TOBACCO USE DISORDER AND DUAL DISORDERS

Joint statement by the Spanish Psychiatry Society and the Spanish Dual Disorders Society

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Sociedad Española de Patología Dual
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Adicciones y otros trastornos mentales
Fundación
PATOLOGÍA DUAL
SEPD

SOCIEDAD ESPAÑOLA DE PSIQUIATRIA

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Tobacco Use Disorder (TUD) and Dual Disorders: Joint statement by the Spanish Psychiatry Society and the Spanish Dual Disorders Society

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EXECUTIVE SUMMARY OF POSITIONING

Tobacco Use Disorder (TUD) is a health problem of the first order in the world population, affecting a vulnerable population, such as people with other mental disorders, whose morbidity and mortality are increased as a result.

The high prevalence of TUD in people with other mental disorders is fundamentally related to common, genetic and neurobiological factors linked to the cerebral nicotinic cholinergic system involved in mental functioning, health and disease.

Patients with mental disorders may find an improvement in their mental functioning at a cognitive and emotional level due to the nicotine released when using tobacco, with positive effects on neurocognition, mood, anxiety and certain pathological traits.

Difficulties in achieving tobacco abstinence, a desirable goal, are evident in a very large proportion of patients, so realistic goals must be proposed to ensure a reduction in harm.

The different pharmacological treatment strategies are not fully effective and need to be administered for prolonged periods of time, as with other psychoactive drugs.

Varenicline would be the first pharmacological option, followed by bupropion or both combined, as they have different mechanisms of action.

In this therapeutic approach, treatment with nicotine replacement agonists in their different forms (e.g. patches, gum or spray) at adequate doses and other unregulated nicotine release devices, such as electronic cigarettes, snus and heat-not-burn products should be considered.

As future prospects, the diagnosis of TUD should gain greater importance so that patients with other mental disorders, dual disorders, can receive appropriate multidisciplinary care and integrated treatment to reduce or stop tobacco use entirely.

1. TERMINOLOGY AND STIGMA

It is well known that stigma and its consequence, discrimination, particularly affect people with addictions and other mental disorders: a clinical condition known as dual disorders.

Despite advances in neuroscience and precision psychiatry, which support the model of brain dysfunction in mental disorders, including addictions, this has not been fully accepted by the healthcare community, which continues to consider addictions as behavioural and lifestyle problems.

The lack of knowledge of the relationship between tobacco use disorder (TUD) and brain systems and circuits, such as nicotinic cholinergic, occurs for both this and other mental disorders, and leads to terminology and care practice away from scientific evidence which is, therefore, doomed to be inefficient.

The stigma associated with TUD in people with other mental disorders hinders the scientific approach at all levels of prevention and treatment.

Although it is an enormously complex phenomenon, we believe that stigmatisation and discrimination are made worse by nomenclature and terms that promote ideas without a scientific basis, despite being incorporated into common (and the medical) vocabulary. Thus, in preparing the consensus, work has been done on the use of unified terminology, based on scientific evidence, leading to an approach to dual tobacco use disorder from a biopsychosocial perspective:

1. The word ***toxic*** is not used to refer to any substance or drug being used. Although in some cases drugs can act as toxic agents for the organism, most of the uses throughout the life of a consumer have an effect on cerebral functional alteration which is not toxic. As a consequence of this argumentation, derivative terms such as detoxification have also been avoided.

2. The word ***abuse*** to describe how drugs are taken has also been avoided. This is because it would imply a random division between drugs **'of abuse'** and other drugs (of use?), which has no neuroscientific correlation. Thus, the consensus will refer to substances, substances with addictive potential and, finally, drugs.

3. Classically, TUD has been referred to as a ***smoking or tobacco habit***. We understand a ***habit*** as a custom, lifestyle or habitual practice of a person, which does not fully correspond to the definition of a disease, which we believe addictions meet. Using this term can lead one to think that TUD is customary or voluntary conduct. Therefore, mentions of 'habits' and all related nomenclature have been avoided (for example, detoxification), which is firmly established in the clinical culture.

4. When referring to the treatment, in addition to avoiding the word *detoxification*, it was also agreed not to use terms such as ***cessation*** since, in many cases, the treatment objective is not necessarily to stop consumption (for some, it is). In general, terms such as TUD treatment, approach to TUD, abandonment of consumption, etc. are used.

5. Instead of ***mental illnesses***, the term *mental disorders* has been widely used, as it is a more inclusive term in line with the latest classifications and diagnostic manuals.

6. In general, the concept of dual disorders in the idiosyncrasy of the document has been attempted to be included. Addictions are brain diseases that involve systems, circuits and functions which are also involved in other mental disorders. Therefore, the phenomenological expression of both disorders will be mutually influenced. Whenever reference is made to the concept of dual disorders, it is intended that the concept should contain this integrating paradigm of mental disorder and addictions.

7. If there is any doubt regarding terminology or other mental disorders, the terminology used and defined in the DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders*) has been chosen[1].

These proposals in relation to nomenclature are a first step in the effort needed to provide the Dual TUD with effective instruments to advance in a therapeutic approach appropriate to the scientific advances of this third decade of the 21st century.

2. OBJECTIVES OF THE DOCUMENT

This document represents an agreement between a group of Spanish specialists in psychiatry, experts in tobacco use disorder and dual disorders. The aim is to establish a position that evaluates the current context of tobacco use disorder among people with other mental disorders and its treatment from the integrative perspective of dual disorders, involving the paradigms of clinical neuroscience and precision psychiatry. The text has the endorsement of the Spanish Psychiatry Association and the Spanish Dual Disorders Society.

3. METHODOLOGY

To prepare the document, a group of representatives from both scientific societies were chosen for their experience in dealing with tobacco use disorder in people with other mental disorders. They formed a working group of the professionals who signed the document: members of the Spanish Dual Disorders Association and the Spanish Psychiatry Society.

The current evidence in the scientific literature was updated and critically reviewed; with articles published in English and Spanish being used. The main database consulted was the US National Library of Medicine, PubMed, online, as well as searches in the Cochrane Library (John Wiley & Sons) and the Scientific Electronic Library Online (SciELO).

The recommendations in this text regarding the TUD approach in dual disorders summarise the opinion of most experts, although they need to be adapted to the specifics of each case, within the aforementioned perspective of precision psychiatry. Their compliance does not guarantee a satisfactory result in all patients, so professionals who consult them must always use their own clinical judgment when treating their patients.

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4. INTRODUCTION

CHAPTER SUMMARY

Over 30% of the general public in Spain have consumed tobacco in the last year.

The percentage of smokers who do not consider stopping is 37-40% and reaches 60% in patients with mental disorders.

Over 75% of patients with severe mental disorders have another mental disorder such as substance use disorder (SUD). Tobacco is the substance with the highest incidence, at 70%.

People with mental disorders have benefited less from policies to reduce consumption than those without mental disorders, and have more than twice the prevalence of use.

People with mental disorders receiving treatment are more likely to decrease the incidence of tobacco use than those without treatment.

Tobacco use is a public health problem that concerns society and health authorities, as it is the main preventable cause of morbidity and mortality in our environment.

According to the United States Centres for Disease Control and Prevention (CDC), tobacco use decreased from 20.9% in 2005 to 14.0% in 2019, with an increase in the proportion of "smokers" who had stopped smoking. According to the WHO, Europe has the highest prevalence of tobacco use (28%) among adults and one of the highest among adolescents, leading to one of the highest proportions of deaths attributable to tobacco. The WHO has estimated that tobacco use is currently responsible for 16% of all deaths in adults over 30 years of age in Europe, with many of these deaths occurring prematurely[1,2].

Over 30% of the general population in Spain used tobacco in the last year, according to surveys by the National Drugs Plan, PNSD[3]. It is clear that not all of them suffer from tobacco addiction, just as not all those who drink alcohol have an addictive disorder.

In the Ministry of Health PNSD survey on alcohol, drugs and other addictions in Spain (EDADES 2019-2020), the percentage of smokers who do not plan to stop smoking stood at 37-40%[3]. In the Spanish Patient Forum HABITA-patients project (v3) report (publication pending, 2021) the percentage of patients with mental disorders who do not intend to quit smoking was 60% of the sample.

According to the PNSD, tobacco use among women aged 15-64 years was lower than that of men with (34.2% vs 44.4%), and has been lower for the last 20 years, although this difference has been decreasing since 2017[3]. Tobacco use and TUD were more prevalent among adults identified as having a minority sexuality compared with heterosexual adults, according to the DSM-5 from the year before, with notable variations based on gender, age, ethnicity and sexual identity-attraction differences. Elevated rates of any tobacco use and TUD among persons of a minority sexuality were more frequent among younger lesbian women and gay men, and all age groups of bisexual men and women. The probability of any tobacco use and TUD were significantly higher among women with sexual identity-attraction differences and significantly lower among men with the same differences, according to the DSM-5[4].

Addiction is a mental disorder and the scientific community considers mental disorders to be disorders of the brain. Mental disorders, depression, psychosis and tobacco addiction are not chosen and depend on the existence of prior genetic and environmental vulnerability factors.

From the scientific perspective, therefore, "use" of tobacco must be distinguished from Tobacco Use Disorder (TUD) as with other substances, for example, alcohol. TUD is a mental disorder recognised by all international classifications (DSM-5 and ICD-WHO) and therefore a disorder of the human brain.

The association between substance use disorders (SUD) and mental disorders (MD) is well established.

It is estimated that more than 75% of patients with severe mental disorders (SMD) also have another mental disorder such as a SUD[5] and, of these, tobacco is the substance with the highest incidence.

Studies have generally not taken into account this link between mental disorders and substance use. This may be important, since the higher prevalence of substance use among individuals with MD may partly explain the strong association between SUDs, including tobacco use disorder, and MD.

According to the USA National Epidemiological Survey on Alcohol and Related Conditions (NESARC), lifetime diagnoses of any MD and, in particular, personality disorders and psychotic disorders were associated in most substance categories with a higher prevalence of transition from substance use to SUD (remembering that using substances is not the same as having a SUD). This association was particularly significant for TUD (adjusted OR = 2.95 (2.72-3.20)[6].

Social circumstances put the population in contact with potentially addictive substances, such as tobacco; however, it is individual, genetic, neurobiological factors and personality traits along with other mental disorders and dual disorders that trigger problematic or addictive behaviour[7]; in this case with tobacco (TUD). Evidence from clinical neuroscience indicates that people choose to use legal or illegal "drugs", but only a minority (about 10%) will develop serious addictive behaviour[8].

People smoke mainly for nicotine, the main active ingredient identified in tobacco. Tobacco causes approximately 50% of people who smoke to die prematurely from a tobacco-related complication, losing on average approximately 10 years of life[9]. Exposure to tobacco smoke also affects and kills non-smokers who are involuntarily exposed to tobacco smoke; in the US, this is estimated at 50,000 people a year[10].

Tobacco is a cause of mortality for its role in the appearance of oncological, pulmonary and cardiovascular diseases. It can also lead to many other conditions that impact the functionality and quality of life: e.g. respiratory infections, decreased fertility, osteoporosis, gastric and duodenal ulcers and diabetes. Most of these complications are due to exposure to toxic gases related to tobacco combustion (of which thousands have been identified - more than 70 of which have been shown to be carcinogenic) and not to nicotine itself; however, nicotine is the main cause of tobacco addiction and its effects[11]. Nevertheless, it cannot be ruled out that other tobacco components enhance the addictive capacity of nicotine.

Regulatory pressures have encouraged industry (including that of tobacco) to develop new products and ways of consuming nicotine. Despite this diversification, traditional cigarettes are still by far the main way of consuming nicotine in Spain and in the rest of the world[12].

The difference in TUD prevalence between people with and without mental disorders is substantial. Despite advances in reducing tobacco consumption in the general population, many studies indicate that people with mental disorders have benefited less from policies to reduce consumption[13], which lies at twice that of the population without mental disorders[14]. Some analyses even suggest that the prevalence of daily and non-daily tobacco use may be increasing among adults with mental disorders, while continuing to decline among those without these vulnerabilities[15].

Thus, it is estimated that half of the smokers in the US suffer from another mental disorder[16], and that they consume between 30.9% and 50% of the total cigarettes sold[14,16,17]. Therefore, efforts to reduce tobacco consumption are not reaching all population groups equally; in the US, 36% of people with mental disorders smoke, while only 21% of the general population do[18].

Recent US publications indicate that tobacco use is declining in the general population, but remains high among adults with mental health problems. The authors indicate the relationship between "serious psychological distress" and the use of cigarettes and electronic cigarettes among US adults from 2014 to 2017[19].

In Spain, patients with mental disorders consume 40% of tobacco and 70% of people with mental disorders are smokers[20]. Among smokers, having a mental disorder is associated with greater use and severity of tobacco addiction[21]. Also, people with an alcohol use disorder who also have another mental disorder are less likely to stop smoking[22-24]. It seems that TUD should be reconsidered to develop public health approaches aimed at people with mental health problems.

In the US, the life expectancy of people with severe mental disorders is 25 years less than for the general population[25]; this represents approximately 200,000 of the more than 500.000 tobacco consumption-related deaths per year[26]. For patients suffering from schizophrenia, this difference is up to 28 years of life, and has lately been increasing[27]. The conclusion of several analyses is that diseases derived from tobacco use are the main cause of this shortening in life expectancy[28]. Approximately half of deaths in the US in people with serious mental illness are causally related to tobacco use[29]. Tobacco is also the leading cause of death among people who use other substances[30].

In addition to tobacco-related morbidity and mortality, there are many other repercussions related to tobacco for people with mental disorders[31]: financially, the money

spent on tobacco can represent a significant part of their income[32]; and, at a social level, tobacco consumption increases discrimination and stigma[33].

People with mental disorders smoke 2-4 times more than the general population. TUD rates are particularly high among patients with severe mental disorders (i.e., those showing greater functional impairment). Although estimates vary, up to 70-85% of people with schizophrenia and up to 50-70% of people with bipolar disorder have TUD. Also, people with a TUD with another mental health disorder tend to smoke more cigarettes than the general population. The average number of cigarettes smoked in the past month was higher among those with a mental illness compared to those without. Having a mental disorder when stopping smoking is a risk factor for TUD relapse, even among those who have not smoked for over a year. Many smokers with mental disorders want to stop for the same reasons cited by others (such as health and family), but may be more vulnerable to relapse related to mental symptoms, such as stress and negative feelings[34].

It seems clear there is a relationship between TUD and other mental disorders and a strong hypothesis is the existence of common brain factors[7,35]. The human brain contains systems and circuits, such as the opioid, cannabinoid or nicotinic cholinergic, which have been identified with the names of substances with an addictive capacity, although their purpose is the survival of humans beings, from an evolutionary point of view. One of its important objectives is mental functioning[35]. These systems, the nicotinic cholinergic, for example, are dysfunctional in people with mental disorders which puts them at risk of developing nicotine addiction behaviour. People with these alterations smoke mainly for nicotine and find it in tobacco. Polymorphisms of the brain nicotine receptor (the alpha-5-CHRNA5 unit) have been found that predict who will be severe compulsive smokers with serious difficulties in stopping this behaviour, including more chances of relapse[36].

The presence of dual disorders, tobacco addiction and other simultaneous or sequential mental disorders, is highly prevalent and not an exception. However, the approach to this clinical condition by mental health services has been ambivalent, if not deficient.

The use of tobacco has been promoted for years in both psychiatry and addictive disorder units in treatment centres[37]. Only recently have restrictive measures been introduced in psychiatric hospitalisation units, but only in short-stay units, and it has been common for years for staff to smoke with patients, even as a strategy to strengthen the therapeutic bond. Tobacco has also been used as a reward or incentive, or given to manage agitation states. This has all contributed to the chronification of consumption and to less benefit being obtained from anti-smoking strategies for this group than for the general population. In addition, despite the general prohibition or limitation of smoking during hospitalisation, this has often been accompanied by the possibility of prescribing drugs for the treatment of TUD during admission. However, in general, it has not been accompanied by integrated treatment programmes or the option of referral at discharge to specific resources for the treatment of TUD.

Although help for TUD has been shown by some authors to be effective and well tolerated in patients with severe mental disorders, these patients are less likely to receive help to stop smoking, even when their motivation is often high[27]. Thus, the motivation to stop smoking has been described as even greater than in the general population in many jobs. It has been found that 65% of patients admitted to psychiatric hospitalisation units who smoke are interested in quitting[38].

However, it is more difficult for people with dual disorders to stop smoking despite their determination and the will, moreover, is not always present. Many patients insist they "like smoking" and that we experts should translate it as "I can't stop smoking", since tobacco, in the words of patients, "makes them feel like better people", calms their anxiety and anger, facilitates sociability and improves depression and cognitive and attention difficulties, for example[39-42].

People who receive treatment for mental disorders have a lower incidence of tobacco use than those who do not receive treatment and are more likely to be successful when they try to stop smoking[13]. Although integrated intervention models (mental health treatment together with the TUD approach) have been shown to be particularly useful, it is still unusual to find centres, devices or programmes that provide joint treatment[25].

Deterioration in the mental health of patients who stop smoking has been an ever-present concern. Although most of the accumulated evidence suggests that stopping smoking can improve the quality of life and affective status of patients with mental disorders[43], there is still a need to expand knowledge in this field, since other studies have suggested an increased risk of psychopathological disorders in the population of ex-smokers[44,45]. In these studies, tobacco and nicotine were not distinguished. However, it remains to be clarified whether the benefits and risks of stopping smoking in people with dual TUD are different to those for the general population.

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5. APPROACH FROM THE DUAL DISORDERS PARADIGM

CHAPTER SUMMARY

Factors such as prior vulnerability, genetics, neurobiological factors linked to the brain's nicotinic cholinergic system and environmental factors facilitate the development of tobacco addiction, which interactively influences other mental disorders.

The treatment of TUD also influences the improvement of other mental disorders, so the approach must always be attempted in an integrated and joint manner, as in general with dual disorders.

The concept of dual disorders has been used in recent times to refer to patients who suffer from an addictive disorder and another mental disorder. They can occur simultaneously or, almost more importantly from a conceptual point of view, sequentially throughout life[1]. The definition implies a relationship that reflects brain factors that may be common, as well as an interaction between both psychopathological expressions, influencing each other in clinical presentation, evolution and prognosis[2]. The relationship between both disorders is complex and is mediated by multiple factors: e.g. genetic, neurobiological, neurodevelopmental, environmental, social, ethnic and cultural.

