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# Recommendations of the Treatment-Resistant Depression expert center network for promoting tobacco smoking cessation based on the results from the real-world FACE-TRD national cohort.

Running title: tobacco smoking and treatment-resistant depression

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Keywords: public health; mental health; psychiatry; depression; impulsivity; suicide; tobacco; women.

**Background.** Tobacco smoking has been associated with suicide, impulsivity and depression in non-clinical populations with differences across sexes.

**Objective.** To determine the role of tobacco smoking in Treatment-Resistant Depression (TRD) according to sex in a precision-medicine approach.

**Method.** The FACE-TRD cohort is a national cohort of TRD patients recruited in 13 resistant depression expert centers between 2014 and 2021 and followed-up at 6 months. A standardized one-day long comprehensive battery was carried out, including trained-clinician and patient-reported outcomes, and patients were reevaluated at 6 months on their smoking and psychiatric hospitalization outcomes.

**Results.** 355 TRD participants were included (222 women). The smoking rate was much higher in TRD women compared to the French general population (34% vs 24%) while it was comparable for men (approximately 29%). In multivariate analyses, compared to non-smoking women, female smokers had significantly increased number of lifetime psychiatric hospitalizations (standardized beta  $B=0.232$ ,  $p=0.014$ ) and electro-convulsive therapy (adjusted odds ratio (aOR)= 2.748,  $p=0.005$ ), increased suicidal ideations (aOR=4.047,  $p=0.031$ ), history of suicide attempt (aOR=1.994,  $p=0.033$ ), and increased impulsivity ( $B=0.210$ ,  $p=0.006$ ) and were more frequently treated by benzodiazepines (aOR=1.848,  $p=0.035$ ) and third- or fourth-line TRD treatments (antipsychotics aOR=2.270,  $p=0.006$ , mood stabilizers aOR=2.067  $p=0.044$ ). Tobacco smoking at baseline was predictive of psychiatric hospitalization within 6 months in persistent smoking women (aOR=2.636,  $p=0.031$ ). These results were not replicated in men, for whom tobacco smoking was only associated with increased clinician-rated and self-reported depressive symptoms (respectively  $B= 0.207$ ,  $p=0.022$  and  $B= 0.184$ ,  $p=0.048$ ). The smoking cessation rate at 6 months was higher in women than in men (12% vs. 7%). No patient was administered nicotine substitute or varenicline at the two timepoints.

**Interpretation.** Combining these results and those of the literature, we recommend that active tobacco cessation should be promoted in TRD to improve depression, suicide and impulsivity especially in women. ~~Nicotine substitute and varenicline should be recommended as first-line treatments for TRD smokers and benzodiazepines should be avoided as often as possible.~~ Female smokers appear as a specific population with heavier mental health outcomes that should be specifically addressed.

## Introduction

Addressing Treatment-Resistant Depression (TRD) is a major therapeutic issue in clinical practice. TRD is usually defined by persistent major depressive disorder after 2 well-conducted antidepressant treatments from two different classes (Rybak et al., 2021). Major depression is the first psychiatric cause of disability worldwide affecting >300 million people (Kupfer et al., 2012), and despite decades of drug development, the effectiveness of antidepressants has reached a glass ceiling. Approximately 68% of the patients do not achieve remission to a first-line treatment (Dodd et al., 2020) and 16% do not respond at all (Park et al., 2021). One explanation for this phenomenon is that different etiologies or maintenance factors may lead to the same clinical diagnosis named “major depressive disorder”. Ignoring these factors may explain therapeutic failure and resistance into treatment.

Among these disturbances, tobacco may play an important role. Tobacco smoking and major depression are two major epidemics of the 20<sup>th</sup> century and their mutual relationship has been questioned for a long time (Goodwin et al., 2017; Mathew et al., 2017). Approximately 1.3 billion people are current active smokers according to the World Health Organization (World Health Organization, 2021). We know now that people with depression are about 1.5 to twice as likely to smoke and are more heavily addicted than the general population (Royal college of physicians, 2013; Stubbs et al., 2018) and that they have still 14 years of life reduction expectancy (Chang et al., 2011). The depression prevalence of American smokers has increased between 2005 and 2013 (Goodwin et al., 2017). It has been estimated that from 2018 to 2060, approximately 484,000 smoking-attributable deaths will occur among adults with major depression, leading to 11.3 million life-years lost (Tam et al., 2020). Tobacco cessation is one of the most cost-effective health interventions (Taylor and Munafò, 2018). A Delphi expert consensus agreed at more than 85% in the first round on the importance for psychiatrists to correctly manage cardiometabolic factors including tobacco smoking (Galderisi et al., 2021). Tobacco cessation has been associated with improved depressive symptoms (Komiyama et al., 2021), which suggests that tobacco smoking may play a role in treatment resistance. In a recent randomized controlled trial (Liu et al., 2021), the participants with high baseline depression severity maintaining smoking had worse depressive symptoms throughout a 1-year period compared with their abstinent counterparts. A recent Mendelian study has concluded that tobacco smoking may have a causal effect on depression (Wootton et al., 2020).

