Anxiety sensitivity as a transdiagnostic vulnerability factor for cigarette smoking: Clinical and treatment implications

Sensibilidad a la ansiedad como factor de vulnerabilidad transdiagnóstico para el consumo de tabaco: implicaciones clínicas y para el tratamiento

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obacco smoking is the leading preventable cause of morbidity and premature death world-wide (López, Pérez-Ríos, Schiaffino & Fernández, 2016; Soriano et al., 2018; World Health Organization [WHO], 2019). Overall, there are 1.3 billion adult smokers around the world and the mean prevalence of past-year quit attempts are estimated at 42.5% (Ahluwalia et al., 2018; Asma et al., 2015). In Spain, the percentage of daily smokers showed an uptrend in 2018, reaching 34% of the population. However, nearly two thirds of them (65.85%) have reported at least one quit attempt within the last year (National Plan on Drugs, 2019).

Despite the existence of a set of efficacious behavioral and pharmacological smoking cessation therapies (see for a review Notley et al., 2019; Stead, Koilpillai, Fanshawe & Lancaster, 2016), the high rates of relapse that occur soon after quitting (García-Rodríguez et al., 2013; Livingstone-Banks et al., 2019) have prompted the necessity to identify individual characteristics related to sustained abstinence and relapse (Layoun et al., 2017; Rafful et al., 2013).

In this context, smokers with mental health comorbidities are one of the most vulnerable populations deserving attention (Leventhal & Zvolensky, 2015). In particular, symptoms of depression and anxiety have shown to be the most prevalent among smokers (Piper, Cook, Schlam, Jor-

enby & Baker, 2011; Secades-Villa, González-Roz, García-Pérez & Becoña, 2017). Rates of cigarette consumption and relapse among smokers with these comorbid mental health problems have shown to be higher than those without them (Cook et al., 2014; Secades-Villa et al., 2017). Factors contributing to such poor treatment outcomes include high nicotine dependence (Williams, Steinberg, Griffith & Cooperman, 2013), increased sensitivity to nicotine reinforcement (Tidey & Miller, 2015; Tidey et al., 2018) and tobacco use for coping motives (e.g., smoking to manage negative mood, stress, and cognitive deficits) (Audrain-McGovern, Leventhal & Strong, 2015; Tidey et al., 2018). Additionally, negative emotional symptoms have shown to increase the severity of tobacco withdrawal and the risk of relapse (Zvolensky, Bogiaizian, López Salazar, Farris & Bakhshaie, 2014a), as well as to reinforce maladaptive cognitive beliefs regarding tobacco consumption (e.g., enhanced negative affect/anxiety reduction expectancies).

Consequently, there exists consensus on the convenience to tailor smoking cessation treatments to specific psychological disorders (Almadana-Pacheco et al., 2017; González-Roz et at., 2019; Jiménez-Treviño et al., 2019; Martínez, Fernández del Río, López-Durán, Martínez-Vispo & Becoña, 2018; Sarramea et al., 2019; Ziedonis et al., 2008; Zvolensky, Yartz, Gregor, Gonzalez & Bernstein, 2008). Sev-

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eral studies have focused on developing specialized interventions for smokers with depression (Leventhal, Piper, Japuntich, Baker & Cook, 2014), schizophrenia (Callaghan et al., 2014; Tidey & Miller, 2015), as well as anxiety disorders, such as posttraumatic stress disorder (Kearns et al., 2018), panic disorder (Zvolensky, Lejuez, Kahler & Brown, 2003) or social anxiety disorder (Kimbrel, Morissette, Gulliver, Langdon & Zvolensky, 2014). The most common approach has consisted of combining traditional smoking cessation approaches with interventions aimed at specific mental health disorders, particularly anxiety and depression. However, and despite such valuable efforts, only modest long-term results have been achieved so far (Leventhal & Zvolensky, 2015; Zvolensky, Bonn-Miller, Berstein & Marshall, 2006; Zvolensky et al., 2019a). In recent years, a novel alternative approach is turning towards a transdiagnostic emotional vulnerability model that includes a set of key clinical factors underlying tobacco use and different emotional conditions (Leventhal & Zvolensky, 2015; Zvolensky et al., 2014a). Amongst the several purported transdiagnostic variables accounting for the relationship between tobacco and emotional psychopathology, anxiety sensitivity (AS) is increasingly becoming the focus of attention (Zvolensky, Garey, Kauffman & Manning, 2019b).