Despite abundant scientific evidence that demonstrates the shared neuroanatomical and neurofunctional bases between addictive and other mental disorders, the concept of dual disorders is relatively new[3]. An addiction is an acquired disease of the brain. After exposure to an initially voluntary substance (usually), differences in individual vulnerability, from a combination of genetic and environmental factors, will protect or increase the risk of addiction and its different phenotypes[4]. Thus, as with other substances, only a small proportion of people who are exposed to tobacco develop the phenotypic presentation of an addiction.

The high prevalence of TUD and other mental disorders cannot be explained by conceptual or appraisal artefacts, strongly suggesting that this dual disorders is not due to random or coincidental factors alone. It seems reasonable to explore the claim that both conditions are somehow causally linked[1].

The clinical perspective of the neuroscience of addictions establishes that an addiction involves a set of interconnected brain processes, rather than being a disorder established primarily by a single behaviour (uncontrollable drug use)[5]. This makes it possible to affirm that addiction always occurs with other manifestations of mental disorders, dual disorders.

Some factors related to an increased risk of developing TUD appear in Table 1.

Table 1 Risk factors for the development of tobacco use disorder

Risk factor	Considerations
Genetics and family history of tobacco use and other mental disorders[6]	• Family history is probably a compendium of genetic and environmental risk factors for developing TUD. • The most strongly involved genetic factor is a polymorphism in the CHRNA5 gene, which encodes the α5 subunit of the nicotinic receptor. It is related to severe TUD. • Another well-identified factor is the CYP2A6 gene that identifies fast or slow metabolisers of nicotine. • Rapid metabolisers smoke more tobacco per day and have less success in specific treatment.
Age of onset[7]	• Increasing risk with decreasing age. Age of onset is delayed in those with low genetic risk. • Most individuals with TUD start smoking before the age of 18. • At this age, brain neurodevelopment has not yet reached maturity and is especially vulnerable to substance use. • A younger age of onset has been associated with higher genetic risk, greater severity of addiction, dual disorders, more years of consumption, less chance of stopping smoking and of maintaining abstinence.
Suffering from other mental disorders	• Mental disorders, with greater severity, are associated with higher rates of substance use and non-substance addiction[8] • The self-medication and self-regulation hypothesis posits that people with a mental disorder use tobacco to improve their cognitive and emotional functioning[9]. • Other models, with less empirical evidence, have causally linked tobacco consumption with the development of mental disorders[10]. • Tobacco use induces the metabolism of some drugs, lowering their serum concentrations, so that people with mental disorders could mitigate side effects when smoking[11].
Suffering from other mental and substance use disorders[12]	• It has been suggested that tobacco is a "gateway" to the consumption of other drugs. Tobacco consumption at an early age would make the brain more sensitive to developing other addictions. This gateway hypothesis has recently been ruled out for cannabis, for example. • Other mental disorders are risk factors for developing TUD. • Tobacco can enhance the rewarding effects of other drugs and decrease unwanted effects (e.g., less sedation with alcohol consumption). • Achieving abstinence with TUD may improve long-term treatment outcomes for other addictions.

Although in practice we are so used to working with categorical or dichotomous models that it does not seem realistic to be able to dispense with them in the short term, the use of a dimensional approach, instead of a categorical or dichotomous one, increases the probability of designing flexible approaches taking into account the specific features of each person[13].

From clinical neuroscience, the "transdiagnostic" approach has been proposed as a promising alternative. This reflects brain science and the evidence that leads us to understand mental disorders as brain alterations reflected in domains such as cognition, emotion and behaviour. This proposal is expected to cut across existing categorical diagnoses and go beyond them, to improve the way we classify and treat mental disorders[14].

However, categorical diagnoses also have many advantages, such as facilitating standardisation of diagnoses and understanding between clinicians and patients. The integration of these models with the dimensional and transdiagnostic nuance of the categorical one may be a non-disruptive advance with the current taxonomy, bringing us closer to a more personalised, precise psychiatry[7,15].

Personalised medicine is based on the concept that a specific person may have a different response to a treatment than the general one[16]. Thus, in the field of dual disorders and, in this case, in dual tobacco use disorder, we would need more exhaustive predictive models to anticipate the therapeutic needs of different individuals and their phenotypes using evidence-based models[17].

Self-medication hypothesis

According to this hypothesis, patients with mental disorders smoke, by trial and error, and find that tobacco use improves their mental functioning at a cognitive and emotional level[18]. This hypothesis, which is progressively corroborated by neurobiological findings, has been refuted by other authors to influence models that have linked tobacco consumption with the development of mental disorders[19]. Bidirectional approaches hold that prior genetic and environmental vulnerability facilitates the development of tobacco addiction, and that this behaviour interactively influences mental disorders[20].

Nicotine use could be a form of self-medication used to improve cognition and mood, attenuate dysphoria and stress, agitation, negative symptoms of the disorder, improve cognitive performance or reduce the severity of side effects of antipsychotic medication[21], as well as appetite and food intake[22], regulating a probable dysfunctional cerebral nicotinic cholinergic system[1].

The self-medication hypothesis has been criticised over concerns that promoting abstinence might worsen symptoms of depression, anxiety, psychosis and other substance use, and be a significant limitation for the treatment of TUD in patients with mental disorders. This proposal has led to much debate in the field of dual disorders, since patients with TUD who achieve abstinence can have a high incidence of mental disorders and relapse rates[23].

Despite this evidence, there are still some authors who have analysed the influence of stopping smoking and point out that worsening at the psychopathological level has not been demonstrated, and even indicate that improvements have been seen[24,25]. One interesting finding is that stopping smoking, in the context of SUD treatment, has been related to a higher probability of success in stopping using other substances[26].

Although personalised interventions to achieve tobacco abstinence in people with severe mental disorders may be successful 6 months after starting, their effects fade after 12 months[23], indicating the problem is more complex and it is a mistake to assess it as a behavioural problem.

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6. NICOTINIC ACETYLCHOLINE SYSTEM AND RECEPTORS

CHAPTER SUMMARY

Brain dysregulation of the nicotinic acetylcholinergic receptor (nAChR) system - involved in the functioning of many other neurotransmitter systems and circuits - may explain the shared vulnerability of TUD and other mental disorders.

The nAChR system may play an important role in basal affective regulation and other dimensions of mental functioning in health and disease.

The inhibition of monoamine oxidase (MAO) in people with TUD, by a mechanism other than nicotine, could have effects on mood and be another addictive mechanism for tobacco.

There is clear scientific evidence for the genetic basis of substance use disorders, as with other mental disorders, such as the identification of variants in various genes that correlate with clinical variables of tobacco addiction.

Positive effects on neurocognition, mood, anxiety and certain pathological personality traits appear to be more pronounced in smokers with severe mental disorders and may be a significant mechanism explaining the dual disorders of severe mental disorders and TUD.

Brain dysregulation of the nicotinic acetylcholinergic receptor (nAChR) system, involved in the functioning of many other neurotransmitter systems, may explain the shared vulnerability of TUD and other mental disorders[1].

nAChRs belong to a superfamily of cys-loop ligand-gated ion channels that respond to endogenous acetylcholine (ACh) or other cholinergic ligands.

These receptors are also the target for substances such as nicotine (the main addictive capacity agent released by cigarette smoke) and are involved in a variety of physiological and pathophysiological processes. Numerous studies have shown that the expression and/or function of nAChRs is compromised in many neurological and psychiatric diseases. Furthermore, recent studies have shown that neuronal nAChRs are found in a large number of non-neuronal cell types[2].

Nicotinic acetylcholine system receptors regulate the neurotransmission of several pathways in the central nervous system (CNS) and are important modulators of cognition and emotions[3], as well as influencing the functioning of practically all the organs in the body; they are also present in the peripheral nervous system (PNS). The binding of nicotine opens the channel and allows the entry of sodium, potassium or calcium, releasing neurotransmitters of many types: dopamine, glutamate, GABA, norepinephrine or serotonin[4].

The rate of nicotine metabolism is associated with the availability of nAChRs at the thalamic level.

Table 2 Neurotransmitters released by nicotine acting on the CNS and their clinical effects.

Neurotransmitter	Modulated effect
Dopamine	Involved in the response to consumption in the brain reward circuit
Norepinephrine	Cognitive enhancement
Acetylcholine	Surveillance and improvement in cognitive functioning and negative symptoms
Glutamate	Increased memory and learning capacity
Serotonin	Involved in anxiety and mood
GABA	Decreased stress and anxiety

nAChR is a heteroreceptor (neurotransmitter release modulation) consisting of 5 transmembrane domains (α 9 isoforms and β subunits -3 isoforms) that combine to form a functional receptor. The different combinations give rise to the

different subtypes; some of these are more susceptible to the action of nicotine and promote dependence on it. They have a low affinity for nicotine, so they require high concentrations to be activated. Chronic exposure to nicotine modifies the expression of the subunits. Changes in the receptor have a profound impact on its function in the brain's reward system.

Tobacco smoke carries nicotine to the lungs, where it is rapidly absorbed, passing into the pulmonary venous circulation, and from there to the brain and the rest of the body, where it binds to the receptors of the nicotinic cholinergic system (ion channels physiologically stimulated by acetylcholine) to exert both its psychoactive and other effects[5]. It is estimated that nicotine takes 15-20 s to reach the brain[6].

The α7 nicotinic cholinergic receptor has been shown to play an important role in cognitive function, both in animal and human studies. Its activation increases cholinergic transmission and glutamate and dopamine release related to its pro-cognitive effects and negative symptoms[7].

There is clear scientific evidence for the genetic basis of SUDs, as with other mental disorders. The study of endophenotypes within the framework of individual differences, such as different personality traits linked to brain systems and specific gene variables, is beginning to offer a manageable approach to studying dual disorders. These personality traits, and the genes that modulate them, dynamically interact with the environment and with substances to ultimately determine vulnerability, the particular effect of the substance and the resilience of an individual to developing an SUD[8].

Recent research has identified variants in numerous genes that correlate with clinical variables of tobacco addiction, such as age of first use, risk of relapse and response to treatment. For example, polymorphisms of the α5 nicotinic cholinergic receptor (CHRNA5) predict more severe addiction to tobacco, with difficulties for withdrawal and frequent relapses. In 2014, polymorphisms were identified for the CYP2A6 gene that encode different rates of nicotine metabolism; fast or slow[9].

This interindividual variability in nAChR and CYP2A6 availability underlies the differences between slow, fast and normal metabolisers of nicotine[10,11].

From precision psychiatry, the NIDA has compiled information on different polymorphisms (SNPs) and developed a polygenic score that can predict responses to primary prevention interventions in schools: All students who received the intervention entered into contact with tobacco later than those without this educational activity, but the difference was highly significant in those with low hereditary risk. Therefore, genetic factors could be strengthened by environmental interventions[12].

Among other actions, as with other substances, nicotine increases the meso-corticolimbic release of dopamine. Dopamine release in the nucleus accumbens (NA) is probably the main mediator of nicotine reward. In vivo, the injection of nicotine has shown a release of dopamine in the NA of a similar magnitude to that produced by cocaine[13]. Dopamine regulation would therefore be a potentially therapeutic mechanism in patients with TUD[14,15]. In human studies, "positive emotionality" traits have been associated with dopamine D2 receptor availability in healthy controls and are associated with resilience to SUDs[16]; in this case, nicotine addiction.

The nAChR system may play an important role in basal affective regulation[13] and other mental functioning dimensions in health and disease. Recent research, for example, finds support for the modulatory role of the cholinergic nicotinic system in clinical situations of social deficit and repetitive behaviours, which makes it a therapeutic target for clinical conditions such as autism spectrum disorder[17].

Genetic variations in the dopamine transporter, dopamine receptors or catechol-o-methyltransferase may partially mediate the relationship between smoking phenotypes, cognitive effects and some mental disorders, ADHD or psychosis[18.]

However, it is now known that compulsive drug use goes beyond the simple reinforcement mechanisms of the brain's dopaminergic reward system[16]. Preclinical evidence indicates that nicotine modulates various neurotransmission systems, including, in addition to dopamine, glutamate and GABA (γ-aminobutyric acid). As an example of a clinical response that supports this claim, nicotine administration can improve certain neuropsychological deficits in patients with psychosis: reaction time, visuospatial memory, sustained attention and modulation of sensory input[1].

NICOTINE

Nicotine is an alkaloid organic compound found in high concentrations in the leaves of the tobacco plant (Nicotiana tabacum). It can be absorbed through the mucous membranes or in the pulmonary alveoli. As explained, the nicotine available in tobacco smoke reaches the CNS quickly, which is believed to be important in its addictive potential. Thus, nicotine consumed by other routes (e.g. transdermal) has less addictive capacity[19].

A smoker is estimated to extract 1-1.5 mg of nicotine per cigarette[6]. It has a half-life of about 2 hours, although

this may vary with environmental and individual (e.g. genetic) factors. Daily tobacco users, however, usually achieve a stable nicotine concentration in their body, except during sleep.

Nicotine metabolism occurs mainly in the liver through the isoenzyme 2A6 of cytochrome P450 (CYP2A6), whose activity is greatly influenced by genetic or environmental factors; one such factor is the consumption of some frequently used antipsychotic drugs, olanzapine and clozapine. Oestrogens also have a significant influence on nicotine metabolism, so premenopausal and especially pregnant women are more likely to need more cigarettes per day[20]. The main metabolite of this reaction is cotinine, which is frequently used as a biomarker of tobacco consumption.

There are genetic, pharmacokinetic and demographic factors that influence nicotine sensitivity in both people with TUD and those who have never smoked.

The effects of nicotine on the cardiovascular system are also controversial, and recent findings have shown that nicotine's angiogenic and proliferative effects are mediated by activation of nicotinic receptors on vascular cells. This could be negative if there are neoplasms and lead to pathological neo-vascularisation[21].

Nicotine can also lead to loss of the endothelial barrier of the lungs, depending on the dose[22]; although other findings indicate that nAChR activation may be a promising molecular target to halt lung cancer progression and reopen mitochondrial apoptotic pathways[23].

It seems proven that nicotine induces abnormalities in the cytoplasm without significantly producing cell death, while conventional tobacco smoke induces massive cell death and various abnormalities at the cellular and molecular levels in surviving endothelial cells and fibroblasts[24].

The subjective, cardiovascular effects and toxicity of nicotine are associated with the presence of reduced-function CYP2A6 alleles, presumably reflecting the slow metabolic inactivation of nicotine. This has implications for understanding individual differences in responses to nicotine, such as nicotine medications, particularly when used to treat medical conditions in non-smokers, and possibly vulnerability to developing nicotine addiction[25].

In general, chronic exposure to nicotine leads to an upregulation of nicotinic receptor density in the CNS[26]. This regulation seems to explain the development of physiological dependence symptoms, as well as those of withdrawal in the absence of consumption. The brain regulates its functioning under repeated exposure to nicotine, and develops tolerance to its effect. When consumption is interrupted, withdrawal symptoms appear: anxiety, irritability, worsening mood, difficulty sleeping, increased appetite or decreased ability to concentrate19. These symptoms lead to an intense desire to smoke to relieve the discomfort. Thus, after prolonged exposure to nicotine, the smoker ends up consuming mainly to reduce the discomfort associated with decreased nicotine concentration in the blood, rather than for the positive effects perceived after initial consumption. We now know that physiological dependence is different from addiction (DSM-5) and that this statement does not reflect the experience of other individuals, with more or less well-identified mental disorders, for whom the "positive" effects of nicotine are very significant.

From precision psychiatry, it is beginning to be known that similar substances can give rise to different behavioural, affective, cognitive and sensory effects in different people, depending on their prior vulnerability. For example, stimulants calm some individuals and decrease their impulsivity, while they can arouse and generate impulsivity in others. These different effects can also be found in relation to alcohol, cannabis, opioids and nicotine[27].

The relevance of the nicotinic system in clinical symptoms of mental disorders can be seen in research suggesting that nicotine administration reduces the frequency of a clinical dimension such as anger in both smokers and non-smokers. Addiction to nicotine may not be necessary for nicotine to have an ameliorating effect on hostility and agitation. Therefore, it is possible that nicotine replacement therapy can reduce aggressiveness in both smokers and non-smokers[28].

Positive effects on neurocognition, mood, anxiety and certain pathological personality traits appear to be more pronounced in smokers with severe mental disorders, such as schizophrenia, and may be a significant mechanism explaining the dual disorders of schizophrenia and other severe mental disorders and TUD.

Although the main drug substance associated with TUD is nicotine, accumulating evidence suggests that nicotine acts mainly as a primary reinforcer and that other factors are involved in the establishment of TUD. Inhibition of monoamine oxidases (MAO) has been suggested to be involved in this process[19,29]. It has been shown that inhibition of monoamine oxidase is significant in smokers, and does not seem to be linked to nicotine. It remains unclear how the inhibition seen in the brain of smokers occurs[30].

Future studies need to address whether the lower MAO level/activity seen in smokers is also seen in users of other tobacco products and whether this change is involved in their TUD-inducing effects[31].

This debate opens the theoretical possibility that smokers find relief in their depressive symptoms due to this MAO inhibitory action of tobacco, independent of nicotine, and this leads to TUD. Also, there is the possibility that modulation of the cholinergic nicotinic system by drugs or nicotine is not sufficient in some patients and explains the failure of the therapeutic measures put in place.

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7. PHARMACOLOGICAL TREATMENT OF TUD IN PATIENTS WITH OTHER MENTAL DISORDERS (DUAL DISORDERS)

CHAPTER SUMMARY

There is a shared genetic and neurobiological vulnerability for TUD and other mental disorders, such as schizophrenia, bipolar disorder, depression, anxiety, PTSD and OCD.

People with severe mental illness start smoking earlier, usually before the first overt symptoms appear, smoke more cigarettes per day, inhale more intensely to extract nicotine and are more vulnerable to developing tobacco-related illnesses than the general population.

Currently, there are pharmacological treatments approved by the AEMPS, EMA and FDA for the indication of TUD with adjuvant motivational therapy: nicotine, varenicline, bupropion and cytisine.

Pharmacological treatment of TUD can have an impact on improving other manifestations of mental disorders, such as mood, anxiety, cognition and attention.

Other nicotine replacement strategies not approved by regulatory agencies, such as the nicotine delivery devices snus, electronic cigarettes or heated tobacco, could be useful tools for the treatment of TUD in patients with other mental disorders.