Tobacco smoking is associated with increased suicidality (Carey and Seibert, 1993; Carrasco-Barrios et al., 2020), psychological distress, anxiety and depression (Hogarth et al., 2017; Jiménez-Treviño et al., 2019; Monroe et al., 2021; A. E. Taylor et al., 2014). Other studies suggest that tobacco smoking may be associated with increased impulsivity in a bilateral relationship in adolescents and young adults (Carim-Todd et al., 2016; DeBry and Tiffany, 2008; Doran and Trim, 2013; R Levin, 2012) but it is unclear if this association is persistent in TRD. Among 470 medical conditions in 24,130 subjects, depression has been associated with the cluster of tobacco-related diseases in addition to cardiovascular diseases and chronic

inflammatory diseases(Han et al., 2021). Genetic liability to depression may increase smoking(Yao et al., 2020). High level of depressive symptoms is predictive of later lung cancer in smokers(Trudel-Fitzgerald et al., 2020). Tobacco smoking is also associated with socioeconomic status, education level, neuroticism and childhood adversity (Gagné and Brown, 2021; Härkönen et al., 2018; Madureira et al., 2020; Oshri et al., 2017; Smith et al., 2016) that are risk factors for TRD(Balestri et al., 2016; Bennabi et al., 2015; Nikkheslat et al., 2020).

Tobacco smoking has different effects according to sex(Gross et al., 2020). In a recent meta-analysis, the relative risk of suicide was approximately twice as high in female smokers compared to male smokers (Echeverria et al., 2021). The authors of this meta-analysis noted the lack of data on suicidal ideation and suicide attempt (Echeverria et al., 2021). In summary, we need additional data to explore the role of tobacco smoking in TRD to guide effective interventions for improving TRD and promoting tobacco cessation.

Our aim was to explore the factors associated with tobacco smoking according to sex in a non-selected outpatient national cohort of TRD patients at baseline and at 6-month follow-up. Our hypothesis was that tobacco smoking would be more frequent in men and would be associated with more severe clinical profile (especially increased suicidal ideations, anxiety, impulsivity, depression), with lower education level and higher exposure to childhood trauma and neuroticism compared to other patients.

## Methods.

### Study population, inclusion and exclusion criteria

The FACE-TRD is one of the four French cohorts of severe psychiatric disorders created to address real-world diagnostic and therapeutic unmet needs. Patients are referred to the Expert Centers by the treating psychiatrist, who receive a report of the evaluation with recommendations for the care.

The inclusion criteria of the FACE-TRD cohort are : 1/ speaking French, 2/ having full insurance coverage, 3/ a diagnosis of current major depressive episode based on the DSM-5 criteria(APA, 2013), 4/ having received two or more well-conducted antidepressant treatments (at least 6 weeks of full dosage antidepressants from 2 different classes among selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, imipraminic/tricyclic agents or alpha-2 antagonist agents).

Exclusion criteria were: diagnosis of bipolar disorders, schizophrenia-spectrum disorders or autism-spectrum disorders, obsessive-compulsive disorder and cannabis use disorder based on the DSM-5 criteria(APA, 2013). The inclusion and exclusion criteria were confirmed by two trained psychiatrists of the resistant depression expert center network (one at the inclusion visit and another one at the full one-day long evaluation).

## Tobacco smoking and alcohol variables

Current daily tobacco smoking, age at regular tobacco consumption, number of paquet/year were rated by the clinician. Nicotine (NIC) dependence was assessed with the self-reported Fagerström questionnaire score (Heatherton et al., 1991). Severe NIC dependence was defined by a Fagerström score  $\geq 7$  (Heatherton et al., 1991). Alcohol misuse was defined according the DSM-5 criteria (APA, 2013).