Anxiety sensitivity (AS) as a transdiagnostic vulnerability factor for smoking

AS refers to the fear of anxiety-related symptomatology that connects with beliefs and cognitions about the potential harmful consequences of aversive internal states, also known as "fear of fear" (Reiss, Peterson, Gursky & McNally, 1986; Zvolensky et al., 2014a). This construct includes three sub-factors, namely: physical, cognitive and social concerns (Capron, Norr, Zvolensky & Schmidt, 2014; Farris et al., 2015; Taylor et al., 2007). High-AS individuals believe that interoceptive sensations are indicators of imminent harm, leading to: 1) higher anxiety levels and risk of panic, which reinforces negative emotional states, triggers physiological arousal reactions, and ultimately increases panic and anxiety reactions as well (Leventhal & Zvolensky, 2015); and 2) increased aversiveness to physical sensations, which promotes maladaptive avoidance responses when coping with emotionally aversive circumstances (Smits, Otto, Powers & Baird, 2019).

Regarding the emotion-smoking binomial, AS levels have shown to be higher among smokers than among non-smokers (Abrams, Zvolensky, Dorman, González & Mayer, 2011; Zvolensky et al., 2014a; Zvolensky et al., 2019b). Smokers with higher levels of AS perceive more difficulties to quit smoking (Zvolensky et al., 2007) and experience more intense withdrawal symptoms (Johnson, Stewart, Rosenfield, Steeves & Zvolensky, 2012). Moreover, high-AS smokers are emotionally reactive to the distressing withdrawal sensations

(e.g., heart rate slowing) that emerge when the abstinence period begins (Leventhal & Zvolensky, 2015). Consequently, those who do not show a reduction in AS during smoking cessation treatments may be at risk of cessation failure or relapse at both short-term and long-term follow-ups (Leventhal & Zvolensky, 2015; Zvolensky et al., 2006; Zvolensky, Stewart, Vujanovic, Gavric & Steeves, 2009).

AS and related constructs (e.g., trait anxiety; Takemura, Akanuma, Kikuchi & Inaba, 1999) have been associated to increased motivation to quit (Zvolensky et al., 2007), perhaps due to concerns about the health effects of smoking (Zvolensky et al., 2007). In this vein, Buckner and Vinci (2013) highlight that if practitioners were able to take advantage of such motivation at an early stage, long-term abstinence rates could be significantly improved (Borland et al., 2010; Leventhal & Zvolensky, 2015).

Counterintuitively, nicotine administration acutely diminishes perceived anxiety symptoms whereas tobacco abstinence increases them (Leventhal & Zvolensky, 2015). Smokers with high AS, especially those endorsing symptoms of panic disorder (e.g., Zvolensky et al., 2003), tend to believe that smoking helps them manage their emotional status by means of reducing negative affect and avoiding anxiety-related symptoms in the short term (Brown, Kahler, Zvolensky, Lejuez & Ramsey, 2001; Gregor, Zvolensky, McLeish, Bernstein & Morissette, 2008; Zvolensky et al., 2003). Consequently, higher levels of AS are related to greater interoceptive threat expectancies due to abstinence (Farris, Langdon, DiBello & Zvolensky, 2014) and to the tendency to use tobacco to cope with withdrawal symptoms (Zvolensky, Farris, Schmidt y Smits, 2014b), increasing in turn the expectation of positive affect after smoking (Wong et al., 2013).

Smoking and AS integrated treatments: A review of the evidence

Preceding research has demonstrated that integrating AS reduction components into broader smoking cessation treatments leads to reduced AS levels as well as improved treatment retention and cessation rates (e.g., Feldner, Zvolensky, Babson, Leen-Feldner & Schmidt, 2008; Zvolensky et al., 2003; Zvolensky et al., 2008; Zvolensky et al., 2014a; Zvolensky et al., 2018). Since high-AS smokers struggle particularly early in treatment with abstinence-related symptoms, treatment approaches are even more relevant to the earlier phases of the smoking cessation process (Brown et al., 2001; Zvolensky et al., 2006; Zvolensky et al., 2009; Zvolensky et al., 2018).