In the field of addictions, replacement therapy strategies have been the most successful. It has been proposed to promote research on the safety and efficacy of nicotine-releasing devices, such as the electronic cigarette, as a substitute treatment strategy for harm reduction in people with mental disorders and TUD.

Heat-not-burn tobacco is another alternative that could be useful for patients with mental disorders to abandon or reduce conventional tobacco use, according to preliminary data; although more scientific evidence is still needed.

Maintenance drug therapy might improve long-term abstinence rates in people with a serious mental disorder, such as schizophrenia or bipolar disorder.

Most mental disorders, including substance use disorders such as SUD, are chronic illnesses, requiring very long-term treatment. This is not considered in technical data sheets or in public system financing.

TUD is a first-order health problem worldwide. In 1984, the World Health Organisation (WHO) recognised this addiction as a public health problem directly related to Chronic Obstructive Pulmonary Disease (COPD), lung cancer, ischaemic heart disease and stroke, which is the leading cause of preventable death in the world. There are groups that are especially vulnerable to this addiction, among them young people and especially those with other mental disorders, for whom the TUD approach constitutes a priority need[1], as will be detailed below, since the prevalence of TUD for them is much higher and more difficult to address than for the general population[2] .

People with severe mental disorders have a prevalence of addiction to tobacco and other substances above 75%[3], more than twice the prevalence in the general population (33%). People with severe mental disorders die on average 15-20 years earlier than the general population, largely due to preventable causes such as TUD[4].

People with severe mental disorders start smoking earlier, smoke more cigarettes per day, inhale more intensely to extract nicotine and are more vulnerable to developing tobacco-related diseases than the general population[5].

The problem of tobacco addiction in patients with other mental disorders is twofold: firstly, the high prevalence of TUD in this group and, secondly, the scarcity of studies and treatment guidelines that specifically address how to approach this clinical condition in dual disorders[6-9]. Therapeutic proposals tend to focus on TUD as a behavioural problem, ignoring that it is a chronic brain disorder, like other mental disorders. For these reasons, it is imperative to prioritise studies in this field to establish the most appropriate treatment strategy for each of the mental disorders.

PHARMACOLOGICAL TREATMENTS FOR DUAL TUD

In the SUD field, medication is frequently labelled (indicated) according to its main symptomatic effects; for example, anticraving drugs or old concepts such as replacement therapy, although the perspective of neuroscience offers a more rational vision based on the mechanism of pharmacological action[10].

Neuroscience-based nomenclature (NbN) has been developed in the last decade to classify the treatments used in this field of mental health, including SUDs[11].

For example, there are drugs approved labelled as anticraving, which describes the therapeutic expectations but not their mechanism of action, and replacement therapy, which simplistically alludes to identifying the class of drugs they actually are. In relation to this review, it is proposed to talk about nicotinic drugs, which modulate nAChRs[10].

Returning to traditional indications, there are currently three pharmacological treatments approved by the Spanish Agency for Medicines and Health Products (AEMPS), the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) for the indication TUD with coadjuvant motivational therapy: nicotine, varenicline and bupropion[12].

There are also other unconventional treatment approaches that deserve special attention due to their peculiarity. The mechanism of action, dosage guidelines, advantages and disadvantages of each of these are detailed below.

Nicotine replacement therapy (NRT): These treatments act as modulators of nAChRs with acetylcholine being an important brain neurotransmission system involved in vital physiological functions, such as mood regulation, vigilance, motility, memory and learning[13]. This receptor system is also involved in the reward process and regulates dopaminergic transmission at the mesolimbic and mesocortical levels, mainly as an agonist of nicotinic cholinergic receptors (nAChR) α4, β2 and α7, which lead to dopamine release in the dopamine brain reward system.

Dopamine is essential in the development of addictive behaviour and until now the mechanism has been considered to depend on dopamine-dependent plasticity processes within neural networks. However, drug exposure also triggers cellular and molecular adaptations that go beyond dopamine[14], and they would go a step further in the identification of the neurobiological mechanisms of addiction.

When nicotine treatment is started, it acts on the nAChRs and in particular on receptor subtypes such as α4, β2 and α7[10].

The symptomatic action includes a wide clinical range, such as improving withdrawal, craving and symptoms not related to physiological dependence, such as irritability, anxiety, depression, drowsiness, difficulty concentrating, headache, hunger and sleep disorders.

Administration approved by nicotine regulatory agencies includes a variety of formulations that are administered as follows: orally (e.g. chewing gum, sublingual lozenges and inhalers), via nasal mucosa (sprays) or with skin patches. The pharmacokinetics for these drugs differs

from that for nicotine released from burning tobacco, for example.

In this positioning document, we have already stated that the effects of administering nicotine will depend on individual variables determined by genetic differences, both pharmacodynamic and pharmacokinetic.

This treatment is almost twice as effective as placebo (OR=1.84; 95% CI=1.71-1.99)[15].

Table 3 summarises the dosage guidelines, safety aspects and other clinical considerations related to NRT[16].

Table 3 Nicotine replacement therapy: dosage guidelines, safety and other clinical considerations

NICOTINE	Patches	Chewing gum	Tablets	Oral spray
Format	24-hr release: 7, 14 and 21 mg 16-hr release: 10 and 15 mg	2 and 4 mg	1, 2, 1.5 and 4 mg	1 mg
Dosage	> 10 cig/day: 21 mg/day (4–6 weeks) 14 mg/day (2 weeks) 7 mg/day (2 weeks) ≤ 10 cig/day: 14 mg/day (6 weeks) 7 mg/day (2 weeks)	1st cig ≤ 30 min after getting up: 4 mg 1st cig > 30 min after getting up: 2 mg 1-6 weeks: 1/1-2 h 7-9 weeks: 1/2-4 h 10–12 weeks: 1/4-8 h	1st cig ≤ 30 min after getting up: 2 mg 1st cig > 30 min after getting up: 1 mg 1-6 weeks: 1/ 1-2 h 7-9 weeks: 1/2-4 h 10–12 weeks: 1/4-8 h	1-2 sprays in the mouth (6 weeks) if you feel like smoking; reduce progressively afterwards
Precautions	Recent myocardial infarction (≤ 2 weeks); serious arrhythmias; angina pectoris; pregnancy and lactation; adolescents (< 18 years) Temporomandibular dysfunction (with gum) and bronchospasm (with spray)			
Most common side effects	Local skin reaction (pruritus, heat, erythema) Sleep disorders associated with nicotine absorption at night (insomnia, vivid dreams)	Oral and pharyngeal irritation Inconvenience Gastrointestinal discomfort (dyspepsia, nausea) Hiccup Jaw muscle pain	Oral and pharyngeal irritation. Gastrointestinal discomfort (dyspepsia, nausea) Hiccup	
Advantages	High adherence Can be combined with other therapeutic drugs 24-hour release	Possibility of oral replacement therapy Lower weight gain Individual dosing to control withdrawal and other symptoms Can be combined with other drugs for TUD		
Disadvantages	No adjustments allowed in monotherapy. Not suitable for patients with dermatological disorders	Requires adequate dose control Not suitable for patients undergoing dental treatment Requires training in the form of use to achieve adequate effectiveness	Requires adequate dose control	

Varenicline: The development of varenicline is preceded by experiences with cytisine, an alkaloid, nicotinic partial agonist, with limited passage to the brain that has been used for years in Bulgaria as a treatment for TUD and is now marketed in the rest of Europe. Varenicline is a partial agonist drug. The mechanism of action of varenicline is attributed to the binding to nAChRs through the α4, β2 nicotinic receptors that are particularly expressed in the brain reward system, giving rise to two complementary effects. The first is a partial agonist effect, substituting nicotine, which causes a dopamine release of 50-60% in the NA, compared to 100% that would be produced by a pure agonist. This effect is responsible for the decrease in withdrawal symptoms and craving. It also has a second antagonistic effect on nAChRs that decreases the reward when administering tobacco, when the patient is in treatment.

In a meta-analysis, the efficacy of varenicline for TUD was found to be almost three times higher than placebo (OR=2.88; 95% CI=2.40-3.47)[15.] In some European countries, it is recommended as a second therapeutic option, only after failure with nicotinic agonists[17], although this recommendation is not based on evidence.

The efficacy of varenicline in patients with TUD and other mental disorders such as depression, anxiety or psychosis has shown no differences and does not vary with diagnosis[18]. In patients with dual disorders with schizophrenia, it is as safe as in the general population. However, despite the fact that benefits similar to those of nicotine would theoretically be expected, it has not been shown to improve cognitive performance[19].

Another important effect of this drug, according to the perspective of neuroscience-based nomenclature (NbN), is that it acts on other mental functioning dimensions; for example, to reduce the number of standard alcohol consumptions per day in patients with alcohol use disorder; however, no significant reduction in consumption was seen[20].

Other actions of varenicline were improvements in: hyperactivity symptoms in patients with subclinical ADHD[21]; efficacy in depressive symptoms related to the need for tobacco; in the treatment of TUD in smokers with depression[22] and with anxiety symptoms[23].

It is clear that modulating the nicotinic cholinergic system produces effects on mental functioning that go beyond tobacco addiction.

The side effect profile includes nausea, gastrointestinal symptoms, sleep disturbances and, very rarely, mood changes with occasional suicidal ideation[10,24]. The serious potential appearance of suicidal ideation should always be monitored, although it is very rare. For gastrointestinal side effects, it is recommended to associate drugs such as sulpiride or antiemetics, at least in the first weeks of treatment, although there is no evidence for this proposal.

In July 2021, some batches of varenicline were withdrawn from the market due to a notification of the possible presence of the impurity N-nitrosovarenicline at a higher than allowed concentration. After an evaluation carried out at the European level, a more restrictive limit was established for the presence of this impurity in September 2021, which led to the complete withdrawal of the entire stock of varenicline. Taking into account the available data, an immediate risk has not been identified for patients treated with this drug, since the oncogenic capacity in short-term treatment is not proven[25]. At the date of the last revision of this text, no specific deadlines are known for the remarketing of the active ingredient.

***Bupropion*:** This is a monocyclic antidepressant that inhibits the reuptake of norepinephrine and to a lesser extent dopamine, marketed under different names depending on whether it is used as an antidepressant or for TUD. Bupropion acts by inhibiting norepinephrine reuptake and as a weak dopamine reuptake inhibitor, along with activation of the serotonergic system by action on the dorsal raphe nucleus[26]. It also has an antagonistic action, not a broad spectrum, on the nAChRs. Its efficacy is less than other available treatments, although its combined use with varenicline or others can be considered. Its therapeutic action also goes beyond TUD; treating depression, anxiety or some ADHD symptoms, for example.

Table 4 summarises the dosage guidelines, safety aspects and other clinical considerations for varenicline and bupropion[16].

Table 4 **Dosage guidelines, safety aspects and other clinical considerations for Varenicline and Bupropion**

	Varenicline	Bupropion
Formats	1st week of treatment: 0.5 mg tablet Rest of treatment period: 1 mg tablet Follow-up: 1 mg 150 mg extended-release tablets	150 mg sustained release tablets
Dosage	Days 1–3: 0.5 mg /24 h Days 4–7: 0.5 mg /12 h Stop smoking between days 7 and 10 Day 8–12 weeks: 1 mg/12 h Start: 1 week before stopping Take with water after eating Dose adjustment in patients with renal insufficiency Duration: 12 weeks, with possible extension of 12 weeks Possible start 1 month before D-day with a weekly reduction regimen	Days 1-6: 150 mg/24 h Day 7 and following: 150 mg twice a day with at least 8 hours between doses and not close to bedtime Stop smoking during the 2nd week of treatment Duration:7-9 weeks
Precautions	Adjust dose for kidney failure (clearance < 30 mL/min consider half the dose) Contraindicated in end-stage renal failure, pregnancy and lactation	Drugs that lower the proconvulsive threshold Liver disease Adolescents Pregnancy and lactation
Contraindications		History of seizures Eating disorders Sudden interruption of alcohol or benzodiazepine consumption (risk of seizure) Use of MAOIs in the previous 2 weeks.
Side effects (most common)	Nausea, headache, insomnia, nasopharyngitis, gastrointestinal disorders	Nausea, headache, insomnia, dry mouth, anxiety, gastrointestinal disorder s and seizures
Advantages	Most effective drug in monotherapy Two daily doses and good adherence Different mechanism of action in second treatments Absence of hepatic metabolism. Lower risk of interactions	Good adherence Less weight gain Useful in patients with depression Possible combination with NRT
Disadvantages		Seizure risk

Other drugs have been studied for the treatment of TUD and considered effective, but are considered as 2nd line, due to their side effect profile or because they were not found in the Spanish market.

***Nortriptyline*:** A second generation tricyclic antidepressant, which acts primarily as a norepinephrine reuptake inhibitor. It can increase dopaminergic transmission in the frontal cortex and at high doses can increase serotonergic transmission[27].

Several studies have been done for its efficacy in TUD[28-30], and it is currently considered as a second-line pharmacological tool; not so much because of its low efficacy but because of its common moderate-severe side effects (e.g. dry mouth, dysgeusia, dizziness).

The nortriptyline doses used are 75 and 100 mg, depending on the study, for 6-13 weeks. It was shown to almost double the long-term abstinence rate compared to placebo, although its efficacy in patients with defined dual disorders is unknown.

Another study with interesting results included a comparison between smokers with a high Fagerström test score (≥ 7), considered severely dependent, with smokers with lower scores. Nortriptyline was significantly more effective than placebo in the severely dependent group (60.4% vs 7% abstinence, p=0.001) but not in the lower scoring group[31].

Another study in combination with NRT did not demonstrate superior efficacy over placebo[32].

Cytisine: An alkaloid of plant origin, with a chemical structure similar to nicotine. It acts as a partial agonist of the alpha4-beta2 nicotinic acetylcholine receptor. Its fundamental action is to reduce tobacco withdrawal symptoms and reduce the positive effects of consumption [33].

It is a generic drug, which has been available since the 1960s, with and without the need for a prescription, mainly in Eastern European countries.

Knowledge of its beneficial effects for stopping smoking led to the study, synthesis and commercialisation of varenicline.

Several systematic reviews support its efficacy in TUD (3 times higher than placebo) after both 6-month and 12-month follow-ups, (RR 3.29, 95% CI -1.84 5.90-)[34,35].

Gastrointestinal, sleep disturbance and headache side effects are similar to, but less intense than, those of varenicline. Nausea is less common than varenicline due to its low affinity for 5-HT3A receptors[36].

More recently, studies have been done comparing it with both nicotine replacement (NRT) and varenicline, with a similar efficacy to the latter and higher than NRT being seen[36-38].

The main difference with respect to varenicline is the administration schedule (Table 5); due to its pharmacokinetics, more frequent doses are required. The recommendation of the data sheet is to stop smoking as soon as possible but no later than the 5th day of treatment.

Also noteworthy is its low price in the countries of origin, although not in the EU. If cytisine is shown to be as efficacious as varenicline, it could provide yet another therapeutic option, perhaps leading to savings for health systems and consumers[39]. However, a price increase is expected for marketing in the EU, as well as not being directly included in the financing.

Table 5 Cytisine administration schedule, according to the technical data sheet[40]

Treatment days	Recommended dose	Maximum dose
Days 1-3	1 tablet / 2 hours	6 tablets
Days 4-12	1 tablet / 2.5 hours	5 tablets
Days 13-16	1 tablet / 3 hours	4 tablets
Days 17-20	1 tablet / 5 hours	3 tablets
Days 21-25	1-2 tablets / day	2 tablets

Other Strategies not approved by the Regulatory Agencies

The arrival on the market of new nicotine release or heat-not-burn products has been seen recently and should be reviewed by regulatory agencies such as the FDA and the EMA. These new products that have gained some popularity in the exposed population must be shown to reduce exposure or disease risk. They should also benefit not only individual smokers, but also the health of the population as a whole[41].

In July 2017, the UK Department of Public Health published its new UK Tobacco Control Plan, entitled "*Towards a Smoke-Free Generation*". It stated that the Government will support smokers, who have been unable or unwilling to stop smoking, to adopt the use of alternatives to traditional cigarettes as a way of reducing exposure to tobacco smoke. Among its objectives are helping people to stop using cigarettes, maximising the availability of lower-risk alternatives and using technologies that considerably reduce the risk of smoking.

Also, a report published by this body in 2015 and updated in October 2018 under the title, *Smokefree mental health services in England*, it stated that people with mental disorders smoke more and are more dependent on nicotine. In line with this document, the Public Health Department in England proposes to promote research the safety and efficacy of the electronic cigarette, a nicotine-releasing device without tobacco, as a strategy for harm reduction in this population group[42].

Continuing with the United Kingdom, where more public recommendations in this regard have been made, it must be remembered that the British Parliament accepted the recommendation on electronic cigarettes published by the Science and Technology Committee in 2018, which stated that these devices "are significantly less harmful" than conventional tobacco and that "they should not be treated in the same way as conventional cigarettes".

The Committee believes that the risk of smokers continuing to use conventional cigarettes outweighs the uncertainty associated with long-term use of electronic cigarettes[43].

Furthermore, the Committee on Science and Technology stated in this report that the percentage of smokers among people with mental health conditions remains high, while declining in the rest of the population; with people with mental health problems being almost 2.5 times more likely to smoke compared to the general population.

Therefore, they consider that the default policy should be to allow the use of electronic cigarettes in all mental health units in the British Health System[44].

Electronic cigarettes

The new electronic devices for administering nicotine, electronic cigarettes (vaporisers), should be taken into account within the treatment strategies marketed. Although the long-term biological effects of these devices are still unknown, the reality is that there is a reduction in exposure to potentially harmful components. An electronic cigarette. according to the definition of Law 28/2005 and Directive 2014/40/EU, is "a product that can be used for consumption of nicotine-containing vapour via a mouth piece, or any component of that product, including a cartridge, a tank and the device without cartridge or tank. Electronic cigarettes can be disposable or refillable by means of a refill container and a tank, or rechargeable with single use cartridges"[45]. E-cigarettes do not contain tobacco, but rather an electronic liquid that contains vegetable glycerin, propylene glycol and may contain nicotine, which is heated to generate an aerosol that the user inhales.