## Clinician-rated outcomes

The following set of variables are captured in the FACE-TRD database with standardized questionnaires:

- Sociodemographic and early-life variables: sex, age (continuous, years), education level (binary: academic level vs. non-academic level), working force status (binary), history of childhood trauma (Childhood Trauma Questionnaire score (CTQ)) (Bernstein et al., 1994) (continuous). The CTQ includes 70 items with a five-choice Likert-type scale (from 1 = "never true" to 5 = "very often true"). Higher score represents higher exposure to childhood trauma.
- Depression characteristics (continuous except for history of suicide attempt): number of lifetime psychiatric hospitalizations, depression severity using Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), suicidal ideation using suicidal ideation scale (Luxton et al., 2011), lifetime history of suicide attempt). MADRS is a 10-item scale, higher scores represent higher depressive symptomatology. The Suicidal Ideation Scale (Luxton et al., 2011) is a 10-item self-report scale designed to assess the severity or intensity of suicidal ideation. Each item is scored from 1 ("Never or none of the time") to 5 ("Always or a great many times") according to how often the respondent felt or behaved during the past year. The total score ranges from 10 to 50.
- Patient-reported outcomes (PROMS) (continuous). The PROMS are now essential complementary data to explore resistant depression issues. Neuroticism was explored as a potential confounding factor mediating the association between tobacco smoking and depression (Zvolensky et al., 2015). The following PROMS were reported: depressive symptoms (Quick Inventory of Depressive Symptomatology /QIDS)) (Rush et al., 2003), anxiety symptoms (State-Trait Anxiety Inventory /STAI-Y) (Spielberger, 1983), impulsivity using Barratt Impulsiveness Scale (BIS) with 3 subscores (motor, attention, planification) (Heatherton et al., 1991), sleep disorders using Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), neuroticism using Big Five Inventory (Courtois et al., 2020). For these scales, higher scores are associated with poorer outcomes. The QIDS (Rush et al., 2003) is a rating scale that assesses the nine criterion symptom domains designated by the American Psychiatric Association's DSM-IV to diagnose a major depressive episode. There are 16 items in the adult versions of the QIDS16 measuring the nine criterion symptom domains (sleep, sad mood, appetite/weight, concentration/decision making, self-view, thoughts of death or suicide, general interest, energy level, and restlessness/agitation). Total QIDS scores range from 0 to 27. The STAI (Spielberger, 1983) is a psychological inventory based on a 4-point Likert scale and

consists of 40 questions on a self-report basis. The STAI measures two types of anxiety – state anxiety, or anxiety about an event, and trait anxiety, or anxiety level as a personal characteristic. The most current revision is Form Y. The BIS(Heatherton et al., 1991) is a questionnaire designed to assess the personality/behavioral construct of impulsiveness. It is the most widely cited instrument for the assessment of impulsiveness. The PSQI(Buysse et al., 1989), assesses sleep quality over a 1-month time interval. The measure consists of 19 individual items. Each item is weighted on a 0–3 interval scale. The global PSQI score is then calculated by totaling the seven component scores, providing an overall score ranging from 0 to 21, where lower scores denote a healthier sleep quality. The BFI includes 44-item measuring the Big Five Factors (dimensions) of personality including the measure of neuroticism vs. emotional stability that was included in the present analyses.

- Treatments: the current treatments classes at the visit were reported as binary variables: antidepressant, antipsychotic, mood stabilizer, benzodiazepines. Treatment adherence was measured with the Medication Adherence Rating scale(Fond et al., 2017). The MARS has been initially developed and validated on the FACE-SZ cohort and is used in the FACE-BD and FACE-DR cohort to compare treatment adherence across severe psychiatric disorders.

- Physical health variables. Tobacco smoking may alter physical health and favor depression(Bortolaschi et al., 2015; Strzelak et al., 2018). Weight, peripheral inflammation and physical activity were explored with the following variables: body mass index (BMI) ( $\text{kg/m}^2$ , continuous), peripheral inflammation (defined by a highly-sensitive C-reactive protein (hs-CRP)  $\geq 3\text{mg/L}$ )(Osimo et al., 2019). The physical activity level was measured with the International Physical Activity Questionnaire (IPAQ)(Craig et al., 2003). The IPAQ is a 27-item self-reported measure of physical activity for use with individual adult patients aged 15 to 69 years old. Higher scores reflect higher physical activity level, the total score is calculated in METS/week as recommended in the questionnaire.

- 6-month follow-up: the following variables were reported at 6 months: current smoking status, psychiatric hospitalization since the last evaluation (y/n), presence of add-on nicotine substitute, varenicline or bupropion treatment in the current treatment.

## Statistical analyses

The power analysis was performed for MADRS score under the following assumptions: 5% significance level, bilateral interaction. A mean MADRS score of 30 (SD 6) was chosen(Shiroma et al., 2020). To detect a difference of 5 points on MADRS scale, a sample size of 31 patients was needed. All variables were presented using measures of means and dispersion (standard deviation) for continuous data and frequency distribution for categorical variables. Tobacco smoking was considered as explanatory variable (independent variable). All variables associated respectively with tobacco smoking with a p value  $< 0.2$  in univariate analyses were included in multivariate models. Multivariate models were adjusted for age. According to the hypotheses and the objectives exposed in the rationale, women and men were analyzed



separately. These analyses were hypothesis-driven (as detailed in the rationale), no correction for multiple testing have been therefore carried out (Bender and Lange, 2001).