Current treatment protocols

So far, several treatment protocols targeting smoking cessation and AS have been developed, all of them in United

States (see Table 1). The AS components most commonly implemented include psychoeducation, acceptance-based behavioral counseling, cognitive restructuring and interoceptive exposure to anxiety-related sensations (e.g., Zvolensky et al., 2003; Zvolensky et al., 2014a). Despite results being positive in terms of cessation outcomes, sustained abstinence rates at medium and long-term follow-ups still remain low. It is worth mentioning that more intensive protocols (in terms of number and length of therapy sessions) seem to produce larger abstinence effects.

smoking cessation outcomes; nonetheless, further cultural adaptations are warranted to disseminate the treatment in other Spanish-speaking populations (for example, in Spain).

Evidence on the AS transdiagnostic vulnerability model in Spain

It is remarkable that all AS transdiagnostic programs have been developed and evaluated in United States and Argentina. Moreover, most published works are case series, do not include a comparison arm and often rely on small samples. So far, only four randomized controlled trials (RCTs) have implemented smoking cessation treatments in combination with a specific AS protocol.

In Spain, research work on the development of smoking cessation treatments for patients with comorbid symptoms of anxiety is scarce. More precisely, and as of today, there are no published behavioral treatment protocols addressing anxiety and smoking concurrently or using a transdiagnostic approach for this population in our country. Only a few studies (e.g., Becoña, Vázquez & Míguez; 2002; Marqueta, Jiménez-Muro, Beamonte, Gargallo & Nerín, 2010) have analyzed whether a relationship exists between state-trait anxiety and quitting success, concluding that state anxiety is significantly higher for unsuccessful quitters at post-treatment, 1- and 12-month follow-ups. Also, Martínez-Vispo, Fernández del Río, López-Durán & Becoña (2016) evaluated abstinence-related changes in AS at the end of a behavioral treatment for smoking cessation. Among the 92 Spanish smokers included in the study, participants who were abstinent at the end-of-treatment endorsed lower AS scores and nicotine dependence levels than those who remained smoking. Of note is that not only higher overall pre-treatment levels in the Anxiety Sensitivity Index-3 (ASI-3; Sandín, Valiente, Chorot & Santed, 2007; Taylor et al., 2007) but also higher levels at its physical subscale, were associated with a lower likelihood of quitting.

So far, the only cultural adaptation of an AS Reduction Program for Smoking Cessation in Spanish-speaking smokers has been developed in Argentina (Zvolensky et al., 2014a). This protocol consisted of a psychoeducational component on the relationship between AS and smoking, followed by training in strategies to effectively cope with fear of physical anxiety symptoms, and to increase tolerance for such states. The authors concluded that this intervention yielded positive results in terms of attendance and

 ${\it Table 1. Main characteristics of transdiagnostic AS and smoking cessation treatments.}$