After years of no regulation, the FDA extended the New Tobacco Products Act to e-cigarettes for the first time in May 2016. E-cigarette manufacturers will be required to register with the FDA and provide a detailed description of the contents of their products as well as their manufacturing processes. Manufacturers will need to apply to the FDA for permission to sell their products, will be subject to FDA inspections, and will not be allowed to market their products as light or mild without FDA approval. In practice, this means that any e-cigarette currently on the US market must file a premarket application with the FDA; otherwise, they are being traded illegally. Finally, in 2020, the FDA issued a guide that essentially prohibits any electronic cigarette that incorporates a flavour in its "cartridge", other than tobacco or menthol; electronic cigarettes for which the manufacturer has not taken adequate measures to prevent access by minors; and any electronic cigarette that is directed at minors or whose use may be promoted by minors. The EU has not yet promoted any similar measure, which, as well as being soundly judged, tries to advance in giving guarantees to users, most of them with dual TUD, of this new reality of the e-cigarette[41]. However, the UK Medicines and Healthcare products Regulatory Agency (MHRA) has issued a policy under which they can approve the use of electronic cigarettes for medical prescription (going through the drug approval process) for people who want to stop smoking[46]. To do this, it has drawn up a guide that includes the requirements the product must meet both in terms of quality and advertising[47]. The US Preventive Services Task Force, in its 2015 update, continues to state that there is still not enough evidence to recommend this method of nicotine administration, although its use in the affected population has been spreading[48] and is a reality that cannot be dismissed only with the fact that "there is a lack of evidence and it is as harmful as tobacco". Most recently, in October 2021, the FDA announced the marketing authorisation of a new tobacco product in three formats, marking the first set of electronic nicotine delivery system products cleared by the FDA under the Premarketing Tobacco Application (PMTA) process. This is for the product Vuse®, which showed that participants who used only these products were exposed to fewer harmful and potentially harmful components (HPHC) from aerosols compared with users of traditional combustion cigarettes[49].

The scientific community has been divided regarding the role of e-cigarettes in controlling TUD. Other recent studies show that a strategy of replacing traditional cigarettes with e-cigarettes would produce substantial gains in years of life, even under pessimistic assumptions regarding cessation, initiation and relative harm[50].

In an experimental study with a small group of patients followed for 3.5 years with non-smokers using nicotine vaping devices, no associated health problems were demonstrated. However, it cannot be excluded that some damage might occur in later stages[51].

These devices have been widely accepted by subgroups of people with TUD who are trying to stop or at least reduce tobacco use. To compare its efficacy with approved nicotine products, a randomised controlled study (sponsored by the National Institute for Health Research and Cancer Research UK) was conducted on 886 patients who were followed up for 1 year. Both groups also underwent behavioural therapy. The

percentage of abstinence achieved was 18% in the e-cigarette group compared to 9.9% in the nicotine group approved by regulatory agencies. The most frequent secondary symptoms were mouth and throat irritation in vaporiser users and nausea in the nicotine group. Adverse respiratory events were more frequent in the e-cigarette group, although without reaching statistical significance. Respiratory infections, however, were reduced in the e-cigarette group due to a likely antibacterial effect of glycerine and propylene glycol. The participants were able to choose the type of nicotine replacement (e.g. patches or spray) and even a combination of them. The other group received an e-cigarette starter pack with a device containing 18 mg/mL of nicotine. In those who did not achieve abstinence, the reduction in smoking was clearly more pronounced for those who used a vaporiser, compared to traditional nicotine. Notably, nearly 100% of subjects continued to use e-cigarettes, while the nicotine replacement cohort stayed off conventional cigarettes for a shorter period of time[52].

Non-treatment issues were discussed, such as whether they may pose a risk of initiation in populations that have never used tobacco, or the risk of nicotine solutions for young children, which are not relevant to the therapeutic approach of people with TUD.

Other nicotine release devices used

Snus: This is a moist powdered smokeless tobacco product placed between the lip and the gums for prolonged periods, and was the first tobacco product to be authorised by the FDA as an MRTP in 2019. It was marketed with the claim that "exclusive use of the snus products instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema and chronic bronchitis". So far, it is the only product that has been allowed such a claim (the highest possible health claim). The FDA granted this authorisation after reviewing the scientific evidence submitted by the company supporting the claim. The fact that this product had a long tradition in Sweden helped, as it was able to provide epidemiological data studies confirming this long-term safety claim[53]. Since 1992, the sale of snus has been expressly prohibited in most EU countries, with only Sweden, Norway and recently Switzerland (non-EU countries) providing an exemption. This is one of the most paradoxical cases, in which the EU authorities allow the sale of conventional cigarettes and prohibit the sale of an alternative tobacco product when scientific evidence, including long-term epidemiological studies, shows a lower risk of cancer, heart disease and chronic bronchitis.

Due to fears of this new tobacco product spreading across Europe and aggressive marketing tactics directed at young people, the European Parliament called for a total EU-wide ban on "oral tobacco" sales in September 1987. This was preceded by a WHO recommendation urging countries with no history of smokeless tobacco use to ban this type of tobacco preventively, in order to prevent a public health problem in the future. In 1992, an EU-wide ban on oral tobacco sales was enacted under the amended Labelling Directive. This ban was reaffirmed in 2001 and again in 2014[54].

Tobacco heated without combustion: This heat-not-burn cigarette contains tobacco heated without combustion at a low temperature. Cigarette smoke emissions are mainly produced by distillation, pyrolysis and combustion reactions when tobacco is burned. Some studies have shown that heating tobacco to temperatures below pyrolysis and combustion temperatures has the potential to reduce or eliminate some toxic substances found in tobacco smoke heated to temperatures above 600ºC.

New products have been marketed to heat tobacco below 300ºC. They have been designed to eliminate the combustion of tobacco while being heated to release nicotine, tobacco volatiles and glycerol to form its aerosol[55].

In a narrative review on heated tobacco by Spanish authors, a total of 52 studies were analysed (46 from the review and 6 found manually). Despite some differences between the studies, most of them point to a reduction in emissions of harmful and potentially harmful constituents (HPHC), as well as exposure to toxic substances and, therefore, on the biological and clinical impact of heated tobacco compared to conventional cigarettes[56].

Despite the controversy, there was an official response in an FDA statement dated 07/07/2020 authorising the marketing of the IQOS (I Quit Ordinary Smoking) heated tobacco product (HTP) system as a "modified risk tobacco product", which reopens the debate on its use for TUD, since most scientific associations do not recommend it[57], despite there being no pronouncements from mental health associations, which should be involved in therapeutic responses to this dual disorder. The therapeutic object would be those patients with severe dual TUD unable to abandon or reduce compulsive use.

The individual benefits of using this type of device have been evaluated in various studies[58-60]. The results have shown that switching from conventional cigarettes to heated tobacco reduces exposure to toxins and improves risk markers: reduction of 8-epi-prostaglandins, thromboxanes, intracellular adhesion molecules and exposure biomarkers, such as carboxyhaemoglobin or mercapturic acids. Therefore, its use in TUD could be useful for patients to stop or reduce the use of conventional tobacco, as has been shown in studies in patients with mental disorders in which both the number of daily cigarettes and the levels of CO were reduced, obtaining

good adherence levels[61,62]. However, the existing studies present a very small sample, so the effect in larger populations would have to be evaluated.

From the population point of view, it is crucial to ensure that the introduction of heated tobacco devices does not lead to a general increase in tobacco consumption. In other words, it would not be beneficial to reduce the individual risk in smokers who switch to heated tobacco while increasing its use among non-smokers, young adults and adolescents. A study from Japan shows that sales of conventional cigarettes decreased when heated tobacco products were made available for sale[63]. It is recommended to monitor the use of these products and carry out long-term studies that can show that any increase in tobacco consumption due to heating comes from decreasing the sale of conventional cigarettes.

This is the second product to be authorised as a modified risk tobacco product, MRTP, (the first was snus, which was also the first tobacco product to receive a "risk modification" order). Its sale is allowed with the following information: "IQOS heats tobacco but does not burn it. The absence of combustion significantly reduces the production of harmful or potentially harmful chemicals. Scientific studies show that switching completely from cigarettes to IQOS significantly reduces your body's exposure to harmful or potentially harmful chemicals"[64]. The FDA indicates that, although risk reduction has not been demonstrated, the totality of the evidence presented suggests that a measurable and substantial reduction in morbidity or mortality among individual tobacco users in subsequent studies is reasonably likely. Despite the concerns that may be raised by some unknowns, the FDA concluded that the available scientific evidence demonstrates that the issue of exposure modification orders for IQOS would be appropriate to promote public health.

According to Mitch Zeller, the director of the FDA Center for Tobacco Products, about this decision, "Through the modified risk tobacco product application process, the FDA aims to ensure that information directed at consumers about reduced risk or reduced exposure from using a tobacco product is supported by scientific evidence and understandable."

Other commercial brands have joined the market with a similar mechanism (Glo) and its manufacturers want to provide it with increasing scientific evidence on its less harmful effects[65].

TREATMENT OF TUD IN PATIENTS WITH OTHER MENTAL DISORDERS

TUD treatment should be proposed in all patients with other mental disorders, without waiting for stabilisation periods; this ensures the best results.

The association between dual disorders, including TUD, and suicide is well known; however, it is difficult to establish whether tobacco is a cause or a consequence of this association. Several studies have tried to identify it as an independent risk factor together with other mental pathologies without demonstrating a solid relationship between these drugs and mental pathologies, and others have objectified the different confounding variables that exist in this association.

In 2009, the FDA published a major safety health warning, a Black Box Warning, on varenicline, due to possible serious neuropsychiatric effects reported in the post-marketing phase that included suicidal ideation or actions. After numerous studies and meta-analyses carried out to clarify the potentially dangerous effects of varenicline and bupropion, both the FDA and EMA drug regulatory agencies carried out different studies. The aim of the EAGLES study[65] from the former was to establish drug efficacy and safety in both the neuropsychiatric and cardiovascular spheres. In the cohort of subjects with mental pathology, the EAGLES study showed that varenicline (1 g twice a day) was more effective for cessation than placebo, the nicotine patch (21 mg a day with progressive reduction) and bupropion (150 mg twice daily); while bupropion and the nicotine patch were more effective than placebo[66].

Later studies have compared the effect of maintenance pharmacotherapy on abstinence rates for smokers with schizophrenia and bipolar disorder, and smokers in the general population without a psychiatric disorder. At 3 months, people with schizophrenia and bipolar disorder were more likely to return to smoking without varenicline maintenance treatment and not more likely with the treatment. Thus, maintenance pharmacotherapy can improve long-term abstinence rates in people with schizophrenia or bipolar disorder, since the rate of relapse in these patients is higher than in the general population[67].

This confirmed the results of a previous study by this working group. Varenicline maintenance pharmacotherapy and cognitive behavioural therapy were shown to improve long-term abstinence rates in smokers with severe mental disorders, compared with cognitive behavioural therapy alone after 1 year of treatment and 6 months of treatment discontinuation. This maintenance treatment may decrease the high prevalence of TUD and reduce the large burden of morbidity and mortality related to smoking in people with severe mental disorders[68].

These drugs are currently considered safe and effective in the general population and in patients with mental disorders, so the Black Box Warning was withdrawn and monitoring maintained in treated patients.

Although the entry of cytisine on the world market is recent, and there are therefore no studies in populations of smokers with differential features, such as psychiatric patients, it can be hypothesised that it may be extremely useful in these patients given its great chemical and functional similarity to varenicline.

TUD IN DIFFERENT DIAGNOSTIC CATEGORIES OF OTHER MENTAL DISORDERS

Although we have expressed our preference for the transdiagnostic perspective offered by neuroscience and precision psychiatry, we will review the TUD data in the different diagnostic categories of the DSM-5.

The shared vulnerability for TUD and other mental disorders based among others on the deregulation of the nAChR system must be remembered[69].

Schizophrenia

The relationship between TUD and schizophrenia has been known for more than 30 years, with various studies showing TUD ratios greater than 80% in this group of patients[70].

Across all settings and nationalities, specific research found a 78% prevalence of TUD and 58% of severe TUD and a 2.6-fold higher probability for psychotic patients with TUD compared to patients with other mental disorders[71]. They have also been described to smoke more cigarettes per day and inhale more deeply than other smokers, reaching higher blood nicotine levels than smokers without serious mental disorders[9].

The research evaluates the involvement of nAChRs in schizophrenia and suggests ways in which this system may contribute to the pathophysiology of this illness. Nicotine receptor expression is reduced in schizophrenia and, given these findings, it has been suggested that vulnerability to both disorders may be related[72]. Recent studies show that nicotine administration normalises the hyperconnectivity of the Default Mode Network topography in schizophrenia, providing direct evidence that the biological basis of addiction is different in people with and without this mental disorder. These findings suggest that the high prevalence of nicotine use in patients with schizophrenia may be an attempt to correct a network deficit that interferes with the cognitive impairment they suffer[73].

Neurocognitive deficit (NCD) is nuclear to schizophrenia, present in 80% of cases and constitutes an endophenotype of schizophrenia, stable in all phases of the disease and inheritable. NCD could constitute a vulnerability factor for the initiation and maintenance of TUD. This shared vulnerability of schizophrenia and TUD would be due to the deregulation of nAChRs. Pre-clinical evidence links this system to neurotransmitters, such as dopamine, glutamate and GABA, while certain associated NCD (reaction time, spatial working memory, sustained attention and sensory synchronisation) improve after nicotine administration in schizophrenia[69].

There are different meta-analyses and reviews that demonstrate the safety and efficacy of varenicline in schizophrenia. Although there is controversy regarding the usefulness of varenicline to improve cognitive impairment in patients with schizophrenia, more powerful trials are desirable, since current evidence cannot confirm its usefulness in this regard[67,68,74].

Available systematic reviews have shown that the use of varenicline is associated with an increase in tobacco abstinence of up to 5 times for this group of patients; with bupropion, the increase in cessation is 3 times higher. For nicotine replacement therapy, a lower effect has been observed in patients with schizophrenia than in the general population, despite the fact that for many authors it represents the first-line treatment for smokers with mental illness[75,76].

Within the non-conventional approaches for TUD in schizophrenia, it has been postulated that electronic cigarettes could be useful as part of the tobacco harm reduction strategy; however, there are very few studies, of mostly very small samples, so research efforts in this field need to be increased[77-80].

Despite the proven efficacy of these treatments in people with mental disorders[81], there is a delay in their use that can affect patients. In a survey carried out by the WHO in several countries, it was highlighted that the delay in the treatment of mental disorders is widespread. Specifically, the median delay in SUD treatment was found to be between 6 and 18 years. In Spain, the median is 6 years, the lowest of the countries surveyed. This country also shows the highest number of patients who are indicated for treatment for SUD in the first year of contact, 18.6%.

For one thing, many patients never make any attempt to treat their disorders, particularly in developing countries, where the financial and structural barriers to accessing mental health services are more notable. Failure to seek help also seems to be greater for disorders in which the need for treatment is poorly perceived, such as SUDs, for which more than half of the cases did not make any treatment attempt at all in most countries[82].

Bipolar Disorder (BD)

Little is known yet about the neurobiological interaction between bipolar disorder and TUD; however, for having one of the highest prevalences, there is a need to advance in its knowledge[83,84].

A study that included Spanish researchers found that TUD and bipolar disorder have a bidirectional relationship. In addition, the risk of developing one disorder after the other was higher at the beginning of the disease. Most of the individuals with TUD had previously suffered bipolar disorder (72.6%), an earlier onset of tobacco use and a greater number of manic episodes that could be attributed to greater severity[85].

There are also few treatment studies in subjects with bipolar disorder[86]. In general, the efficacy of varenicline in smokers with bipolar disorder is similar to the main results reported by the EAGLES study. Varenicline may be well tolerated and effective for TUD with bipolar disorder. Regarding bupropion and nicotine replacement therapy, despite being effective, they had a smaller effect size than varenicline[87].

Another important study was after a standard 12-week pharmacotherapy course, where people with schizophrenia and bipolar disorder were more likely to suffer TUD relapse when stopping varenicline maintenance treatment. Maintenance pharmacotherapy was able to improve long-term results and not for short periods of time[68]. This proposal should be extended to other therapeutic modalities for longer periods of time.

Depression

TUD and depression are reciprocally related. Tobacco is the leading preventable cause of illness and death in patients with depression, and depression is one of the most important risk factors for the development of TUD. It has been shown that patients with depression have a higher prevalence of TUD than the general population and that there is a probable relationship between the severity of consumption and depressive symptoms[88,89].

Based on the currently available evidence, the results of a Cochrane review support the effectiveness of adding a psychosocial mood management component to a smoking cessation intervention for depressed smokers. The results also appear to support the effectiveness of bupropion use for smokers with past depression, although the evidence is relatively weak due to the small number of studies using post hoc subgroups. For interventions without specific mood management components for depression, including nicotine replacement therapy and psychosocial interventions, insufficient convincing evidence was found to support their use in clinical practice for smokers with depression[90].

Despite decades of research on this dual disorders, treatment success rates for TUD in this population remain consistently lower for depressed smokers than for smokers in the general population; highlighting the need for theoretical models of TUD and depression.

Theoretical models, such as incentive learning theory, postulate that depressed smokers experience greater effects on the expected value of smoking[91].

The relationship between emotional regulation disorders and the brain's nicotinic cholinergic system is evident. Depressed patients have a lower availability of β2-nAChR than healthy subjects. Modulation of nAChRs, specifically those containing the β2 subunit, may be effective in treating patients with major depressive disorder[92].

Cotinine, the predominant metabolite of nicotine, appears to act as an antidepressant. Cotinine may be an effective antidepressant that positively influences mood through a mechanism involving preservation of brain homeostasis and expression of critical growth factors[93].

Taking into account the pro-cognitive properties of nicotine, its transdermal use has been tested in patients with depression and cognitive symptoms in the elderly, with promising results[94].

Although most studies of smoking cessation between subjects with and without depression have shown no difference between them, depression was associated with worse outcomes[95]. In the TUD group with depression, nicotine replacement therapy has been shown to be more effective than placebo. Bupropion is also an effective treatment for smokers with depression and manages to reduce the relapse rate during abstinence, as does varenicline[96]. One of the first studies conducted with nortriptyline[28] included smokers with a history of major depressive disorder (MDD) and was used together with cognitive-behavioural therapy (CBT). The results showed significantly greater efficacy than placebo whether or not the smoker had a history of MDD while the use of CBT was especially effective in smokers with a history of MDD.