We finally carried out a sensitivity analysis. As tobacco smoking is a CYP1A2 inducer, we conducted the same analyses removing patients being administered CYP1A2 substrates i.e. duloxetine, olanzapine and clozapine. As only duloxetine was the only CYP1A2 sufficiently frequent in our sample to carry out subgroup analyses, we also compared smokers being administered duloxetine with non-smokers being administered duloxetine at baseline.

### Ethical considerations

The study was carried out in accordance with ethical principles for medical research involving humans (WMA, Declaration of Helsinki) and the French Jardé law. The assessment protocol was approved by the relevant ethical review board (CPP-Ile de France IX, January 18th, 2010). All data was collected anonymously. As this study include data coming from regular care assessments, a non-opposition form was signed by all participants.

### Results

Overall, 355 TRD patients (222(62.5%) women) were consecutively recruited in the 13 resistant depression expert centers between 2014 May 1<sup>st</sup> and 2021 Jan 30<sup>th</sup>. Among TRD women, 77(34.5%) were smokers (of whom 18(26.5%) were classified in the severe NIC dependence group) vs. 39(29.3%) in men (of whom 16(35.1%) with severe NIC dependence). The mean lifetime tobacco consumption was 23.96 packet/year (SD 18.28) for women and 24.06(20.62) for men. The mean age at regular tobacco smoking onset was 20 years (SD 7.86) for women and 21 years (SD 8.53) for men. No patient was administered nicotine substitute or varenicline. Two non-smoker patients were administered bupropion.

The factors associated with tobacco smoking in men and women are presented in **Table 1** (univariate and multivariate analyses).

In multivariate analyses, compared to non-smoking women, female tobacco smokers had significantly more lifetime psychiatric hospitalizations (standardized beta  $B=0.232$ ,  $p=0.014$ ) and electro-convulsive therapy adjusted odds ratio (aOR)= 2.748 (1.349-5.600),  $p=0.005$ ), increased suicidal ideations (aOR=4.047 (1.133-14.460),  $p=0.031$ ), more frequent history of suicide attempt (aOR=1.994 (1.057-3.761),  $p=0.033$ ), increased impulsivity (total BIS score  $B=0.210$ ,  $p=0.006$ ) (attention impulsivity  $B=0.194$ ,  $p=0.011$ , planification impulsivity  $B=0.188$ ,  $p=0.014$ ) and were more frequently administered benzodiazepines (aOR=1.848 (1.043-3.272),  $p=0.035$ ) and third or fourth-line TRD treatments (antipsychotics aOR=2.270 (1.266-4.071),  $p=0.006$ ), mood stabilizers aOR=2.067 (1.020-4.189),  $p=0.044$ ).

In multivariate analyses, compared to non-smoking men, male smokers had significantly increased objective and subjective depressive symptoms (MADRS total score  $B = 0.207$ ,  $p = 0.022$ , QIDS total score  $B = 0.184$ ,  $p = 0.048$ ).

At 6-month follow-up, 199 (56%) of the participants were reevaluated. Tobacco smoking at baseline was predictive of psychiatric hospitalization within the 6 following months in persistent female smokers (aOR=2.636 (1.094-6.349),  $p = 0.031$ ) but not in persistent male smokers ( $p > 0.05$ ).

There was no significant difference between loss of follow-up patients and the patients reevaluated at 6 months in regard of age, sex, depression severity or tobacco smoking status (all  $p > 0.05$ , data not shown). Among the patients evaluated at 6 months, 8 patients (6 women and 2 men) quit smoking since the last visit. The smoking cessation rate was 12.5% for women and 7.4% for men. No smoker was administered nicotine substitute, varenicline or bupropion at the 6-month visit.

When we removed patients being administered CYP1A2 substrates at baseline (duloxetine, olanzapine and clozapine), the multivariate associations between tobacco smoking in women and respectively lifetime psychiatric hospitalizations, increased impulsivity and antipsychotics remained significant, but not those with increased suicidality, benzodiazepine and mood stabilizers prescription (data not shown). In men no association remained significant in multivariate analyses when removing CYP1A2 inducers (all  $p > 0.05$ )(data not shown).

When comparing smokers being administered duloxetine at baseline and non-smokers being administered duloxetine, smokers were found to have higher impulsivity level (BIS total score  $B = 0.315$ ,  $p = 0.048$ ) and to receive more benzodiazepines (aOR=4.968(1.222-20.195),  $p = 0.025$ ) and antipsychotics (aOR=5.244(1.232-22.331),  $p = 0.025$ ) independently of age (data not shown).