Study (country)	Aim	Sample	Method (inclusion criteria, study design, measuring instruments, description of the intervention, duration, follow-ups)	Findings
Capron, Norr, Zvolensky & Schmidt (2014) United States	To assess whether an AS augmented smoking cessation program would predict lower suicidality among smokers.	169 adult smokers endorsing elevated AS cognitive concerns Active group: 60.2% females Control group: 56.8% females Mean age 42.22, SD = 12.81	Inclusion criteria: 18 years or older; daily smoker for at least 1 year; smoke a minimum of 8 cigarettes per day; motivation to quit smoking within the next month. Study design: - Standard cognitive-behavioral smoking cessation program (N=81). - Cognitive behavioral smoking cessation program with an added AS component (N=88). Measuring instruments: - ASI-3; IDAS; CO levels. Description of the intervention: AS treatment (see Funk, Zvolensky & Schmidt, 2011) consisted of an integrated anxiety prevention/management smoking cessation group (Panic/Smoking Program, PSP). This protocol combined elements of CBT for AS and panic (i.e., interoceptive exposure exercises). Duration: 4 weeks; 90-minute sessions with a trained therapist. Target quit day: Final session. Follow-ups: - Short-term: Prospective data (e.g. current suicidality) was collected at the 4th (final) treatment session via self-reported computerized questionnaires.	No mediation effect of AS levels between treatment group and suicidality; however, participants in the active treatment with high baseline AS showed reduced suicidality risk. No effect of treatment group on current depression. Data regarding smoking reduction or abstinence not available.
Gonzalez et al. (2017) United States	To analyze whether smokers with elevated WTC-related PTSD symptoms, who received CSC-T, show greater smoking cessation rates and reductions in PTSD and LRS than similarly affected smokers who received the CSC treatment alone.	90 adult smokers exposed to the 9/11 WTC disaster with elevated PTSD symptoms CSC treatment: 71.7% males; mean age 48.74, SD = 10.66 CSC-T treatment: 72.7% males; mean age 51.32, SD = 7.87	Inclusion criteria: 18 years or older; smoking ≥ 5 cigarettes per day; reporting interest in quitting smoking; direct exposure to the WTC disaster (e.g., responding to the event or witnessing the event in person); scoring at least in the intermediate range (≥ 30) on the PCL. Study design: - CSC-T treatment (N= 44) - CSC treatment alone (N= 46) Measuring instruments: - SCID-NP; PCL; SHQ; FTND; TLFB for daily cigarette use; LRS; CO and cotinine levels. Description of the intervention: CSC: Included CBT skills and NRT (24-hour transdermal nicotine patches). Standard cessation elements: (1) Psychoeducation on reasons for smoking and barriers to quitting; (2) Enlisting social support, monitoring and tapering cigarette use; (3) Counseling regarding high-risk smoking situations and unhelpful ways of thinking about smoking; (4) Abstinence and relapse prevention strategies. CSC-T: Also included trauma management techniques and transdiagnostic CBT-based anxiety reduction skills. Main components: (1) Interoceptive exposures to feared bodily sensations; (2) corrective information about anxiety and cognitive interventions to teach patients alternatives to catastrophic misinterpretations of somatic sensations; (3) use of graduated in-vivo exposure to feared and avoided situational experiences related to anxiety, WTC-related PTSD triggers, and smoking. Duration: 8 sessions (1.5h/session). Target quit day: week 6. Follow-ups: - Short-term: Primary outcome measures (7-day point abstinence, average number of cigarettes smoked per day in the past 7 days, PCL score, and LRS score) were assessed at each treatment session and at the EOT. - Medium- and long-term: 1-, 2-, 4-, 12-, and 26-weeks post-treatment.	The two treatments did not differ regarding: (1) PTSD symptom improvement; (2) 7-day (~15%) and 6-month (~20%) abstinence rates; (3) the number of cigarettes smoked; (4) PTSD and LRS outcomes. Both treatments led to slightly high quit rates compared to previous treatments for smokers with PTSD.