A meta-analysis of several studies also described how a change in mental health occurs after stopping smoking. Smoking cessation regulates the affective response and is associated with a reduction in depression, anxiety and stress and an improvement in mood and quality of life compared

to continuing to smoke[97]. These results are consistent with what is known about neuroadaptations in brain nicotinic pathways that occur in chronic TUD. Neuroadaptations in these pathways are associated with the appearance of a state of depression, agitation and anxiety after smoking a cigarette. However, the neurological functioning of people who stop smoking may return to the same level as that of non-smokers within 3 weeks of stopping smoking[98], which is consistent with the decrease in withdrawal symptoms after a few weeks.

In recent times, there has been great interest in new treatments with new mechanisms of action for depression. One of them is psilocybin, a secondary serotonin receptor agonist. Moderate to high doses (20 and 30 mg/70 kg) of psilocybin, in combination with cognitive behavioural therapy (CBT) for smoking cessation resulted in substantially higher 6-month tobacco abstinence rates than those typically seen with other medications or CBT alone[99].

Another of the new treatments in the field of depression is ketamine and its derivatives such as esketamine. In animal studies, ketamine treatment significantly reduced nicotine self-administration in a dose-dependent manner. In addition, differential sensitivity between the sexes was observed as male rats responded to a lower dose of ketamine and with a greater effect than in female rats. It is concluded that glutamatergic receptor manipulations may offer a novel and potentially gender-dependent intervention in nicotine addiction[100].

As mentioned in previous chapters, the activity of MAO is reduced in smokers, since it increases the availability of some neurotransmitters, such as serotonin, GABA and glutamate, by preventing the degradation of catecholamines. This effect of tobacco smoke would be similar to that of antidepressants in that both tobacco and antidepressants modify the release of neurotransmitters that enhance the effect on the reward system. Loss of MAO inhibition during periods of withdrawal and possible associated mood swings make withdrawal difficult in smokers. Thus, treatment with antidepressants for smoking cessation is being considered since the lack of monoaminergic neurotransmitters would be reduced after smoking cessation and an improvement in the symptoms caused by withdrawal could be observed[101,102].

Anxiety disorders

Most anxiety disorders increase the risk of TUD. For people with phobias or panic disorder and also with PTSD, this risk is multiplied, even if the symptoms have been absent for years, with consumption being higher in symptomatic periods[103]. However, in those patients with TUD and anxiety disorder, nicotine replacement therapy and bupropion are associated with a worse response than varenicline[95].

Patients with social or generalised anxiety also have a higher prevalence of TUD than the rest of the general population. In this group of patients, neither monotherapy nor the combination of first-line drugs was more effective than placebo[104]. The subanalysis for anxiety disorders (PTSD, GAD, panic disorder) in the EAGLES study showed greater continued abstinence between weeks 9 and 12 for all 3 types of pharmacological treatment compared to placebo[105]. In a recent study in patients with anxiety and low tolerance to distress, it was observed that those who tolerated distress or discomfort better were more likely to drop out 4 weeks after D-day if they were treated with replacement therapy with nicotine patches and tablets than only with patches[106].

For patients with TUD and post-traumatic stress disorder (PTSD), a pharmacological treatment pilot trial which randomised placebo and bupropion showed adequate tolerance to the latter, associating 40% abstinence compared with 20% for placebo after 6 months of follow-up; however, the study was carried out with 15 veterans and did not reach a level of significance[107]. For nicotine cessation in patients with PTSD, a recent randomised trial with placebo and nicotine patches showed that patch replacement therapy was useful in reducing tobacco consumption; however, this treatment was not considered sufficient due to high dropout rates[108].

Post-traumatic stress disorder (PTSD)

The prevalence of SUD in people with PTSD has been established at 21.6-43.0% compared to 8.1-24.7% of the population without PTSD. In patients with both disorders, the symptoms are usually more severe and are more resistant to treatment. Some theories have been established that could explain this relationship. The first (and most accepted) is that PTSD precedes SUD, through self-medication with substances such as alcohol, cannabis, etc. to improve symptoms. Therefore, when the patient tries to reduce consumption, the appearance of withdrawal symptoms (together with the reactivation of PTSD symptoms) can make the patient more vulnerable. The second theory is the other way around: that SUD precedes PTSD. People who abuse substances face dangerous or traumatic situations to maintain consumption. Its chronic use causes neurosensitisation of biological stress systems, leading to high levels of anxiety and a higher level of vulnerability for the development of PTSD after exposure to trauma[16,109].

The treatment of these patients is based on achieving controlled and stable consumption to stabilise the SUD, when abstinence is not possible, together with individual and group psychotherapeutic treatment to treat PTSD, with close monitoring of symptoms to prevent relapses[16].

Obsessive-Compulsive Disorder (OCD)

OCD is a biologically heterogeneous disorder associated with both impulsive and compulsive neurocognitive mechanisms. It is one of the mental disorders with the lowest incidence of TUD. Patients with OCD and TUD could represent a differentiated phenotype notable for phenomenologically showing greater impulsiveness.

Smokers with OCD scored significantly higher on the Barratt Impulsivity Scale ($p < 0.001$). compared with non-smokers with OCD. They also scored significantly higher on the Temperament and Character Inventory (TCI) measures of novelty seeking ($p < 0.001$) and reward dependence ($p < 0.001$) and significantly lower on measures of harm avoidance ($p < 0.001$)[110]. Therefore, these traits of greater impulsiveness should be taken into account at the time of treatment.

Tourette syndrome

Treatment with nicotine gum or patches seems to reduce complex tics and improve the impaired attention that these patients usually present. A double-blind study with placebo in a small number of non-smoking children and adolescents under treatment with neuroleptics, proposed the intermittent use of therapeutic nicotine, with significant results, which would allow reducing the use of antipsychotics in these patients[111-113]. However, there are currently no studies to evaluate this syndrome in patients who have stopped using tobacco.

Attention Deficit Hyperactivity Disorder (ADHD)

Attention deficit hyperactivity disorder (ADHD) is one of the most common mental health problems in childhood, adolescence and often persisting into adulthood. This diagnosis of ADHD is very prevalent in people with mental disorders and is generally underdiagnosed. ADHD in childhood and adolescence is a strong predictor of tobacco and illicit substance use in adulthood[112,113]. Related to environmental and character factors, but above all to genetic and epigenetic factors, young people with ADHD are 2-3 times more likely to smoke tobacco regularly and to develop TUD than those without ADHD[114,115]. In addition, subjects with ADHD start smoking tobacco at a younger age and have a more rapid progression to a more severe TUD, generally consuming a greater number of cigarettes per day than those without ADHD[116,117]. Also, it has been described that smokers with ADHD would have more intense withdrawal symptoms and craving for smoking during periods of abstinence, and would have greater difficulty stopping smoking[118] with higher relapse rates for TUD[119] than smokers without ADHD.

Patients medicated for ADHD since childhood delay the onset of tobacco smoking[120]. Several studies have evaluated the possible efficacy and tolerability of drugs commonly used for ADHD in patients with dual disorders, ADHD and smoking. The efficacy and tolerability of methylphenidate in patients with ADHD and smoking have been explored. A large multi-centre randomised placebo-controlled study evaluated the efficacy of OROS methylphenidate (72 mg/day) as adjunctive treatment to improve smoking cessation rates associated with transdermal nicotine patches (21 mg/day) and individual brief therapy in a sample with 255 adult subjects with TUD and ADHD[121]. A significant reduction in ADHD symptoms, number of cigarettes per day and smoking withdrawal symptoms[122] was observed in the OROS methylphenidate group compared to placebo, but abstinence rates were similar for both groups. However, a secondary analysis of the study results found that more severely dependent smokers treated with OROS methylphenidate had significantly higher rates of continued abstinence than those who received placebo; while no difference in smoking cessation rates was found between the two therapeutic options among smokers with less severe nicotine dependence[123]. Lisdexamfetamine is another drug evaluated in association with transdermal nicotine patches in patients with ADHD and TUD. In a small randomised, placebo-controlled study of 32 subjects with this dual disorder, a significant improvement in ADHD symptoms was observed compared to placebo, as well as a significant decrease in daily cigarette consumption but which was similar with lisdexamfetamine and placebo[124].

Partly due to its efficacy in the treatment of ADHD and due to its indication and recognised efficacy in the treatment of smoking, bupropion ER has been evaluated in patients with ADHD and TUD. In a small open-label study with 6 weeks of follow-up, bupropion ER (300 mg/day) associated with short-term therapy as a treatment for smoking cessation in an adolescent population, in which 11 of the 16 participating subjects also had ADHD, good tolerability of the drug along with a significant reduction in cigarette consumption was observed in adolescents with and without ADHD[125]. To date, there are hardly any data on the efficacy of other drugs used in the treatment of smoking, such as varenicline, a selective partial agonist of the nicotinic cholinergic receptor $\alpha4\beta2$, although this drug has been proposed as first-line treatment in dual patients [126].

Considering that ADHD symptoms can interfere with successful smoking cessation, it is recommended that the first priority should be to stabilise ADHD through the use of long-acting psychostimulants, at least in severe ADHD. Subsequently, cognitive-behavioural therapy or motivational interviewing in combination, or not, with NRT or smoking cessation drugs, like bupropion or varenicline, can be used for

additional treatment[127,128]. In fact, bupropion and possibly also varenicline could be promising agents for the treatment of smoking cessation.

Autism Spectrum Disorder (ASD)

The evidence gathered suggests the nicotinic cholinergic system is involved in the pathobiology of autism spectrum disorder (ASD). Neuropathological studies suggest that nicotinic acetylcholine receptor (ACh) subtypes (nAChR) are altered in the brains of autistic individuals. Furthermore, strategies that increase ACh, the neurotransmitter at nicotinic and muscarinic receptors, appear to improve cognitive deficits in neuropsychiatric disorders and ASD. Recent findings support the hypothesis that the nicotinic cholinergic system modulates social and repetitive behaviours and may be a therapeutic target to treat social and behavioural deficits in ASD[129].

Personality disorders (PD)

Surprisingly, it seems little or no attention has been paid to examining the influence of personality traits, with clear neurobiological underpinnings, on the neural correlates of TUD.

Trait impulsivity, an endophenotype, has been related to craving and relapse in the consumption of certain substances and tobacco. A functional magnetic resonance imaging study showed that the role of impulsivity in cigarette craving was mediated by frontocingulate mechanisms. Given the high prevalence of TUD in various psychiatric disorders characterised by significant levels of impulsivity, further neurobiological studies on this relationship are needed[130].

Various studies refer to the shared and specific pathogenic factors of some categorical personality disorders and TUD and find a relationship between schizotypal, borderline, narcissistic and obsessive-compulsive traits and the hypothesis of self-medication and the role of cholinergic neurotransmission[131].

Borderline Personality Disorder (BPD)

BPD is a heterogeneous disorder with a lot of variability among patients whose symptoms overlap with SUD. This makes it difficult to study the features of BPD-SUD dual disorders. The prevalence of comorbidity between BPD and SUD is high (64-66%), although there are discrepancies with these data. There is a need therefore for studies that describe the different aetiopathogenic models to improve diagnostic and therapeutic strategies. A worse response to treatment is observed in patients with BPD-SUD, as well as a higher risk of suicide, self-harm and self-destructive behaviour in general. In treating BPD-SUD, it is essential to combine psychopharmacological and psychotherapeutic treatment. Normothymic drugs can decrease impulsiveness and the risk of aggressive behaviour in BPD and of SUD, reducing substance use[16,132].

Gambling disorder

This is defined as persistent and maladaptive gaming behaviour, according to the DSM-5, and TUD is the other most common accompanying mental disorder. Clinically, "dual gaming disorder" would be expected and not be the exception, since it is always accompanied by other mental disorders including TUD[133].

People with TUD had significantly more severe gambling addiction symptoms when treated. The severity of TUD has been associated with greater gambling severity and more frequent psychiatric problems[134].

Daily tobacco use, however, is not significantly associated with the number of days played or with treatment completion. Although individuals with TUD had greater problems with gambling, they had similar rates of treatment completion and treatment outcomes as non-users[135].

Other Substance Use Disorders (SUD)

People with other SUDs show the same interest as smokers in the general population in stopping smoking. In a follow-up study of 272 patients who began a treatment programme for SUD in a US veterans centre, all patients with Alcohol Use Disorder (AUD), 72% of patients with cocaine use disorder and 70.5% of the patients with heroin use disorder were interested in stopping smoking; with 50%, 52% and 42%, respectively, thinking it would be good to do so at the same time as starting treatment to stop the other addictions. Although there is a popular belief, present even in many health professionals, that stopping smoking can precipitate relapses in patients being treated for an addiction, the evidence obtained from research shows the opposite; and it can currently be stated that the joint approach to combat a combination of tobacco use disorder with other addictions can lead to higher rates of alcohol abstinence and a decrease in cocaine use[136]. In addition to the explicit benefits of stopping smoking, patients often do not know that it can help them in their other addictions, so giving them this information is a priority.

The best studied relationship within the SUD field is that between TUD and AUD. Previous studies have shown that AUD and TUD frequently occur concomitantly, as well as the relationship between a history of TUD and a history of harmful alcohol use. This association is so evident that severe TUD can be used as a marker for alcohol problems[137], and, likewise, the use of alcohol is one of the psychiatric predictors of tobacco

use onset. In other words, the relationship between alcohol and tobacco is bidirectional and dose dependent. Alcohol consumption frequently precedes a tobacco relapse, and active alcoholic patients often fail TUD treatments[138].

The simultaneous use of tobacco and alcohol is associated with premature morbidity and mortality compared to the use of either substance separately. For this reason, it is essential to develop integrated and effective therapeutic approaches. Integrated interventions and new pharmacotherapeutic combinations targeting smoking and drinking behaviours may be promising[139].

Until now, the idea that smoking cessation could make it difficult to abstain from other substances had prevented this association from being addressed from a neuroscientific evidence-based perspective; although there is currently no data that smoking cessation increases rates of relapse in alcohol consumption. However, it is known that smokers with AUD have higher levels of TUD, as measured by higher scores on dependency scales such as the Fagerström test or the DSM criteria for SUD. In addition, they smoke more cigarettes and have more and more intense withdrawal symptoms after stopping smoking.

Regarding treatment, the efficacy of bupropion, widely recognised in the treatment of TUD in the general population, has also been demonstrated among smokers with a history of AUD, although its use in patients actively consuming alcohol is contraindicated due to the increased the risk of causing seizures, and so should be restricted to stable patients in withdrawal. The data are contradictory for nicotine substitutes, since several studies have been found them to be as effective or less effective than among the general population. A clinical trial with consumers of alcohol and tobacco who wanted to stop smoking and reduce alcohol consumption found that treatment with varenicline combined with naltrexone showed reduced alcohol use rates by approximately one drink per occasion[140]. However, the combination treatment did not improve smoking cessation rates and perhaps worsened them. Despite these results, other studies have shown varenicline to be safe for alcohol and tobacco users seeking treatment for either behaviour. In fact, it has a broad effect on craving, and promotes the reduction of alcohol consumption[139]. Therefore, varenicline could be a first-line pharmacotherapy for TUD in users of both substances; although other possible combination therapies and treatment guidelines should be investigated for these patients with a great variability in consumption patterns[139].

Regarding psychological or support techniques, cognitive behavioural therapy is thought to be particularly useful for these patients.

In the aforementioned Australian study[137], Degenhardt and Hall found an association between regular tobacco use and cannabis consumption, since 20% of those who had not used cannabis in the previous year were defined as regular tobacco smokers, with these rates being 50% in cannabis smokers and 70% in those who met criteria for cannabis addiction. There were no differences, however, between the degree of cannabis use and the use of other substances. Currently, we have few specific data on the treatment of patients with cannabis abuse; however, the high rates of TUD among this population suggest a need for this type of study[141] and that we bear in mind the high dual disorders of tobacco when treating a patient for cannabis addiction problems[142]. One study of patients who attended consultation for cannabis use disorder found that those who were also tobacco smokers had more psychosocial problems and responded worse to treatment. In addition to the fact that tobacco use worsens the treatment of people with cannabis addiction, the opposite also occurs, with cannabis use being observed to have a negative impact on TUD. Several studies found that any level of cannabis use in the month prior to TUD treatment worsened abstinence rates[143].

In one of the first studies on nicotine and other substances[144], it was found that patients with cocaine use disorder (CUD) had higher rates of tobacco consumption (75%) than the general population (22%). In addition, patients reported increased tobacco consumption coinciding with cocaine consumption; this was consistent with laboratory studies that showed that stimulants such as cocaine or amphetamine can increase tobacco consumption. In a study of 200 patients trying to stop cocaine use, differences were found in the pattern of this use between smokers and non-smokers, with the former consuming more and on more days, and were also three times more likely to use the injected or smoked route. There were no differences in treatment success according to tobacco use. Another study found that cessation of cocaine use led to a decrease in tobacco use[145]. People with CUD have higher levels of TUD. The use of cocaine together with tobacco has been shown to greatly increase cardiovascular risk, which, together with the fact that smokers consume more cocaine than non-smokers, should make us see the importance of comprehensive, integrated treatment in these patients.

For TUD and opioid use disorder, it has been shown that patients in a methadone maintenance programme were more disposed to stop using tobacco than those who had intravenous heroin use. Those with a greater predisposition to stop smoking were generally in methadone maintenance, over 35 years of age and without a recent history of alcohol abuse[146-148]. In the USA, there are a large number of opioid-addicted patients in methadone maintenance treatment, approximately 200,000 of the total of 3,000,000 addicted patients[149]. For this reason, many studies have been carried out on this type of patient,

finding that their patterns of tobacco use are different from those of the general population, with TUD prevalence rates of 85-98%; curiously finding more prevalence among women than men, unlike in the general population[150]. They also had worse abandonment rates: 12% compared to 50% in the general population, and a higher number of attempts[150].

In a recent study, it was found that increasing severity of TUD, from non-use, moderate use to severe use, was shown to be a more powerful predictor of cocaine and opiate use than the daily dose of methadone. Initiation of consumption of both cocaine and opiates was found to be associated with the degree of nicotine consumption, such that the greater the consumption of nicotine, the greater the probability of initiating consumption of other substances. These data, together with the very high rates of TUD among opiate users, should prompt us to systematically offer the possibility of TUD treatment to these patients. As in users of other substances, opiate addicts have shown a great interest in stopping tobacco use, with figures from 58% to 80% of patients who defined themselves as very or quite interested in stopping smoking[151].