## Discussion

Our results suggest that tobacco smoking is associated with a wider range of poor outcomes in TRD women compared to men, including increased suicidality, non-motor impulsivity, psychiatric hospitalizations and increased prescription of third or fourth-line TRD treatments, suggesting a specific resistance profile. The follow-up evaluation has confirmed tobacco smoking as a predictor of psychiatric hospitalization in persistent female smokers, consistently with the baseline association with increased suicidality and increased lifetime number of hospitalizations.

The first major finding is the sex ratio inversion of tobacco smoking behavior between TRD population and the general French population. We found much higher rates of tobacco smoking in TRD women compared to the French general women population (34.5% vs. 24.2%)

while the prevalence of tobacco smoking in TRD men was comparable (29.3% vs. 29.8%)(Pasquereau, 2018). The overrepresentation of TRD female smokers is a first argument to suggest a specific role of tobacco smoking in this population.

The second major finding is the association of tobacco smoking with suicidal ideations, suicide attempts, non-motor impulsivity and psychiatric hospitalizations (both retrospectively and prospectively) in these female smokers. A recent meta-analysis including twenty prospective cohort studies involving 2,457,864 participants (Echeverria et al., 2021) has confirmed the association between smoking and suicidality. Among these studies, 10 were carried out in the general population, 2 in twins, one in physicians, one in nurses, 2 in health professionals, one in pregnant women, one in pesticide applicators and one in Harvard alumni. The authors have even suggested to include tobacco smoking in the suicide scale evaluation(Echeverria et al., 2021). The association of impulsivity with tobacco smoking has not been explored in a meta-analysis thus far(Hughes et al., 2015) but has been reported in several cross-sectional studies including various populations (children/adolescents, young adults and HIV-infected individuals) (Chang et al., 2017; Doran and Tully, 2018; Ozga-Hess et al., 2020; R Levin, 2012). This is consistent with repeated dose of nicotine increasing impulsivity, which has been found in general population as in our TRD sample (Bos et al., 2019; Kale et al., 2018; Martinez et al., 2020; Round et al., 2020). Impulsivity has been associated with tobacco smoking withdrawal symptoms in non-clinical populations but the evidence of the effect of tobacco abstinence on impulsivity is still lacking(Hughes et al., 2015). Non-clinical young adults with impulsive profile experience less decrease of tobacco use over 2 years compared to those without impulsivity(Doran and Tully, 2018). We found that TRD women had an earlier age at first regular tobacco consumption compared to men, and smoking during adolescence in non-clinical populations has been suggested to have neurotoxic effects altering inhibitory control/impulsivity circuits (DeBry and Tiffany, 2008). Further studies should determine if smoking onset in young women may explain increased impulsivity and increased risk of later TRD.

As mentioned in the rationale, the association between tobacco smoking and increased risk of depression is well established (Royal college of physicians, 2013; Stubbs et al., 2018). It was therefore expected that tobacco smoking would be associated with increased depressive symptoms in both sexes in our TRD cohort. However, this result was confirmed only in men. This discrepancy is probably explained by the differences in drug prescriptions between men and women. Female smokers were found to be more frequently administered benzodiazepines and third or fourth-line TRD treatments including antipsychotics and mood stabilizers. We hypothesize that these treatments may have “erased” the association between smoking and depressive symptoms in female smokers, except for suicidality and impulsivity that may respond to different mechanisms. However, long-term benzodiazepines are not recommended in the TRD background regimen due to increased tolerance, dependence, accidents and mortality and decreased vigilance. More than half of our sample (and more than 60% of smokers) were administered benzodiazepines, this is much higher than the general

French population (3.8% for women and 2.8% for men)(Airagnes et al., 2019). Benzodiazepines are prescribed to manage anxiety, and anxiety disorders have been identified as a risk factor for TRD(Bennabi et al., 2015; Huang et al., 2020). Early benzodiazepine treatment has also been identified as a risk factor for later TRD(Huang et al., 2020) and benzodiazepine may worsen TRD prognosis(Dold et al., 2020; Parker and Graham, 2015). Smokers report an anxiolytic effect as a frequent motive for tobacco consumption(Piirtola et al., 2021). Of note, we found the same association between tobacco smoking and benzodiazepine use in a national sample of French medical students(Bourbon et al., 2019), suggesting that this association is not limited to TRD. Benzodiazepine consumers and tobacco smokers may both seek a “magic bullet” for their depression rather than pursue other self-management strategies using a large amount of medications (Parker and Graham, 2015). Benzodiazepine may also inhibit psychotherapy efficacy by increased avoidance of feelings (Parker and Graham, 2015). It appears therefore that anxiety issues should be specifically addressed in TRD smokers to guaranty the success of tobacco cessation, with other strategies than long-term benzodiazepines.