Study (country)	Aim	Sample	Method (inclusion criteria, study design, measuring instruments, description of the intervention, duration, follow-ups)	Findings
Smits et al. (2016) United States	To analyze the efficacy of exercise as an aid to quit among adult smokers with high AS.	136 adult smokers endorsing elevated AS levels ST+EX: 50.0% females; mean age 43.12, SD = 11.26 ST+CTRL: 54.7% females; mean age 45.39, SD = 11.30	Inclusion criteria: 18 years or older; daily smoker for at least 1 year; smoke a minimum of 10 cigarettes per day; elevated AS (prescreen score of ≥ 20 on the ASI-16); sedentary (moderate-intensity exercise less than twice a week for 30 minutes or less); motivation to quit smoking (reporting a motivation of at least 5 on a 10-point scale). Study design: - Exercise intervention (ST+EX; N = 72). - Wellness education control condition (ST+CTRL) (N = 64). Measuring instruments: - TLFB procedure; ASI-16; IDAS; CO and cotinine levels. Description of the intervention: AS treatment (exercise condition): Vigorous-intensity aerobic exercise for smoking cessation and reestablish a sense of safety around intense bodily sensations. Wellness education (control condition): Discussions of healthy lifestyle topics (e.g., healthy diet, time management) alongside setting small weekly wellness goals, prior to quitting smoking. Duration: 15 weeks; 7 weekly 60-minute sessions of CBT for smoking cessation. Target quit day: week 6. At week 6, participants were also provided with optional NRT patches for up to 8 weeks. Thrice weekly, 35- minute sessions for 15 weeks for both Exercise vs. Wellness education intervention. Follow-ups: - Short-term: Primary outcome measures (PPA and PA) were measured at EOT. - Long-term: 4-month and 6-month follow-ups.	PPA and PA rates were significantly higher for ST+EX than for ST+CTRL among smokers with high AS, but not among those with low AS. Vigorous-intensity exercise regimen may be useful to facilitate smoking cessation among high-AS smokers.
Zvolensky et al. (2018) United States	To examine abstinence effects of a novel AS reduction-smoking cessation intervention relative to a standard condition.	529 treatment-seeking adult daily smokers STAMP condition: 55.28% females; mean age 37.48, SD= 14.38 SCP condition: 50.78% females; mean age 40.23, SD = 12.98	Inclusion criteria: 18 years or older; smoking ≥ 8 cigarettes per day for at least 1 year; motivation to quit smoking (reporting a motivation of at least 5 on a 10-point scale). Study design: - STAMP condition (N = 296). - SCP condition (N = 233). *Because authors were interested in smoking cessation outcomes, participants were included if they attended at least one session when PPA was assessed. Final sample: STAMP condition (N= 161) vs. SCP condition (N= 129). Measuring instruments: - Demographics questionnaire; SCID-NP; SHQ; FTND; PANAS; ASI-3; TLFB; CO and cotinine levels. Description of the intervention: SCP condition (see Schmidt, Raines, Allan & Zvolensky, 2016): Included a standard care intervention for smoking cessation plus provision of general health-related information. Main components: Discussion of prior quit attempts, high-risk situations for smoking, social support, health risks of smoking, and perceived benefits of smoking. STAMP condition: (1) Interoceptive exposure, cognitive restructuring, and psychoeducation exercises developed for panic prevention; (2) standard smoking cessation (relapse prevention counseling). *Both treatment groups received NRT (transdermal nicotine patch) from session 4 (quit day). Duration: 4 weekly sessions (1h/session). Follow-ups: - Short-term: Primary outcomes were: (1) In-treatment AS reduction; (2) early PPA (quit week to 2-weeks post EOT); (3) late PPA (1-month post-EOT to 1-year post-EOT); (3) changes in AS (as a mediator of the effects of treatment on PPA outcomes). ASI-3 was completed at all treatment sessions. - Medium and long-term: 1-month, 3-month, 6-month, and 12-month post-EOT.	There was a significantly greater decline in AS in the STAMP condition, in comparison to the control group. Smoking reduction was significantly greater in the STAMP condition. There was an indirect effect of STAMP on early PPA, but not late PPA, through AS reduction during treatment. AS was reduced in both conditions, suggesting that individuals engaged in smoking cessation programs could reduce AS levels (regardless of whether AS is a key treatment target).

Note. AS = Anxiety Sensitivity; SD= Standard Deviation; ASI-3= Anxiety Sensitivity Inventory-3; IDAS= Inventory of Depression and Anxiety Symptoms; CO = Carbon monoxide; CBT = Cognitive-behavioral treatment; WTC = World Trade Center; PTSD = Post-traumatic Stress Disorder; LRS = Lower respiratory symptoms; CSC = Comprehensive Smoking Cessation; CSC-T = Comprehensive Smoking Cessation and Trauma Management; PCL = PTSD Checklist-Specific Version; SCID-NP = Non-patient version of the Structured Clinical Interview for DSM-IV; SHQ = Smoking History Questionnaire; FTND = Fagerström Test for Nicotine Dependence; TLFB = Timeline follow-back; NRT = Nicotine Replacement Therapy; EOT = End of treatment; ST+EX = Standard smoking cessation treatment, that is, CBT plus nicotine replacement therapy + Wellness education control condition; ASI-16=16-item Anxiety Sensitivity Index; PPA = Point-prevalence abstinence; PA = Prolonged abstinence; STAMP = Smoking Treatment and Anxiety Management Program; SCP = Standard Cessation Program; PANAS = Positive and Negative Affect Schedule.

