
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19 schizophrenia. In this case, we show how emotion regulation strategies can be improved
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21 through an intervention targeting the affective sphere of the disorder. In turn, this
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23 allowed the patient to better tolerate intense emotions, leading to improvements in
24
25 personal recovery. These promising results position UP as a possible treatment of choice
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27 in people with persistent psychotic symptoms. However, future studies on the
28
29 application of the UP in a larger number of cases would help to more accurately
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31 establish the extend duration of this improvement. Similarly, future studies could assess
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33 the effectiveness (in terms of achieving the desired changes) of the sequencing of the
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35 modules used in the present case.
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42 **12. Recommendations to Clinicians and Students**

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45 For clinicians interested in applying the UP to patients with schizophrenia, we offer the
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47 following advice based on our experience. First, in refractory patients, we suggest to consider
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49 the application of the UP in an individual format (rather than a group format) (Lockwood et
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51 al., 2004). Second, the assessment process should be used to promote patient engagement
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53 with the therapeutic relationship. Third, clinicians should consider including new
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55 technologies in the therapy (e.g., audio summaries of the session contents) to improve
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57 patients’ understanding of the content and encourage them to complete homework
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3 assignments. Fourth, it is important to invest time in psychoeducation to help the patient
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5 better understand how to differentiate between emotions and thus improve clarity. Fifth, it
6
7 may be advisable to deliver the modules in a different order to suit the specific characteristics
8
9 of a given patient. In this regard, one interesting option to consider might be to induce
10
11 hallucinatory experiences as a substitute for the module on “confronting physical sensations”.
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13 Finally, it may be advisable to consider increasing the number of sessions dedicated to
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15 cognitive flexibility, perhaps by including this module as an additional follow-up in order to
16
17 strengthen the patient’s understanding of this key skill.
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Table 1. Original order of the Unified Protocol (UP) modules and how they were implemented in the present case study, including the aims of each module

Original UP modules	Modified order and aims	
	UP modules	Aims
Module 1. Setting goals and maintaining motivation	Module 1. Setting goals and maintaining motivation	Therapeutic alliance and normalization of the patient's psychotic experiences. Identify therapeutic aims.
Module 2. Understanding your emotions	Module 2. Understanding your emotions	Normalize and explain the adaptive function of emotions. Learn to analyze the emotional response.
Module 3. Mindful emotion awareness	Module 3. Mindful emotion awareness	Practices of observation and induction of emotional experiences without judging, and anchoring in the present moment through breathing.
Module 4. Cognitive flexibility	Module 5. Countering emotional behaviors	Identification of emotional avoidance strategies and discussion of alternatives.
Module 5. Countering emotional behaviors	Module 7. Emotion exposures	Exposure to previously-identified situations of discomfort and practice of alternative behaviors such as staying with friends or with her nephew
Module 6. Understanding and confronting physical sensations	Module 4. Cognitive flexibility	Identification of thought distortions (e.g., jumping to conclusions and catastrophizing), and practicing of alternative thoughts.
Module 7. Emotion exposures	Module 6. Understanding and confronting physical sensations	Modified to induce hallucinatory experiences through behavioral experiments and a review of the evidence for and against possible alternative explanations for the originals of the hallucinations.
Module 8. Moving up from here	Module 8. Moving up from here	To review the main important messages of the program. To evaluate the progress, the treatment goals, and to develop a practice plan for the future. To anticipate difficulties and manage setbacks.

Table 2. Distressing situations identified by the patient, associated reactions, and possible alternatives

Distressing Situation	Reaction	Possible Alternatives
<i>“When I am with my sister and her family, I am afraid that sexual thoughts about my nephew will appear.”</i>	<i>“I don't spend time alone with him.”</i>	Spend the afternoon with her nephew.
<i>“When I'm on the sofa watching TV with my partner: I pay attention to his movements as he plays with his mobile phone, and I follow the signs he gives me with the mobile phone.”</i>	<i>“I close my eyes. I cover myself with the blanket. I go to bed and take extra medication.”</i>	Focus on the TV show.