Our database did not capture the motives of hospitalization. However, we may reasonably hypothesize that the association between tobacco smoking and respectively lifetime psychiatric hospitalizations and hospitalization at 6 months may be mediated by the increase of suicidality and impulsivity in female tobacco smokers found in baseline associations. Tobacco smoking has been recently shown as a causal role for depression and schizophrenia onset in a Mendelian randomization study(Wootton et al., 2020). Further studies carried out in adolescents and young adults should determine if tobacco smoking onset predicts the risk of later psychiatric hospitalization, and if this risk is mediated by increased suicidality and impulsivity.

We found high rates of smoking in our TRD cohort, especially in women (with approximately 10% higher rates of smoking compared to the general population). Contrary to the general population, our TRD cohort was already followed-up for years in psychiatric settings that should deliver smoking cessation interventions. The smoking rates would therefore have been expected to be much lower. These high rates of tobacco smoking may confirm the tolerance of psychiatric settings for tobacco smoking that is debated for decades at the international level(Taylor and Munafò, 2018). We found that only 12% of female smokers and 7% of male smokers quit smoking at 6 months, while effective tobacco cessation interventions may provide up to 70-100% success rates(Degenhardt et al., 2008; Jegede et al., 2018; Muladore et al., 2018; Okoli et al., 2020; Rogers and Wysota, 2019; Williams et al., 2020). However, we should also moderate these rates as no data on the effectiveness of tobacco cessation programs in TRD is available thus far. Nicotine substitute and varenicline are the current gold-standard treatments for tobacco-smoking cessation in depression in France (Degenhardt et al., 2008) and are recommended in the last World Health Organization guide for tobacco cessation in mental disorders(World Health Organization, 2020). However, we found no patient being administered nicotine substitute or varenicline in our sample that has a long

history of tobacco smoking (with a mean of 23 packet-year). We could therefore recommend the systematic prescription of nicotine substitute combined with varenicline in TRD patients, with a benefit/risk ratio largely in favor of a pharmacological intervention.

Tobacco smoking is a CYP1A2 inducer and may reduce blood levels for clozapine, olanzapine and duloxetine. Our sensitivity analyses have shown that this effect may explain some associations reported in our work, but not all (especially not the association with increased lifetime psychiatric hospitalization and increased impulsivity in women). Further studies with drug dosage are needed to determine the role of tobacco smoking on clinical profile of TRD patients being administered CYP1A2 substrates.

In the light of these results and of the current scientific literature, we suggest recommendations to improve tobacco cessation in TRD (summarized in **Table 2**).

**Strengths.** The 13 centers recruitment at a national level of real-world/non-selected TRD patients, the standardized 1-day long battery (including detailed tobacco, symptomatology, treatments data, personality traits (neuroticism), childhood trauma and patient-reported outcomes), the exclusion of bipolar disorders, schizophrenia-spectrum disorders and autism-spectrum disorders and the follow-up data are major strengths of the present study. The inclusion of important confounding factors like childhood trauma or physical activity strengthens our results.

**Limitations.** Exposure to air pollution and diet were not captured in the database while they may be potential confounders between tobacco smoking and depression (Lassale et al., 2018; Lin et al., 2017).

**Conclusion.** While all TRD smokers have poorer clinical outcomes compared to non-smokers, female TRD smokers have specific issues including 10% higher rates of smoking compared to the general population, increased suicidality, impulsivity, psychiatric hospitalizations (both retrospectively and prospectively) and prescription of long-term benzodiazepines and third or fourth-line TRD treatments. ~~Nicotine substitute and varenicline should be recommended as first-line tobacco cessation treatments in TRD smokers.~~ Female smokers appear as a specific population with heavier mental health outcomes that should be specifically addressed.

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Table 1. Factors associated with tobacco smoking in respectively women and men with Treatment-Resistant Depression, univariate and multivariate analyses.