For the interrelationship between TUD and use of other substances, TUD treatment programmes should be designed for this type of population, since they have particular features that must be included in the approach to TUD to ensure success. Among these are the greater severity of TUD shown and the enhancement of the significant repercussions on health when consuming tobacco with other substances. Above all, the significant interweaving of behaviours, triggers and facilitators of consumption seen when consuming various substances appears as fundamental; stressing the importance of an integrated, comprehensive approach identifying all dual disorders, to prevent focusing on treating partial aspects of this complex clinical condition[152].

CONCLUSIONS

The treatment of TUD in people with other mental disorders should be a priority in clinical practice to reduce morbidity, mortality and premature death. Randomised controlled trials to date have shown varenicline and bupropion to be effective treatments for people with schizophrenia. Varenicline has been shown to be helpful in people with depression and bipolar disorder. There is still not enough evidence supported by controlled, randomised clinical trials in anxiety disorders, PTSD, ADHD, gaming disorder, autism spectrum disorder and personality disorders; hopefully, such trials and evidence will arrive in the near future.

However, the treatment of dual disorders must be addressed simultaneously, leaving the sequential proposal for those situations indicated by common sense.

They must be treated with all the psychopharmacological and psychotherapeutic tools available for mental disorders, with abstinence being a desirable objective, but it must not be the only one in patients with dual disorders, as they also require the perspective of replacement therapy and decreased consumption.

It must be remembered that most mental disorders, including SUDs such as TUD, are chronic diseases and require very long-term treatment, which is not considered in the technical data sheets or the financing of the public system.

The possibility of combining treatments to optimise results must be considered in these strategies.

Nicotine replacement strategies should also be considered, not only those approved by regulatory agencies, which are not always effective, but also nicotine delivery devices such as snus, the electronic cigarette and heated tobacco. Although these need more solid scientific evidence, they constitute a therapeutic reality that many users have decided upon which could benefit the evolution of other mental disorders involved with dual TUD.

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8. PSYCHOLOGICAL INTERVENTIONS FOR TUD IN PEOPLE WITH OTHER MENTAL DISORDERS

CHAPTER SUMMARY

Psychological treatments for TUD that rarely assess dual disorders are addressed in this section.

Empirical evidence regarding the psychological treatment of patients with dual disorders is scarce and the methodology used is heterogeneous.

People with mental health problems are less likely to be offered systematic support for TUD compared to the general population. There is also a lack of screening for risk factors.

The following are notable among the psychological interventions for TUD: Cognitive-Behavioural Therapy (CBT) and its different components in isolation, Behaviour Therapy (especially Contingency Management), relapse prevention and mindfulness.

Motivational interviewing has been shown to be effective in motivating smokers with severe mental disorders, such as schizophrenia, schizoaffective disorder, bipolar disorder and PTSD in seeking treatment for TUD.

There are several multimodal initiatives combining psychological and pharmacological techniques adapted to each person that have been applied in patients with TUD with another serious mental disorder.

PSYCHOLOGICAL TREATMENTS FOR TUD

One of the main obstacles in developing specific treatments is that people with mental health problems are less likely to be offered systematic support for TUD compared to the general population and there is a lack of screening for risk factors[1,2]. Furthermore, despite the strong association between smoking and poor mental health, many smokers find that smoking offers mental health benefits by relieving feelings of depression, stabilising mood and relieving stress[3,4]. However, scientific evidence indicates that tobacco does not improve social or general cognition in patients with TUD and other mental disorders[5,6]. Despite these obstacles, the seriousness of this addictive disorder, however, does not detract from the great motivation to address TUD in these people who have expressed their desire to stop smoking[7].

As reflected in the Clinical Practice Guideline for the pharmacological and psychological treatment of adult patients with a severe mental disorder and an SUD, the empirical evidence referring to the psychological treatment of patients with dual disorders is scarce and the methodology used is heterogeneous in terms of the sample (e.g., outpatients with other associated psychopathology or patients in a psychiatric hospital admission who use various substances); the type of substance (e.g., there is often no difference between the type of substances); the psychological intervention administered (treatment components are not specified); and the outcomes considered when evaluating the intervention. This chapter will take into account those consolidated interventions for the treatment of TUD, which have shown at least probable efficacy or promising results as these are defined[8], see Table 5.

TOBACCO ABSTINENCE AS A DYNAMIC PROCESS

It is over 40 years since the Transtheoretical Model of Behaviour Change[9] and the Motivational Interviewing (MI) approach[10] highlighted that people who come to treatment are not always "ready to stop using". Both therapeutic approach models are the great references in the field of addictions and can be consulted in greater depth in other manuals. Briefly, the Prochaska and DiClemente model could be described as defending the theory of the psychological process of stopping smoking according to five dynamic stages:

- Precontemplation: the person seems satisfied with their addictive behaviour and does not feel the need for a change (e.g. "Smoking is a pleasure for me. Even if it is a vice, don't bother explain anything to me, I'm not going to stop").
- Contemplation: the person expresses the need for a change in the medium term, but is not yet strong enough to undertake the change behaviour or prepare an action plan (e.g. "I like smoking, but I should probably smoke less").

- Preparation for change: the person has decided to try to change their addictive behaviour and is prepared for it to happen in the near future (e.g. "I'll stop smoking next Monday").

- Action: the patient has started the change attempt (e.g. "I haven't smoked for 2 weeks").

- Maintenance: abstinence for over 6 months (e.g. "I stopped smoking 8 months ago").

Of course, people do not necessarily go through each stage in a linear fashion; it is considered to be more of a spiral process, such that they can move up or down depending on their state of motivation, circumstances and understanding that they will probably have relapses which are part of the learning process towards achieving sustained abstinence[9,11]. The maintenance phase, also known as Relapse Prevention[12,13,] is considered as the phase aimed at maintaining long-term gains through training in coping skills to avoid the stimuli that provoke the craving; learning to detect and avoid high-risk situations, in addition to possible relapses. When people do not have sufficient support, training in social skills and assertive communication can be carried out. Finally, self-control, relaxation and even mindfulness techniques can be incorporated[14,15] to maintain abstinence after treatment.

PSYCHOLOGICAL TREATMENTS FOR TUD

Among the notable psychological interventions for stopping smoking or preventing relapses are the following: cognitive-behavioural therapy (CBT) and its different components in isolation, behaviour therapy (especially contingency management) and relapse prevention. There is also evidence for combined interventions, such as community counselling with NRT, multicomponent treatment, which includes pharmacological treatment, NRT, MI and components of CBT[16]. Other behavioural and psychological strategies that seem to show promising results in the field of smoking cessation are acceptance and commitment therapy (ACT) and mindfulness. Most research on psychological treatments has considered packages of a number of treatment components rather than comparing one component with another (e.g., treatment optimisation studies); this makes a review of each treatment approach challenging[17]. In general, the data show a robust dose-response curve, in which more intensive treatments (e.g., greater amounts of contact time or more sessions) produce greater chances of sustained cessation[18].

MOTIVATIONAL INTERVIEW

Similarly, Miller and Rollnick, pioneers in the field of addictions with the design and preparation of the motivational interviewing (MI) approach, have given rise to a solid body of evidence that seeks to bring out reasons for change via strategic interventions with the subjects (who take an active role in their process of abandoning the addictive behaviour). Multiple interventions have been described from this perspective, including brief advice (3-5 minutes) that can be given by any health service provider, and have been shown to significantly increase attempts at stopping smoking and long-term abstinence rates. Meanwhile, MI is under constant study with evaluation of its results. In the field of comorbidity, a study that evaluated the impact of a new GMI (Global Medical Implants) protocol that included specific components of tobacco (Tobacco GMI) is notable, and a greater participation in the treatment to stop smoking was obtained with decreased substance use in patients with alcohol and other drug use[19]. MI has also been shown to be effective in motivating smokers with schizophrenia or schizoaffective disorder to seek treatment for TUD[20]. In Spain, the use of motivational intervention in a multicomponent smoking cessation support programme in clinically stable outpatients with schizophrenia, schizoaffective or bipolar disorder has also been demonstrated[21]. Other initiatives have attempted to incorporate MI into a distance homecare management plan for war veterans diagnosed with PTSD and TUD. The authors observed favourable rates of smoking cessation, as well as an improvement in symptoms of depression and post-traumatic stress disorder[22]. Evidence-based strategies include individual treatments in stages for readiness to stop, combining smoking cessation medications with behavioural therapies, supported by smoke-free policies in treatment and residential settings[23].

COGNITIVE-BEHAVIOURAL PSYCHOLOGICAL TREATMENTS (CBT)

Among cognitive behavioural treatment techniques are problem solving, coping and stress control techniques. Training in strategies such as distraction, control of activation through relaxation or development, improvement of communication skills and cognitive restructuring of dysfunctional thoughts are also included in this type of treatment.

According to Peckham, et al.[24], the first smoking cessation intervention trial for adults with mental health problems was published in the USA in 1999. Simultaneously, the 1998 publication of the UK government white paper *Smoking Kills* resulted in the development of services for smokers in the NHS. Smoking cessation resources were not mandatory, so it is unlikely that smokers with mental health

Table 6 Evidence levels for psychological therapies to stop smoking

Evidence levels			
Well-established	*Likely*	*Experimental/Promising*	*Other**
Multi-component treatment - Pharmacotherapy + Nicotine Replacement Therapy + Cognitive-behavioural therapy	Cognitive-behavioural therapy: - Coping strategies - Problem solving	Behavioural therapy: - Contingency management	
	Motivational Interview	Behavioural therapy - Exposure to cues, extinction and stimulus control	Aversion techniques
	Relapse prevention	Gradual reduction strategies	

* No evidence in smokers with dual disorders

problems used many cessation interventions[25]. A Cochrane review brought together trials that tested smoking cessation interventions which included specific mood management components for depression vs a standard intervention. A significant positive effect was shown for smokers with current depression (11 trials; n = 1,844; RR = 1.47; 95% CI, 1.13-1.92), past depression (13 trials; n = 1,496; RR = 1.41; 95% CI, 1.13–1.77)[26]. Interventions largely followed a Behavioural Therapy approach, offering individual or group counselling sessions. For example, the treatments encouraged participants to monitor their mood using a daily rating scale and to learn and apply skills to decrease negative moods and increase pleasant ones, such as recognising maladaptive thoughts, challenging negative thoughts, engaging in enjoyable activities, increasing positive social relationships and realistic goal setting[27]. Again, these results should be interpreted with caution, as the trials included had considerable variability in type of treatment and protocol heterogeneity (e.g., length of treatment, face-to-face or self-help, amount of contact with a therapist). Although CBT has been included in several studies, in most cases it is combined with pharmacotherapy or nicotine replacement therapy; therefore no data are available on the differential effect of this approach on TUD behaviour among people with current depression[28].

BEHAVIOURAL THERAPY

Contingency management (CM)

A systematic review and meta-analysis to assess the evidence for the effectiveness of contingency management (CM) in promoting tobacco abstinence among people with SUD or in recovery. The CM for smoking cessation in people with substance use disorders performs significantly better than the control conditions in reducing smoking at the end of treatment[29]. Contingency management (CM) techniques have recently been employed in a pilot study that examined its feasibility plus brief cognitive behavioural therapy (CBT) to promote tobacco use cessation among trauma-exposed individuals with and without PTSD with promising results[30]. A study of 1,468 Medicaid recipients with mental disorders (schizophrenia, bipolar disorder, major depressive disorder and anxiety disorders) examined whether abstinence-dependent monetary incentives improved outcomes when added to cessation treatments at community mental health centres. The authors concluded that the participants who received monetary incentives were more likely to stop smoking over time (adjusted odds ratio [AOR] = 1.77, p = 0.009), and that these findings did not differ significantly between diagnostic groups[31]. Other interventions that have included CM through a mobile phone application, cognitive-behavioural therapy (CBT) and pharmacotherapy to stop smoking show treatment feasibility and acceptability results in smokers with schizophrenia[32] and smokers with PTSD, using combined MC + phone app, Stay Quit Coach[33]. This demonstrates the potential usefulness of mobile interventions for patients with different dual pathologies.

Other behavioural techniques

Another subgroup of interventions widely used in the 1970s and 1980s included aversive techniques (rapid smoking, smoke retention, satiation and covert sensitisation). Although they have been shown to be effective in a certain smoker profile (if they have exhausted

other techniques or have little time), a person's physical comorbidity (e.g. hypertension, COPD, cardiovascular disease) may discourage their use and, since people with dual disorders tend to have poorer physical health, it is highly likely that their use will not be extended in this population.

Regarding other techniques encompassed within behavioural therapy, such as the nicotine fading technique (gradual reduction of nicotine and tar ingestion), exposure to stimuli (cue exposure), extinction and stimulus control, there is no evidence of their isolated use in people with other comorbidities, although they are often used as one of the parts in multi-component programmes.

THIRD GENERATION OR CONTEXTUAL PSYCHOLOGICAL THERAPIES

This third wave of psychological treatments emerged in the 1990s, following the development of previous therapy modes: behavioural therapy and CBT. These therapies are based on the functional analysis of behaviour and radical behaviourism, with their main interest focusing on verbal behaviour. Third-generation therapies pose psychological problems in terms of the function that each behaviour fulfils in the context of the person. Therefore, from this new wave, addictive disorders are conceived as experiential avoidance, an emotional regulation problem or as the vital situation in which the person in particular is immersed[34].

One of these treatments is acceptance and commitment therapy, which has been shown to be a treatment leading to abstinence rates similar to CBT and NRT[35,36]. It is one of the third-generation therapies with the most empirical evidence in the field of addiction; however, there is still no consistent scientific literature in the population with dual disorders[37].

Another third wave therapy is mindfulness or full attention. A recent meta-analysis[38] shows a higher rate of long-term abstinence in the intervention groups with mindfulness compared to other treatments, mainly CBT. However, these are studies with small samples, no control group and whose participants have no other comorbidities[39].

A third-generation therapy that has further development in the field of affective disorders, behavioural activation (BA), has also shown significant intervention effects at 6 and 12 months of follow-up in patients with TUD and depression.

Table 7 **Third-generation psychological therapies and dual disorders data**

Name	*Description*	*Dual disorders data*
Acceptance and Commitment Therapy (ACT)	Accept thoughts, detach from them and commit to one's values and goals. Addiction as experiential avoidance.	Scarce
Mindfulness-Based Cognitive Therapy Mindfulness-Based Relapse Prevention (MBRP)	Pay full attention to present-moment experience with interest, curiosity and acceptance. MBRP integrates mindfulness meditation with a relapse prevention programme of various cognitive-behavioural therapies.	Scarce
Behavioural Activation (BA)	Subcomponent of Beck's cognitive therapy, dealing with the performance of potentially reinforcing activities through rigorous monitoring, analysis and programming the patient's routine.	Scarce
Eye Movement Desensitisation and Reprocessing (EMDR)	Bilateral brain stimulation of the patient through eye movements, tones or touches to facilitate reprocessing of psychological emotional discomfort factors.	None
Dialectical Behaviour Therapy (DBT)	Based on behavioural therapy, it combines some of its techniques with reality acceptance principles derived from Zen and dialectical philosophy.	Scarce
Functional Analytic Psychotherapy (FAP)	The interaction between therapist and patient is the basis of therapeutic change. The therapist functions as an agent of reinforcement and extinction of behaviours. The subject's behaviour is shaped to achieve an adapted and functional behaviour.	None

* No evidence in smokers with dual disorders

Along these same lines, adding contingency management to CBT + behavioural activation to stop smoking was successful in a recent study by Secades-Villa et al. (2020)[29]. Other therapies in this new wave of treatments, such as dialectical behaviour therapy (DBT), Functional Analytical Psychotherapy (FAP) and Eye Movement Desensitisation and Reprocessing (EMDR) have not yet been used in studies for patients with TUD in dual disorders.

MULTICOMPONENT PSYCHOLOGICAL PROGRAMMES

This TUD treatment modality dates from the early 1980s and owes its name to the fact that it includes several intervention techniques or components. The most widely used multicomponent treatment for smokers is cognitive behavioural multicomponent therapy with relapse prevention[40], which is recommended for patients with dual disorders in conjunction with pharmacological treatment and/or NRT[41]. Multicomponent psychological programmes have three phases: preparation to stop smoking, stopping smoking and maintenance of abstinence[42.] There are several multimodal initiatives that use different interventions, combining psychological and pharmacological techniques adapted to each subject[43], which have been applied effectively in smokers with severe mental disorders[44-48]. A multicomponent treatment model used in people with severe mental illness and TUD is offered below in Table 8.

Therefore, the multicomponent programme for the cessation of TUD seems to be a good option, combining the biopsychosocial perspective in such a way that each component addresses the needs of the individual subject[49].

Table 8 Main parts of a multicomponent programme to stop smoking

Phase	Components
Preparation	Increase motivation and commitment to change Decision balance: Review the reasons for and benefits of stopping smoking Self-observation: self-recording to increase awareness and knowledge of one's own behaviour. Set the day you are going to stop (1 to 3 weeks): D-Day. Use self-management and self-control training techniques: Alternative behaviours to smoking Stress management: relaxation, physical exercise
Abandonment	Non-aversive strategies Gradual reduction of nicotine and tar consumption Pharmacological strategies: varenicline, bupropion. Nicotine replacement therapy (nicotine patches)
Maintenance and relapse prevention	Self-management strategies to avoid the stimuli associated with smoking behaviour and encourage alternative behaviours Cognitive-behavioural coping strategies: Anticipate high-risk situations Training in social skills such as assertive communication Problem solving techniques Relaxation techniques Strategies for Recognising and Relieving Withdrawal Symptoms Strategies for managing relapses or setbacks Promoting and strengthening social support Use of mutual aid (group intervention) Support team (partner, friends, therapists)

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9. NEW LINES OF APPROACH FOR DUAL TUD

CHAPTER SUMMARY

Due to the very poor results achieved in patients with Dual TUD, new lines of approach are being considered and studied to increase the expectations of abstinence or reduction of consumption, with intensification of combined pharmacological and psychological therapies.

The use of new nicotine delivery devices that have reached the market may be other tools to be considered and not simply ruled out for treating patients with dual TUD.