Or Peer Review

Table 3. Examples of automatic thinking, thought distortions, and alternative explanations

Situation	Automatic Thinking	Emotions	Thought Distortions	Alternative Explanation
After an hour of being at her sister's home, she began to feel uncomfortable.	<i>"I have to go. If I stay more time, voices will appear and say bad things about my nephew."</i>	Anxiety	Catastrophic thinking	<i>"There is no reason for anything bad to happen; I'm not going to hurt my nephew"; "When I have anxiety, the voices don't always appear."</i>
<i>"My boyfriend and I are in a bar. A friend is outside, calling me. The voices tell me: "be careful with mobbing."</i>	<i>"He's talking about me"; "this is mobbing"</i>	Anxiety	Jumping to conclusions	<i>"Voices make me think this, but he may be talking about many things that have nothing to do with me."</i>

Table 4. Examples of hallucinatory experience induction

Setting				
When watching TV, Blossom often sees people who she thinks she remembers or who she thinks are from her environment (family, co-workers). When this happens, voices appear. For this reason, she had stopped watching some TV programs and shows.				
Behavioral experiment	Presence of voices?	Thoughts	Emotion	Behavior
Watch the show Modern Family	Yes	<i>“This boy looks like my nephew”; “I don’t want to think anything bad”</i>	Anxiety	Anchoring through breathing. Continue watching the TV show. Not to talk to the voices.

Table 5. Pre- and post-intervention raw scores and Reliable Change Index (RCI) values

Measure	PRE	POST	RCI
DERS			
Lack of emotional attention factor	4	8	1.65
Emotional confusion factor	9	9	0.00
Emotional rejection factor	30	17	4.54*
Life interference factor	20	13	3.61*
Emotional lack of control factor	36	19	5.64*
Total	99	66	5.01*
EQ-5D-5L VAS	60	85	
OASIS			
Total	16	5	4.80*
ODSIS			
Total	16	0	8.99*
PSYRATS-AH			
Physical Factor	7	8	
Cognitive Factor	9	5	
Emotional Factor	15	12	
Total	30	24	
BCIS			
Self-reflectiveness	14	12	0.47
Self-certainty	4	8	-1.24
BCSS			
Negative-self	12	3	
Positive-self	3	4	
Negative-others	0	0	
Positive-others	16	12	

Note: DERS: Difficulties in Emotion Regulation Scale; EQ-5D-5L VAS: 5-level EQ-5D visual analogue scale; OASIS: Overall Anxiety Severity and Impairment Scale; ODSIS: Overall Depression Severity and Impairment Scale; PSYRATS-AH: Psychotic Symptom Rating Scale-Auditory Hallucinations; BCIS: Beck Cognitive Insight Scale; BCSS: Brief Core Schema Scales

*Significant change: $p= 0.05$

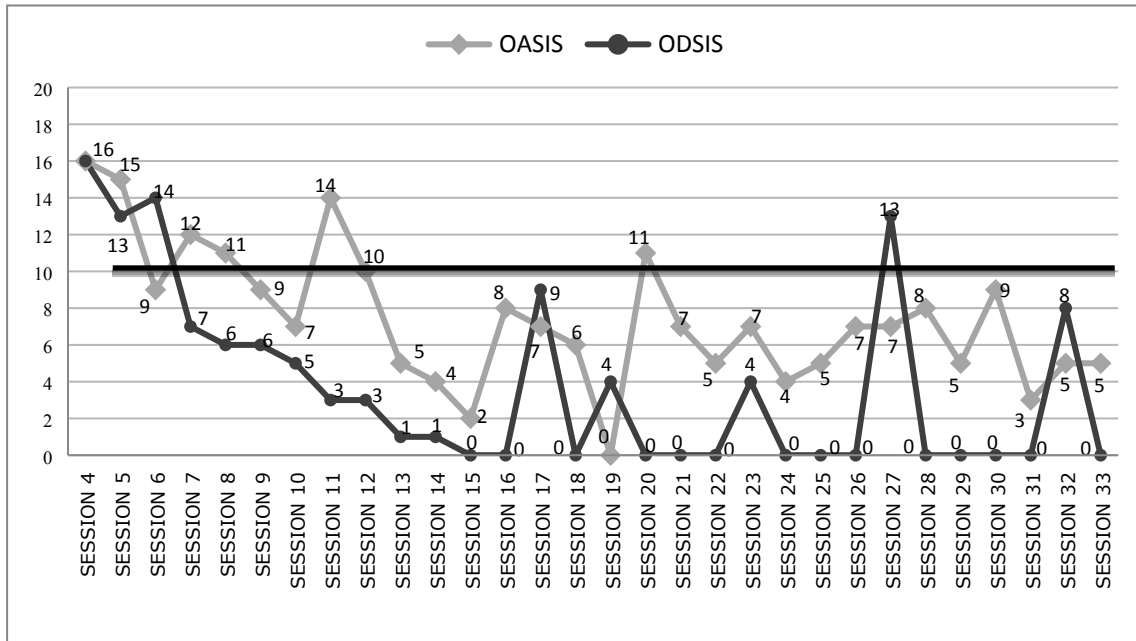


Figure 1. Changes in OASIS and ODSIS scores over the course of the intervention

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