Conclusions

Clinical recommendations and novel proposals for tobacco clinical research

Several guidelines can be drawn from the present analysis of the state of the art with regards to the relationship between AS and smoking cessation treatments. Firstly, both clinicians and researchers should focus on designing novel smoking cessation treatments from a transdiagnostic approach. Incorporating transdiagnostic components to address both emotional problems and smoking into existing smoking cessation treatments could enhance cessation rates and improve clinical services (Leventhal & Zvolensky, 2015). Secondly, adapting the AS Reduction Program for smoking cessation to the Spanish context, as previously done in Argentina (Zvolensky et al., 2014a), would allow researchers and clinicians to test the acceptability and clinical implications of the program in our country. However, further attempts to include protocols for AS into broader smoking cessation treatments must overcome prior research limitations. For example, most of the existing evidence has relied on case studies (Zvolensky et al., 2003; Zvolensky et al., 2008) or small samples (Martínez-Vispo et al., 2016; Zvolensky et al., 2014a). Also, since most of these previous studies are secondary in nature (i.e., works informing on ancillary outcome measures from randomized trials) there is no comparison group (i.e., control group). Consequently, further studies with experimental designs that allow us to ascertain the unique effect of AS on smoking outcomes are much needed.

On another note, follow-ups in previous studies are commonly conducted at short- (1-month follow-up; Zvolensky et al., 2008) or medium-term (3- or 6-months; Gonzalez et al., 2017; Smits et al., 2016; Zvolensky et al., 2014a). Abstinence at one year is a robust predictor for sustained abstinence (Nohlert, Ohrvik, Tegelberg, Tillgren & Helgason, 2013) and future studies should consider conducting longterm follow-ups. It is also important to mention that some interventions are still limited in their overall scopes as they comprise a narrow range of clinically-relevant variables from a transdiagnostic perspective (Martínez-Vispo et al., 2016; Richards, Cohen, Morrell, Watson & Low, 2013; Zvolensky et al., 2014a), hindering the generalizability of their results. In this sense, it is necessary to assess and treat other underlying transdiagnostic vulnerabilities (such as anhedonia or distress tolerance) in the same subsample of smokers, allowing us to better understand the relationship between emotional psychopathology, cigarette consumption, and smoking cessation (Leventhal & Zvolensky, 2015).

It should be noted that in our review, only four RCTs were found that included an AS protocol in combination with smoking cessation treatments, which may itself be a limitation in this field. Such RCTs are not exempt from shortcomings such as the inclusion of treatment-seeking smokers with only moderate levels of dependence (Smits

et al., 2016; Zvolensky et al., 2018) and moderate retention rates, which underpowers the detection of significant differences (Gonzalez et al., 2017). Perhaps these reasons explain why some studies have traditionally suggested modest improvements or even mixed results (Brown et al., 2007; Hitsman, Borrelli, McChargue, Spring & Niaura, 2003; Zvolensky et al., 2014a). With the aim of overcoming such limitations, RCTs designs should be developed comparing the efficacy of traditional cognitive-behavioral treatments (CBTs) for smoking cessation (e.g., see Becoña & Vázquez, 1997; Secades-Villa, Alonso-Pérez, García-Rodríguez & Fernández-Hermida, 2009) with CBT plus AS Reduction Programs for quitting. Relatedly, it would be essential to do so in different cultures and settings to guarantee generalization of results to other community settings (beyond controlled laboratory studies).

Finally, it seems essential to explore the AS construct among Spanish treatment-seeking smokers from a gender perspective. Women have increased their levels of tobacco consumption in recent years (Amos, Greaves, Nichter & Bloch, 2012; National Plan on Drugs, 2019), and being a female represents a risk factor for maintaining smoking behavior, since they show significantly fewer quit attempts and perceive more barriers to quit smoking (Allen, Oncken & Hatsukami 2014; Allen, Scheuermann, Nollen, Hatsukami & Ahluwalia 2016). In particular, previous studies have shown that female sex is positively related to high levels of anxiety (Nakajima & al'Absi, 2012) and AS (Norr, Albanese, Allan & Schmidt, 2015; Stewart, Taylor & Baker, 1997; Zvolensky, McNeil, Porter & Stewart, 2001). When analyzing lower-order AS dimensions (that is, physical, cognitive and social concerns), some authors have also found that women present higher physical sensations (Zvolensky et al., 2001) when compared to men. Nonetheless, these findings are limited to undergraduate and nonclinical samples (Norr et al., 2015). Future research should address these gaps in the literature by differentially exploring the AS construct among male and female emotionally vulnerable smokers, including as well other clinically relevant variables related to both smoking behavior and smoking cessation, such as negative affect, anhedonia or distress tolerance.

Conflict of interests

The authors declare no conflicts of interest regarding this study.

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