New technologies have proven useful in enhancing the impact of non-pharmacological measures, with the new research on the role of magnetic brain stimulation having to be considered. Information and communication technologies (ICT) have allowed the medical care model to evolve towards a more virtual one.

Despite the availability of first-line pharmacological and psychological interventions, the treatment results we have in the general population barely reach 40-50% of sustained abstinence at one year of follow-up[1]. This is also evident and will surely be higher in smokers with other mental disorders diagnosed.

Therefore, new lines of approach are being proposed to increase sustained cessation expectations. Notable ones are those proposing a decrease in consumption or temporary interruptions, by seeking to increase the motivation and self-efficacy necessary to consolidate abstinence. When supported by pharmacological treatments, these interventions must surely increase efficacy.

This perspective would help promote other motivational strategies in patients who are often immobilised by their sense of inefficiency, who may consider an entirely tobacco-free future as overwhelming.

INTENSIFICATION OF PHARMACOLOGICAL AND BIOLOGICAL STRATEGIES

Although there is no scientific literature on patients with dual disorders, there have been publications in which modifications are used in the usual guidelines for the use of first-line drugs in the general population.

The first involves the use of nicotine replacements (NRT) before stopping, known as preloading[2-4]. This approach consists of starting treatment with nicotine, at normal and high doses, before the day set for complete abstinence. It is often useful in smokers with previous failures in standardised protocols or patients with TUD with severe addiction; for examples, many patients with other psychiatric disorders. These studies show an increase in abstinence rates linked to these interventions.

Another novel strategy is increasing the dose of oral nicotine devices, where a 4 mg gum has already been shown to be more effective in controlling craving in severely addicted smokers. The appearance of studies with 6 mg gum could improve results even more[5].

Another example of therapeutic intensification is the use of a combined treatment of varenicline and bupropion in smokers who previously failed an attempt with NRT[6]; this combination proving more effective than varenicline alone, especially in men with severe TUD.

Transcranial Magnetic Brain Stimulation

In a double-blind, multicentre RCT in 262 chronic smokers who met DSM-5 criteria for TUD and who had failed to stop smoking at least once before (with 68% failing at least three times), repetitive transcranial magnetic resonance imaging (rTMS) was administered bilaterally, actively or simulated, daily in the lateral prefrontal and insular cortices for 3 weeks, followed by rTMS once a week for 3 weeks. Cigarette smoking was reduced and craving was significantly higher in the active group than in the simulated group at 2 weeks of treatment. This study establishes a safe treatment protocol that promotes TUD abstinence or reduction by stimulating relevant brain circuits. It represents the first large multicentre RCT for brain stimulation and has led to the first US FDA authorisation for this rTMS procedure (H-4 coil) as an aid to TUD in adults for short-term tobacco cessation[7].

QUITLINES: TELEPHONE TREATMENT EXPERIENCES FOR TUD

The experiences of telephone treatment in the cessation of TUD in the general population have already shown efficacy. "Quitlines" increases success by increasing the number of smokers who make an attempt, reducing the likelihood of relapse. They have been shown to be effective in both clinical trials and observational studies of routine clinical practice[8,9].

The Cochrane review assessed the effects of telephone interventions, both proactive and reactive, on cessation. It concluded that proactive telephone counselling helps smokers seeking help from these lines, while providing important access to support, with call-back counselling increasing effectiveness. Although the evidence is limited, 3 or more calls significantly increase the chances of stopping smoking[10].

There are fewer data showing acceptance and efficacy in smokers with dual disorders, although there are some published studies that show that it may be a useful, generally well-accepted tool. However, there is evidence, collected in the quitlines themselves, that the population with other psychiatric diagnoses has sought help from them since the beginning of their implementation.

The available data highlight the importance of identifying smokers with other mental disorders in their first contacts through open questions about medication, follow-up in psychiatric units and/or clinical stability. This recognition is essential to be able to adapt the intervention to the specific needs of this population.

The recommendations adapted during the telephone intervention, especially in patients with greater deterioration, include the need for a greater number of calls, a somewhat shorter duration of them (they can last between 30-40 mins) and interventions with no more than one or two objectives to facilitate retention and application. Trying to set a cessation date during the first contact, without giving the patient time to feel safe, can even be counterproductive.

During the process of abandoning consumption, it is important to recommend that patients go to their mental health professional to regularly evaluate any changes in symptoms and to adjust the psychopharmacological treatment, if necessary[11].

The specific experience in treating smokers and the mental health training for the personnel who take these calls is essential; not only for effectiveness, but also to reduce the stress that may be involved in approaching this population. Being advised and supervised by psychiatry and/or psychology professionals and having clear protocols for intervention in situations that may be frequent in these patients (e.g. anxiety crisis and suicidal ideation) is considered part of the training[12].

ELECTRONIC NICOTINE DELIVERY DEVICES (ENDS) AND TOBACCO HEATING DEVICES

Although the use of inhaled nicotine delivery devices as a strategy for the treatment of people with TUD - to achieve abstinence or harm reduction - is a controversial subject for many clinicians and researchers, one of the populations in which its clinical use is proposed is that of smokers with other mental disorders.

The use is based on the high prevalence of TUD that has not decreased significantly with preventive strategies, and on the difficulties in stopping smoking in people with other mental disorders, i.e. dual disorders. In some cases, it is considered part of the strategy to reduce risk, harm or consumption; while, in others, as a preliminary step towards attempting complete cessation.

A recent, very comprehensive review of this topic was published by the UK Department of Public Health[13].

Data on the prevalence of consumption have been compiled in studies in the USA, with rates of 3-20% being found for the general population and 7-45% for patients in clinical settings.

Before 2020, no randomised trial was found assessing their use in cessation or reduction. Five "pre-post" studies were identified that included patients with severe mental disorders (e.g. schizophrenia, schizoaffective disorder and bipolar disorder), other diagnoses (depressive disorder, PTSD) and dual disorders patients. The results for complete cessation are low but are better in the studies comparing with nicotine patches. All studies showed significant reduction in the number of cigarettes smoked per day, in CO levels and in the Fagerström test score assessing dependence severity.

The most frequent adverse effects (AE) found were throat irritation, dry cough, nausea and dry mouth and did not differ from those found in the general population. Serious AEs of decompensation of psychotic and depressive symptoms were described in hospitalised patients, which were assessed independently of treatment.

For benefits of their use, patients refer to a decrease in cough, improvement in insomnia and feeling less addicted.

A significant percentage acknowledge breathing better and being able to exercise more when using these devices than when smoking traditional tobacco.

Also of interest are the reasons why a patient with dual disorders decides to use them. The most frequent was "why not?", the second was a desire to stop and the belief that they were safer and easier to use, cheaper in the case of electronic cigarettes, and that they help reduce the number of cigarettes smoked.

Although studies are scarce among health professionals, a lack of knowledge was found, leading to ambivalence about the use smokers might make of these devices, to outright rejection, when comparing them to traditional cigarettes.

One of the implications highlighted by this review is that a considerable number of patients with TUD and other mental disorders use cigarettes and devices together, and should be counselled about their risks, maintaining an open attitude towards their TUD and to continue trying to stop completely, even if continuous treatment is required.

NEW INFORMATION AND COMMUNICATION TECHNOLOGIES

New technologies have proven to be a useful tool to enhance the impact of non-pharmacological measures[14]. Information and communication technologies (ICT) have allowed the medical care model to evolve towards a more virtual one. The recent pandemic demonstrated possibilities in many health fields, among them, intervention in tobacco use[15]. ICT include programmes based on remote medicine (TLM), gamification (GMF) and smartphone applications (apps).

TLM is defined as the set of ICT-based tools for remote interviewing, assessment and medical treatment[16].

Regarding use in smoking cessation programmes, Segrelles Escribano *et al.*[16] carried out a bibliographic review of 26 articles. The mobile phone was the most used resource along with some social networks to promote communication between users and professionals. Efficacy results were variable, but in no case was TLM inferior to conventional care.

TLM use in psychiatry has already come a long way and is now a useful tool well accepted by patients; however, some professionals show reservations, due to ignorance of the procedure or because they consider it increases their workload[17].

GMF began as a business strategy combining marketing, gaming and psychology techniques to provide the user with positive experiences and to be more involved in the product offered. In itself, it has to capture, retain and make the person evolve. Its use has entered medicine mainly in the fields of healthy lifestyles, rehabilitation and improvement of therapeutic compliance.

For tobacco, the El-Hilly group[18] published a study including the perception of behavioural control and intrinsic motivation as positive factors for patient involvement. As critical factors that the programme had to meet, they found the existence of an explicit purpose, congruence of the game's objectives and user and the functional design.

The use of mobile phones has increased dramatically in recent years and has opened the market for apps, of which there are currently over 100,000 related to health and healthy lifestyles[14].

There are currently apps for the treatment of TUD and various studies are being carried out. Vilardaga's team[19,20] carried out several studies in the general population and people with severe mental disorders (SMD). The first shows the design, feasibility, use and assessment of an app ("Learn to Quit"), designed for people with SMD; while the second analyses the objectives and user experiences with it. It includes content from acceptance and commitment therapy (ACT) and from the US Clinical Practice Guideline aimed at providing strategies for cessation taking into account psychiatric symptoms, a set of behavioural principles with visual design to facilitate understanding and finally a gamification component to increase daily use of it and simple concepts, understandable for a population with possible cognitive deficits.

The combination of new technological resources, such as those described here, with biological treatments that affect the nicotinic cholinergic system should be encouraged.

INTERVENTIONS IN HOSPITAL ADMISSION DEVICES

Traditionally, people with TUD have been attended in outpatient facilities, mostly in primary health care; only relatively recently have professionals from addiction and/or mental health units been involved.

The allowance of smoking in psychiatric admission units, with the lack of knowledge about the chronic disease condition linked to other serious mental disorders in certain patients, did not promote positive changes in the patterns of tobacco consumption, and in fact constituted a risk factor for relapse in patients who had stopped smoking.

However, this situation is currently changing significantly for the better with smoke-free units, where those admitted have nicotine replacement therapy, specific drugs and motivational actions for which specific interventions are beginning to be considered during psychiatric admissions. However, there is a need to increase the awareness of health personnel to scale up these smoking cessation interventions during and at discharge from psychiatric hospitalisations.

Hospital admission for tobacco withdrawal

After several attempts to achieve outpatient abstinence, it was observed that the main difficulty faced by some patients was managing the initial period when nicotine withdrawal was more intense. Despite pharmacological treatment, these symptoms can make it difficult to implement cognitive and behavioural strategies aimed at consolidating substance withdrawal. This situation can be found especially in smokers with high dependency, low self-efficacy and poor psychological skills profiles. These features have significant correlation with those of patients with other chronic, debilitating psychiatric disorders.

In these cases, having a tobacco withdrawal room where smoking is not allowed and tobacco addiction is worked on with the same perspective and intensity as the rest of the substances increases success at discharge. Admission thus becomes a containing device and controlled environment to establish individualised risk situations, management strategies at discharge, and even assessment and possible positive changes in the environment together with the patient.

Motivational intervention in Psychiatric Units

As already mentioned, having a smoke-free environment in a hospital room in acute psychiatric units, together with motivated health personnel, trained and involved in dual disorders, make it possible to approach tobacco consumption during admission. In some units, this is already being done, often by integrating into group interventions that work on aspects of healthy living. Although empirically, an increase in knowledge of the risks of tobacco in patients and an impulse towards change is evident[13,21].

Opportunistic intervention: assessing admission to a psychiatric hospitalisation unit as an opportunity

A step beyond motivational interventions is to assess admission to a smoke-free psychiatric hospitalisation unit as an opportunity to stop using and maintain abstinence at discharge with specific follow-up and treatment[22].

An experience carried out for years in Catalonia, framed in the Catalan Network of Smoke-free Hospitals (XCHsF), led by the Tobacco and Mental Health group, is the "smoking cessation programme-mental health (PDT-SM)". This project proposes a protocolised intervention in psychiatric admission units, both general and for abandonment or dual disorders. Staff are trained and they subsequently implement information and motivational actions for TUD. Patients motivated to maintain abstinence are offered the possibility of follow-up and financed pharmacological treatment upon discharge. This experience has been carried out in 12 hospital units in patients who had not thought about stopping smoking prior to admission, with significant results of 10% abstinence at 1 year of follow-up[23,24].

In international clinical trials, very promising results have been found after motivational intervention and pharmacological treatment during psychiatric admission and follow-up after discharge, significantly increasing the success of cessation at 6 and 12 months, compared to control groups[25].

While these results are important, they are not impressive and continue to show that therapeutic responses to TUD in patients with other mental disorders need to improve significantly.

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10. SPECIAL POPULATIONS

CHAPTER SUMMARY

Adolescents are a special interest group, since mental disorders are manifested mostly at this age. Intervention in health centres is an opportunity for tackling these disorders. One of the barriers to carrying out these actions is the professionals themselves, with their lack of training and their own scientific perspective of TUD.

In the general population, specific barriers must be erected to prevent adolescents from accessing any tobacco product, including electronic cigarettes. In the vulnerable adolescent population, suffering from dual disorders or having a high density of biological relatives with mental disorders, the risk of developing TUD is high.

The treatment of adolescents with TUD and other mental disorders or dual disorders is backed by less scientific evidence than for the adult population. The controlled trials carried out, however, do not indicate greater risks or adverse effects, although their effectiveness seems to be very limited.

More studies are needed in patients older than 65 years for the treatment of TUD. In addition, specific recommendations should be included in the general guidelines for this population, since they have shown better rates of success in abandonment.

People with intellectual disabilities are another group whose specific features must be taken into account, prioritising the quality of the information and adapting it to the degree of disability.

Genetic factors have been shown to influence TUD and Obesity which should be considered in the therapeutic approach.

It would be of interest to start this chapter with a reflection on the difference in meaning that "special populations" can have for different health groups. All medical professionals consulting this document will be aware that the patients we treat are a special population for our colleagues in other specialities. Therefore, it may be considered that including this chapter when we are already talking about dual disorders is repetitive. In fact, this is true because, if it was difficult to find studies on tobacco in dual disorders until relatively recently, nowadays it is even more difficult to find studies that combine tobacco use, dual disorders and special populations.

When dealing with TUD, chapters about special groups deal with groups such as adolescents, elderly people, LGTBI people, ethnic minorities, migrants or people with a low economic and sociocultural level.

Another question for reflection is whether a separate chapter is really necessary to address tobacco intervention in these groups or would it be enough simply to adapt our interventions to their specific situations, as is done when seeking individualised treatment for each new patient, in accordance with the perspective of precision psychiatry.

Despite finding no references specifically studying these groups in dual disorders patients, the results that may be useful are reviewed.

CHILDREN AND ADOLESCENTS

During adolescence, the brain has not yet completed its neurodevelopment. This population tends to have more exploratory and sometimes impulsive behaviour to prepare them for adult life, but which is not without risks in a vulnerable population.

Tobacco use often begins in adolescence, and this age group has a higher risk of developing addiction, attributed to the fact that the brain at this stage is more susceptible to its neuroinflammatory effects[1]. Approximately 75% of adult tobacco users report having tried it for the first time between the ages of 11 and 17. However, many who do not smoke as regularly did not use tobacco as adolescents[1].

Surprisingly, little is known about the effects of these initial episodes of tobacco use and their influence on patterns in adulthood. In particular, understanding the role that tobacco and nicotine play in these early experiences may be important in understanding the development of TUD[1].

There is increasing evidence of the inflammatory effect of nicotine on microglial cells during adolescent development, which could promote the development of TUD. Furthermore, microglia are also involved in synaptic function and plasticity, supporting different mental functions. Nicotine-induced neuroplastic changes are triggered by initial exposure, causing significant changes in brain physiology, structure, function and behavioural responses[2].

Tobacco use and mental disorders in adolescents

Adolescence can be a critical period for the appearance of TUD[3]. Thus, various studies have investigated the association between mental disorders, risk behaviours and TUD among adolescents.

Within the positive predictive factors for consumption, there is a group of factors in common with other psychiatric disorders, such as a sensation-seeking trait, marked impulsiveness, school failure, poor social adaptation, insecurity, low self-esteem, and a high rate of negative emotions. There is also the relationship with the consumption of other substances: e.g. having been drunk at one time or the habitual consumption of cannabis. Several authors conclude that the high degree of rebellion and thrill-seeking in childhood correlate with a higher probability of smoking tobacco in adolescence[4].

One such study, conducted in Australia, compared rates of tobacco use among youngsters with major depressive disorder, ADHD and conduct disorder. The results of the survey conducted in 2013-2014 showed higher rates of TUD among adolescents with mental disorders (20% vs. 5%). Additionally, rates were higher for those with conduct disorder (50%), major depressive disorder (24%) and anxiety disorders (19%). It is also noteworthy that 38% of current tobacco smokers had a mental disorder, 32% reported self-harm and/or suicidal ideation, compared with 10% and 5% in adolescents who had never smoked. Additionally, females with mental disorders or those who reported self-harm or suicidal ideation had higher rates of TUD than males. Other significant factors associated with current TUD were school problems, binge eating and having more than one sexual partner[5].

A US study with 3,005 participants suggests that adolescents with high sensitivity to anxiety tend to experience symptoms of emotional disturbance, which may increase the risk of substance use problems[3].

In addition to anxiety and depression, the possible relationship between TUD and adolescents with ADHD has also been studied, since its association is very frequent[6]. Youngsters diagnosed with ADHD are 2-3 times more likely to smoke. In addition, they start smoking at a younger age and progress faster and more frequently to regular use and addiction[6]. One of the possible explanations is the improvement effect (self-medication) produced by tobacco. There are also improvements in ADHD with usual drugs for the treatment of TUD such as nicotine, bupropion and varenicline. Other hypotheses are peer pressure or genetic and environmental factors that may contribute to addiction[6].

Another study in adolescents with more severe ADHD symptoms in childhood showed they were more likely to start smoking and to do so at a younger age. Another surprising result was that females had a greater association between ADHD symptoms and daily tobacco consumption, the number of cigarettes per day and nicotine dependence[7].

Electronic cigarettes

It is important to erect barriers preventing access to electronic cigarettes in uninitiated adolescents, as it could represent a risk factor for a vulnerable population suffering from mental disorders or with a high density of relatives in their family; quickly leading to TUD with conventional tobacco[8].