	Whole sample	Women(N=222(65.5%))				Men (N=133(37.4%))				
	N=355	Non-smokers N=145 (65.3%)	smokers N=77 (34.7%)	Univariate analysis (p) value	Multivariate analysis OR (95% IC) or standardized Bêta	(p)	Non-smokers N=94 (70.7%)	smokers N=39 (29.3%)	Univariate analysis (p) value	Multivariate analysis OR (95% IC) or standardized Bêta (p)
<b>Sociodemographics / early life variables</b>										
<b>Age (years), mean (SD)</b>	<b>52.75 (12.89)</b>	<b>54.96 (13.08)</b>	<b>49.84 (10.58)</b>	<b>0.002</b>			<b>54.17 (13.93)</b>	<b>46.82 (11.11)</b>	<b>0.004</b>	
Education level, n (%)	170 (64.9%)	65 (61.3%)	42 (65.6%)	0.573			43 (67.2%)	20 (71.4%)	0.687	
Single, n (%)	67 (20.9%)	20 (16.0%)	13 (18.1%)	0.710			20 (22.7%)	14 (40.0%)	0.053	1.495 (0.563-3.966) 0.419
Working force status, n (%)	108 (33.6%)	41 (32.5%)	29 (40.3%)	0.273			27 (30.7%)	11 (31.4%)	0.936	
History of childhood trauma (CTQ score), mean (SD)	42.45 (14.07)	43.65 (15.75)	46.87 (16.23)	0.178	0.059	0.407	37.53 (8.38)	41.11 (9.93)	<b>0.045</b>	0.148 0.114
<b>Alcohol and Tobacco consumption</b>										
Current alcohol misuse, n (%)	8 (2.7%)	2 (1.5%)	1 (1.7%)	1.000			4 (5.3%)	1 (3.1%)	1.000	
<b>Depression characteristics</b>										
<b>Number of hospitalizations (lifetime), mean (SD)</b>	<b>2.75 (2.42)</b>	<b>2.57 (2.30)</b>	<b>3.65 (3.02)</b>	<b>0.032</b>	<b>0.232</b>	<b>0.014</b>	2.36 (1.76)	2.13 (2.34)	0.670	
<b>Current depressive severity (MADRS score) , mean (SD)</b>	<b>28.80 (7.14)</b>	<b>28.88 (6.77)</b>	<b>28.93 (8.28)</b>	<b>0.955</b>			<b>27.69 (6.84)</b>	<b>31.08 (6.42)</b>	<b>0.011</b>	<b>0.207 0.022</b>
<b>Suicidal ideation (SIS scale)</b>	<b>242 (84.3%)</b>	<b>92 (80.0%)</b>	<b>64 (95.5%)</b>	<b>0.004</b>	<b>4.047 (1.133-14.460)</b>	<b>0.031</b>	59 (80.8%)	27 (84.4%)	0.663	
<b>History of suicide attempt, n (%)</b>	<b>102 (35.5%)</b>	<b>34 (29.6%)</b>	<b>32 (47.8%)</b>	<b>0.014</b>	<b>1.994 (1.057-3.761)</b>	<b>0.033</b>	22 (30.1%)	14 (48.8%)	0.176	1.401 (0.569-3.446) 0.463
<b>Patients-reported outcomes</b>										
<b>Total QIDS score, mean (SD)</b>	<b>16.87 (4.78)</b>	<b>17.37 (4.33)</b>	<b>17.15 (5.01)</b>	<b>0.740</b>			<b>15.45 (5.10)</b>	<b>17.81 (4.61)</b>	<b>0.017</b>	<b>0.184 0.048</b>
Anxiety (STAI_Y score) , mean (SD)	51.38 (9.60)	51.67 (9.40)	51.92 (10.40)	0.871			49.37 (9.65)	53.53 (8.23)	0.038	0.195 0.059
Motor impulsivity (BIS subscore), mean (SD)	19.59 (3.62)	19.40 (3.50)	20.00 (3.21)	0.274			19.17 (4.16)	20.37 (3.54)	0.174	0.099 0.347