Studies in adolescents in the general population, not identified as being at risk, show controversial results:

A meta-analysis of 17,389 adolescents and young adults of 14-30 years old found that 30.4% of e-cigarette users started with conventional tobacco, while only 7.9% were non-smokers who had not previously consumed it. Thus, the use of e-cigarettes in adolescents could be associated with a higher risk of initiation in conventional tobacco and consumption[8].

Another systematic review provided similar results. It attempted to determine whether e-cigarette use by adolescents who had never smoked conventional tobacco cigarettes was associated with later initiation of use. Their ages ranged from 13 to 19 years and included adolescents from Europe and North America. The results found that the use of e-cigarettes was associated with a greater initiation of conventional tobacco consumption among adolescents, which could mean greater related health damage[9].

Other studies based on large surveys in the United Kingdom, however, show different results. A study based on 5 national surveys, which collected data from 60,000 young people aged 11-16 from 2015-2017 revealed that

the prevalence of regular use of e-cigarettes did not change in the period studied, remaining at just 1%. The surveys analysed consistently showed that the levels of regular use of e-cigarettes in young people who had never smoked remained very low, thus concluding that e-cigarettes did not constitute an entry into consumption of conventional tobacco[10]. Comparable results were obtained by analysing the data on youngsters of 17-18 years of age in one of the UK surveys carried out between 2015 and 2017: the percentage of e-cigarette users who had never smoked was very low[11].

A study conducted in New Zealand on almost 27,000 students showed that less than 2% of them had used e-cigarettes on a daily basis. Students who smoked were 25 times more likely to use e-cigarettes than those who had never smoked. Less than 1% of those who had never smoked used e-cigarettes daily[12].

The controversial data are not an obstacle to recommending that regulations preventing adolescents from access to any tobacco-derived product, as this is also done with alcohol and other substances[9].

Treatment of TUD in the adolescent population

Many young people will not go beyond experimental use and others will abandon regular use early without much effort. The various social strategies to control tobacco use and brief health advice will contribute to this abandonment. There is evidence that young people respond to this health advice and so it is important to include it in the interventions carried out at child and youth health centres, including those for mental health. Medium-term stay centres, such as day hospitals or community rehabilitation, can be highly effective for educational prevention strategies, motivational interventions, brief advice and cessation for smokers.

The first step in improving youth access to treatment programmes is capturing their interest. An interesting experience on this point is the ACCESS Project[13], a European Union project with the aim of increasing the impact of plans to help adolescents. It started in 2009-2010 and has 11 European associates. The basic idea is to establish non-smoking as a social norm, with proactive recruitment of smokers, understandable information on effective and affordable treatments, personalised interventions, use of incentives and nearby professionals. As mentioned, this could be a project included in child and adolescent health day centres, which are a very affordable way of access for adolescents and for professionals to have more opportunities to explore consumption, motivation and perform cessation interventions. One of the barriers to carrying out these actions is the professionals themselves, with their lack of training and their own scientific perspective of TUD.

The therapeutic interventions used do not differ from those in adult smokers: cognitive-behavioural interventions, use of incentives, group therapies, pharmacological treatments, quitlines, interactive programmes and peer intervention. A review[14] found a mean cessation rate at 3-12 months of 12%, vs 7% in the control group, with groups and quitlines (15-20%) and individualised computer interventions being more effective.

Nicotine replacement therapy

Study results for this are inconclusive: some show that the use of nicotine patches and minimal intervention achieves a decrease in the number of cigarettes consumed in motivated adolescents, but does not achieve better results than cessation without help[15]. Other meta-analyses, however, do show better results for the treatment groups than in the controls[16,17].

Bupropion treatment

Trials in adolescents support the efficacy of the 300 mg dose, but not the 150 mg dose. One of the problems in adolescents is the difficulty in compliance for two doses a day, which is necessary for the normal bupropion SR treatment[18]. Another study evaluated the comparative efficacy of a combined treatment with patches and bupropion SR (150 mg) vs patches and placebo; no differences between them were found[19].

Safety and efficacy of varenicline in treating adolescents

Although TUD usually begins in adolescence, pharmacological interventions in this population are scarce[20]. Its efficacy in adults has been demonstrated in randomised clinical trials; however, there are hardly any studies in adolescents[21].

One of these trials was carried out on 157 youngsters between the ages of 14 and 21 who smoked conventional tobacco. Abstinence rates at the end of the treatment did not differ between groups (p=0.96). In contrast, participants who had received varenicline achieved abstinence at least 7 days earlier (p=0.02), and had higher rates of overall abstinence during treatment and at subsequent follow-up, compared with placebo (p=0.02). Treatment was generally well tolerated and adverse events did not differ between groups[21].

However, another study did not shown any advantage for varenicline, compared to placebo, for treating withdrawal symptoms in adolescents. These results indicate that further research is needed to identify strategies that improve outcomes among adolescents[20].

The feasibility and safety of varenicline and bupropion as therapies for smoking cessation in adolescents have also been explored in a randomised trial. Both treatments were well tolerated, with no serious adverse events. Participants receiving varenicline reduced from 14.1 ± 6.3 (mean ± SD) to 0.9 ± 2.1 cigarettes/day (with 4 stopping altogether); while those receiving bupropion XL reduced from 15.8 ± 4.4 to 3.1 ± 4.0 cigarettes/day (2 stopping altogether). These preliminary results support the feasibility and safety of conducting adequately powered, placebo-controlled efficacy studies of varenicline and bupropion XL for TUD in adolescents[22].

TUD IN THE ELDERLY AND RELATIONSHIP WITH COGNITIVE IMPAIRMENT AND DEMENTIA

Despite the fact that a large proportion of the efforts in prevention and treatment of TUD are focused on the young or middle-aged population, a significant part of the morbidity and mortality derived from consumption occurs in people over 65 years of age. The global trend of population ageing leads to a progressive increase in the presence of cognitive impairment and dementia, and the evidence supports tobacco use as a risk factor for these disorders.

When compared to the general population, people over 65 years of age smoke less tobacco, as can be seen in Table 9, which summarises the European and Spanish Health Surveys of 2020 and 2017, respectively. Tobacco consumption throughout life shows significant consequences among the elderly[23]. The lower proportion of tobacco consumption at this time of life seems to be related both to the decision to stop smoking itself and to medical advice. In many cases, medical advice is given after the detection of somatic diseases or when identifying other risk factors that produce a synergistic deleterious effect on health. In addition, people who continue to smoke do so in smaller quantities, with a lower prevalence of heavy smokers[24]. Smoking cessation in this age group is higher among women than among men[24].

Given the wide availability of nicotinic receptors in the brain and their influence on a large number of circuits and systems (noradrenergic, serotonergic and dopaminergic, among others), nicotine exerts an influence on a wide spectrum of cognitive domains, such as attention, motor capacity, executive functions, learning new tasks and memory[26]. Tobacco use throughout life has been consistently associated with poorer cognitive performance from middle age and with an increased risk of dementia in old age, both vascular and Alzheimer's disease[27-29].

Mild cognitive impairment is very common among older people. It is characterised by a deterioration in memory, attention and general cognitive performance with respect to the previous level of functioning (and with respect to what is expected for their age and educational level), but which does not significantly affect performance in the daily activities of the person. It can be considered a transitional phase towards dementia, with an annual conversion rate of between 10 and 15%. Smoking cessation may be one of the factors that helps prevent cognitive decline in old age and the transition from mild cognitive impairment to dementia[27].

It is estimated that one-third of dementia cases are attributable to modifiable causes, such as hypertension, sedentary lifestyle or smoking. Thus, it seems clear that a reduction in tobacco consumption would be directly related to a reduction in the prevalence of cognitive impairment and dementia in the population, even when smoking cessation occurs in adulthood and the final stages of life[28,29].

People who do not smoke but are affected by tobacco smoke, known as passive smokers, are also at increased risk of cognitive decline; so non-smokers avoiding exposure to tobacco smoke is another measure that can preserve cognitive performance in the elderly[30].

Regarding vascular dementia, the same mechanisms that produce a greater risk of vascular diseases related to tobacco in other locations of the body (damage to the vascular endothelium) seem to explain the greater risk of vascular pathology at the brain level[31]. The higher incidence of Alzheimer's disease in smokers has been related to oxidative stress in brain tissue[32].

The relationship between TUD and other mental disorders observed in other age groups is maintained in old age, with dual disorders being one of the main barriers to successfully stopping smoking. Thus, older people with depression or who suffer from other SUDs (e.g., alcohol use) have more difficulty stopping smoking[33].

Very few studies have focused on studying therapies for tobacco use disorder among those over 65 years of age. Logically, more evidence of the use of different strategies among the elderly is desirable[34]. In any case, it seems that

Table 9 **Tobacco consumption according to age groups (% population aged 15 and over)**

Age (years)	European Health Survey 2020[24]		Spanish Health Survey 2017[25]	
	Men	Women	Men	Women
Daily smokers	23.3	16.4	25.6	18.8
15-24	18.3	12.0	20.0	15.1
25-34	30.9	21.6	32.9	24.3
35-44	27.8	20.3	32.5	24.8
45-54	26.2	23.8	29.4	26.4
55-64	27.3	20.0	26.1	22.2
65-74	14.4	8.5	16.5	7.8
75-84	9.1	2.8	9.0	2.5
≥ 85	2.8	0.6	3.5	0.9
Occasional smoker	2.6	2.1	2.7	2.0
15-24	3.2	3.9	3.6	2.6
25-34	3.9	2.9	4.3	2.8
35-44	2.8	2.6	2.6	2.6
45-54	3.0	1.9	3.5	2.8
55-64	1.9	2.0	1.7	1.9
65-74	1.5	0.9	0.9	0.8
75-84	1.4	0.4	0.8	0.0
≥ 85	1.4	0.0	1.2	0.2
Ex-smoker	27.6	16.7	32.2	18.0
15-24	4.6	3.5	6.7	6.6
25-34	13.5	10.8	16.2	14.4
35-44	20.6	23.2	22.8	21.6
45-54	26.1	20.1	32.5	25.1
55-64	38.2	27.5	48.2	28.0
65-74	51.3	17.9	55.6	16.1
75-84	51.8	6.8	57.4	7.4
≥ 85	49.5	3.9	59.6	3.8
Non-smoker	46.4	64.8	39.5	61.2
15-24	73.9	80.6	69.7	75.8
25-34	51.7	64.7	46.7	58.5
35-44	48.8	54.0	42.2	51.0
45-54	44.7	54.2	34.5	45.7
55-64	32.6	50.5	24.1	47.9
65-74	32.8	72.7	27.0	75.3
75-84	37.8	90.1	32.8	90.1
≥ 85	46.4	95.6	35.7	95.1

being older is related to better success rates in stopping, which justifies intensifying the detection of smokers, working on motivation and supporting treatment for this age group. The study by Croizet et al. (2016) showed a success rate of 83% higher in people over 60 years of age than in the population under that age (OR=1.83; 95% CI, 1.29-2.59)[35]. The recommendations used in the general guidelines should also be applied to the elderly, unless there is evidence suggesting interventions with specific considerations for this age group.

TUD, other mental disorders and obesity

The relationship between mental disorder and increased Body Mass Index (BMI) or obesity is well known. In addition to the health dangers posed individually by mental disorders including TUD and obesity, the combination of these conditions poses a particular health detriment.

Smoking influences body weight, such that smokers weigh less than non-smokers and stopping smoking often leads to weight gain. The relationship between body weight

and smoking is explained in part by the effect of nicotine on appetite and metabolism. The brain's nicotinic cholinergic system is involved in the control of both food and tobacco intake. Research strongly points to a common biological basis for regulation of appetite for tobacco and food, and thus vulnerability to nicotine addiction and obesity[36].

Genetic factors have been shown to influence TUD and obesity and, to understand the connection between these conditions, research has been done examining both the observed and genetic relationship between adiposity (an electrical impedance measure of BMI) and cigarettes smoked per day. The results point to common biological genetic influences behind TUD and obesity[37].

PEOPLE WITH INTELLECTUAL DISABILITIES

Intellectual disability is characterised by limitations in intellectual functioning and, secondarily, in learning, which gives rise to alterations in the skills necessary for daily living (social and conceptual). It originates before the age of 18, and may be genetic, acquired, environmental or of sociocultural aetiology and affects between 0.7-3% of the population[38]. They require support in education, employment, social life, daily activities and health to varying degrees.

A third of this population suffers from some type of psychopathology, which represents a higher percentage than in the general population. They also suffer from other inequalities, including health. These are given in part by the individuals themselves and their difficulty in communicating and accessing health services, and in part by the difficulties of the system, which minimises or attributes physical reasons to their cognitive condition or is indifferent to their problems.

The first data published on health indicators in Spain[39] highlight the high rates of overweight and obesity and the high proportion (65%) of subjects with psychotropic drugs, without a clear diagnosis to justify this.

A study conducted in the United Kingdom[40] found higher premature mortality than in the general population, and higher in men than women. The most frequent causes are cardiovascular, respiratory and neoplastic diseases, some of which are very significantly related to the use of tobacco and exposure to environmental smoke.

There are not many epidemiological studies on tobacco use in this population, but there is growing concern about the effects it can have on their health and their economic impact, since they are 3 times more likely to live in poverty[41].

Despite the fact that they consume tobacco or derivatives in a lower proportion than the general population, the consequences for increased morbidity and mortality are high. Another point of concern is their unequal access to health services, which means they have less information and access to programmes to improve their health and prevent harmful behaviours.

Although the data are not very reliable, the prevalence of tobacco consumption varies over the range 8-36%, in a greater proportion in men than women, and more of mild or moderate disability than severe. Daily consumption is also lower than in the general population and more frequent the lower the degree of disability and the greater the independence of the subject[39].

Smoking cessation in this population must take into account its specific features[42]. It is essential to prioritise the quality of the information and adapt it to the degree of disability; pen and paper, visual aids during a visit or simple brochures are all very helpful. It is also important to keep in mind that their concept of time may not be the same as in the general population, which makes anamnesis difficult.

Family members and/or caregivers are essential, both in taking medical history and in help with prescriptions.

The process of stopping smoking, and its risks and benefits must be explained in a way they understand.

During consultation, longer times should be given, with waiting done in quiet places and visits scheduled at appropriate times for the patient and caregivers.

In this review work by Kerr[42], the lack of protocolised interventions and therefore the lack of cessation effectiveness results is made clear, showing the need for more exhaustive studies. However, the feasibility of a school programme is shown, which would be useful to increase understanding of the social and health risks that tobacco and alcohol consumption entails and modifications suggested in psychosocial interventions for greater treatment effectiveness[43].

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11. NEW PERSPECTIVES: LOOKING TO THE FUTURE

CHAPTER SUMMARY

There will be no improvement in results until training in addictions and dual disorders occupies a more prominent place in health teaching; however, specific training in TUD and dual disorders is a clear commitment to the future.

SPECIFIC TRAINING

One of the actions that most correlates with the intensity of intervention in health problems is the knowledge and training of professionals on the pathology to be treated. This is especially important to consider when preparing academic curricula in health sciences.

Training in addictions and dual disorders occupies a very minor place in health teaching, at the medical, nursing and psychology levels, so many professionals face their practice with little knowledge. TUD is oriented more as a risk factor for other health problems than as a disorder in itself that needs to be diagnosed, evaluated and treated. It does not improve the situation in mental health training, which is more focused on other "classic" psychiatric disorders than on addictions and lastly on tobacco.

This situation makes it essential, in our opinion, that the subject of training be a clear commitment to the future.

MIR, PIR, EIR training

Specific training for new professionals in all fields of mental health is a strategy for the future so that TUD and its treatment are considered in our daily work.

There are already experiences where the theoretical-practical training carried out during the training of interns and the approach to tobacco addiction is included, both in smokers without apparent psychiatric pathology and in psychiatric patients; with positive changes in the assessment of these young professionals regarding their interventional ability being seen.

Training and motivating older staff

While this issue is being addressed in the new generations of professionals, we must also consider the mental health staff currently working who, in many cases, have had to face changes in legal measures, consumption restrictions, both in outpatient centres and in hospitalisation, without much management knowledge.

Some work provides preliminary lines that seek team training to increase the possibilities of intervention and the effectiveness of the programmes[1,2].

INTEGRATED INTERVENTIONS IN MENTAL HEALTH SERVICES

Many of the patients with psychiatric pathology are candidates for long follow-ups in mental health networks, cared for by different professionals, psychiatrists, psychologists, specialist nursing and health agents in follow-up tasks and individualised support (ISP). This reality makes contact with a health network continuous and multidisciplinary. Increasingly, the mental health network has been integrating practices to improve lifestyles and control somatic situations, which, in general, has led to a favourable change in the quality of life of users.

From the point of view of the patients, the bond created with their most direct professionals means that the degrees of trust, adherence to controls and compliance are greater than those obtained from specific consultations with other professionals who sometimes have fewer resources to intervene in their specific difficulties.

This reality and a good training in dual disorders provide a very clear possibility of being the best professionals who can intervene in all phases of TUD in our patients. Integrating this approach into daily practice often depends only on identifying the problem, understanding the cerebral nature of TUD, how tobacco negatively affects physical and mental health and carrying out the work with the support of the entire multidisciplinary team[3,4]. Specific training courses in TUD and dual disorders is an objective that scientific associations could address.

CARING FOR THE MENTAL HEALTH CAREGIVER

No more than 30 years ago, health professionals (doctors and nurses) had a prevalence of tobacco consumption higher than the average in the general population[5]. Despite the fact that this situation has improved significantly and that the surveys carried out in the European Smoke-free

Hospital Networks clearly demonstrate this reality[6,7], it is true that many professionals continue to smoke. Beyond what it may mean for intervention in the TUD of patients, in which professional smokers are less involved[8], the objective is the protection of our health.

Many years ago a study was carried out on the consumption of tobacco in the different medical specialities. Time has passed and there does not seem to have been another effort of this type except in the Spanish Association of Pulmonology and Thoracic Surgery (SEPAR)[9], where there was an interest in knowing the reality of its members and offering treatment alternatives.

The first step in taking care of ourselves could be a study of this type among the participants of the two associations, gathering an important sample of different age groups. The use or adaptation of the European survey for Smoke-free Hospitals would allow us to assess consumption and the attitudes of our colleagues towards the intervention.

A second more ambitious step would be to offer intervention possibilities through the companies' own website and with the support of professionals already specialised in it. Taking advantage of new technologies, with telephone visits or video calls, a service could be provided to achieve one of the most important changes in health that we can make.

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