	Whole sample	Women(N=222(65.5%))					Men (N=133(37.4%))				
	N=355	Non-smokers N=145 (65.3%)	smokers N=77 (34.7%)	Univariate analysis (p) value	Multivariate analysis		Non-smokers N=94 (70.7%)	smokers N=39 (29.3%)	Univariate analysis (p) value	Multivariate analysis	
					OR (95% IC) or standardized Bêta	(p)				OR (95% IC) or standardized Bêta	(p)
Attention impulsivity (BIS subscore), mean (SD)	16.49 (3.97)	15.84 (3.50)	17.50 (4.23)	0.007	0.194	0.011	16.25 (4.33)	17.43 (3.88)	0.203		
Planification impulsivity (BIS subscore), mean (SD)	28.03 (5.41)	27.82 (5.12)	29.67 (5.06)	0.025	0.188	0.014	26.86 (5.89)	28.13 (5.55)	0.322		
Impulsivity (BIS total score) , mean (SD)	64.28 (9.49)	62.95 (9.11)	67.05 (9.47)	0.006	0.210	0.006	63.18 (9.75)	66.10 (9.32)	0.173	0.089	0.410
Neuroticism (Big five inventory score), mean (SD)	3.96 (0.60)	3.94 (0.56)	4.08 (0.63)	0.140	0.111	0.169	3.81 (0.66)	4.10 (0.44)	0.015	0.175	0.094
Sleep disorders severity (PSQI total score), mean (SD)	10.95 (3.77)	11.22 (3.84)	11.16 (3.43)	0.928			10.40 (4.17)	10.77 (3.20)	0.660		
<b>Treatment at inclusion</b>											
Antidepressant, n (%)	290 (81.7%)	117 (80.7%)	64 (83.1%)	0.657			80 (85.1%)	29 (74.4%)	0.142	0.488 (0.188-1.269)	0.141
Antipsychotic, n (%)	130 (36.6%)	45 (31.0%)	38 (49.4%)	0.007	2.270 (1.266-4.071)	0.006	33 (35.1%)	14 (35.9%)	0.931		
Mood stabilizer, n (%)	71 (20.0%)	20 (13.8%)	20 (26.0%)	0.025	2.067 (1.020-4.189)	0.044	24 (25.5%)	7 (17.9%)	0.346		
Benzodiazepines, n (%)	179 (50.4%)	64 (44.1%)	46 (59.7%)	0.027	1.848 (1.043-3.272)	0.035	47 (50.0%)	22 (56.4%)	0.501		
Adherence to treatment (MARS score), mean (SD)	6.23 (1.85)	6.25 (1.90)	6.10 (1.50)	0.606			6.39 (1.77)	6.06 (1.97)	0.419		
<b>Lifetime non-pharmacological treatments</b>											
Electro-convulsive Therapy	74 (20.8%)	23 (17.7%)	23 (32.9%)	0.015	2.748 (1.349-5.600)	0.005	20 (24.4%)	8 (23.5%)	0.921		
Stimulation Therapy (VNS, rTMS, tDCS)	40 (11.2%)	13 (10.0%)	10 (14.5%)	0.345			11(13.4%)	6 (17.6%)	0.375		
Psychotherapy	134(37.4%)	47 (38.8%)	35 (51.5%)	0.093	1.300(0.6892.452)	0.418	36 (46.2%)	16 (50.0%)	0.714		
<b>Physical health</b>											
BMI (kg/m2), mean (SD)	26.09 (5.48)	25.99 (6.10)	25.76 (6.01)	0.799			26.19 (4.07)	26.77 (5.06)	0.503		



	Whole sample	Women(N=222(65.5%))				Men (N=133(37.4%))			
	N=355	Non-smokers N=145 (65.3%)	smokers N=77 (34.7%)	Univariate analysis (p) value	Multivariate analysis OR (95% IC) or standardized Bêta (p)	Non-smokers N=94 (70.7%)	smokers N=39 (29.3%)	Univariate analysis (p) value	Multivariate analysis OR (95% IC) or standardized Bêta (p)
Hs-CRP $\geq$ 3mg/l, n (%)	73 (27.5%)	31 (30.1%)	13 (23.2%)	0.354		19 (25.0%)	10 (33.3%)	0.386	
Physical activity MET score (QIAP score), mean (SD)	1838.49 (4585.91)	1500.39 (3811.75)	1018.51 (1725.28)	0.340		2621.42 (6421.49)	2871.24 (5567.12)	0.844	

In the multivariate analyses, tobacco smoking is an explaining variable (independent variable). All models were adjusted for age (forced). Significant associations in multivariate analyses are in bold ( $p < 0.05$ ).

CTQ Childhood Trauma Questionnaire. MADRS Montgomery-Asberg Depression Rating Scale. SIS Suicidal ideation scale. QIDS Quick Inventory of Depressive Symptomatology (self-reported). STAI-Y State-Trait Anxiety Inventory. BIS Barratt Impulsiveness Scale. PSQI The Pittsburgh Sleep Quality Index. MARS Medication Adherence Rating Scale. BMI Body Mass Index. QIAP International Physical Activity Questionnaire. hs-CRP: highly-sensitive C-Reactive Protein. VNS Vagus Nerve Stimulation. TMS: Transcranial Magnetic Stimulation. tDCS Transcranial direct current stimulation.

Table 2. Recommendation of the Treatment-Resistant Depression (TRD) expert centers for promoting tobacco smoking cessation.

- TRD smokers should be informed that smoking cessation is not associated with worsened mental health status(Taylor et al., 2021) but on the contrary with reduced depression, anxiety, stress and improved positive mood and quality of life compared with continuing to smoke(Jia et al., 2018; Taylor et al., 2014).
- Psychiatrists should play an active role in promoting active tobacco cessation, including behavioral interventions promotion and the prescription of nicotine substitute and/or varenicline that are insufficiently prescribed. Smoking relapse are expected and should be addressed with all available strategies that have shown effectiveness in smoking cessation.
- TRD female smokers are more frequently administered benzodiazepines that should be avoided as often as possible due to their long-term consequences. The management of anxiety should be specifically addressed in smokers to prevent smoking relapse.