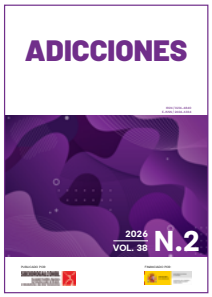
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ORIGINAL

Pharmacological interventions for smoking cessation in patients with bipolar disorder

Intervenciones farmacológicas en cesación tabáquica en pacientes con trastorno bipolar

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Abstract

Background: Bipolar disorder (BD) is a chronic mental illness associated with increased premature mortality. Tobacco use is highly prevalent in BD and contributes substantially to physical morbidity. *Objective:* To critically appraise the evidence on pharmacological interventions for smoking cessation in patients with BD. *Methods:* A structured narrative review was conducted in PubMed, The Cochrane Library, and Web of Science, including studies published between January 1985 and March 2025. Original studies evaluating pharmacological smoking cessation treatments in patients diagnosed with BD according to DSM or ICD criteria were included. Due to clinical and methodological heterogeneity, no meta-analysis was performed. *Results:* Fifteen studies were included. Most trials evaluated patients with BD within broader psychiatric cohorts. Varenicline showed higher abstinence rates than placebo, with odds ratios ranging approximately from 3.0 to 8.1 in randomized trials, and was superior to bupropion and nicotine replacement therapy (NRT) in several large studies. Bupropion and NRT were generally more effective than placebo, although results were less consistent. Treatments were generally well tolerated, without increased severe neuropsychiatric adverse events. *Conclusions:* Pharmacological interventions, particularly varenicline, appear effective and generally safe for smoking cessation in BD, especially when combined with behavioral support. Evidence remains heterogeneous, highlighting the need for BD-specific trials.

Keywords: bipolar disorder, smoking cessation, pharmacological treatment, varenicline, nicotine replacement therapy

Resumen

Introducción: El trastorno bipolar (TB) es una enfermedad mental crónica asociada a un mayor riesgo de mortalidad prematura. El consumo de tabaco es altamente prevalente en esta población y contribuye de forma relevante a la morbimortalidad física. *Objetivo:* Analizar críticamente la evidencia disponible sobre las intervenciones farmacológicas para el abandono del tabaco en pacientes con TB. *Métodos:* Se realizó una revisión narrativa estructurada en PubMed, The Cochrane Library y Web of Science, incluyendo estudios publicados entre enero de 1985 y marzo de 2025. Se incluyeron estudios originales que evaluaban tratamientos farmacológicos para la cesación tabáquica en pacientes con TB diagnosticado según criterios DSM o CIE. Debido a la heterogeneidad clínica y metodológica, no se realizó metaanálisis. *Resultados:* Se incluyeron 15 estudios. La mayoría evaluaron pacientes con TB dentro de cohortes psiquiátricas más amplias. La vareniclina mostró mayores tasas de abstinencia que el placebo, con odds ratios aproximadas entre 3,0 y 8,1, y fue superior al bupropión y a la terapia sustitutiva con nicotina (TSN) en varios estudios de gran tamaño. El bupropión y la TSN fueron generalmente más eficaces que el placebo, aunque con resultados menos consistentes. Los tratamientos fueron, en general, bien tolerados, sin aumento de eventos adversos neuropsiquiátricos graves. *Conclusiones:* Las intervenciones farmacológicas, especialmente la vareniclina, parecen efectivas y generalmente seguras para el abandono del tabaco en pacientes con TB. No obstante, la evidencia es heterogénea, lo que subraya la necesidad de estudios específicos en esta población.

Palabras clave: trastorno bipolar, abandono del tabaco, tratamiento farmacológico, vareniclina, terapia sustitutiva con nicotina

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Bipolar disorder (BD) is a severe, chronic, and recurrent mental illness characterized by alternating depressive and manic or hypomanic episodes, frequently interspersed with periods of euthymia (American Psychiatric Association, 2022). The lifetime prevalence of bipolar spectrum disorders has been estimated at approximately 2–3% worldwide (Merikangas et al., 2011). Beyond its psychiatric burden, BD is associated with a markedly increased risk of premature mortality compared with the general population, largely driven by physical comorbidities rather than suicide alone (Leverich et al., 2003; Sylvia et al., 2015).

Respiratory diseases, particularly chronic obstructive pulmonary disease (COPD) and pneumonia, represent a major cause of excess mortality in individuals with BD, along with cardiovascular disease and cancer (Callaghan et al., 2014; Su et al., 2017). Tobacco smoking is the principal modifiable risk factor underlying these conditions and remains highly prevalent in patients with BD. Epidemiological studies estimate smoking rates between 30% and 70% in BD, substantially exceeding those observed in the general population (Heffner et al., 2011). Moreover, lifetime exposure to tobacco among individuals with BD has been reported to approach 80%, reflecting both higher initiation rates and lower cessation success (Heffner et al., 2011).

The relationship between tobacco use and BD appears to be bidirectional. On the one hand, individuals with BD are more likely to develop nicotine dependence; on the other, smoking has been associated with greater illness severity, including more frequent mood episodes, rapid cycling, and increased suicidal behavior (Diaz et al., 2009; García-Jiménez et al., 2023; Martínez-Ortega et al., 2013). Shared vulnerability factors have been proposed, including genetic susceptibility, environmental influences, and neurobiological mechanisms involving reward processing and dopaminergic dysregulation (McClave et al., 2010).

Smoking cessation in BD poses particular clinical challenges. Compared with the general population, individuals with BD show lower quit rates and higher relapse risk, potentially influenced by depressive symptoms, impulsivity, cognitive dysfunction, and concerns regarding mood destabilization during abstinence (Heffner et al., 2011). These difficulties are further compounded by pharmacokinetic interactions between tobacco smoke and psychotropic medications, as well as by comorbid substance use disorders (Qiu et al., 2024).

Although robust evidence exists supporting pharmacological smoking cessation treatments in the general population and in psychiatric cohorts more broadly, the evidence specifically focused on bipolar disorder remains fragmented. Many clinical trials include BD patients within heterogeneous samples of severe mental illness or mood disorders, and findings are often derived from subgroup or post hoc analyses. Consequently, clinicians face uncertainty when extrapolating results to patients with BD in routine practice.

The aim of this study is to provide a structured narrative review of the available literature on pharmacological interventions for smoking cessation in patients with BD, critically appraising their effectiveness, tolerability, and clinical applicability, with the goal of informing evidence-based decision-making in this high-risk population.

Methods

A structured narrative review of the literature was conducted using PubMed, The Cochrane Library, and Web of Science databases, identifying relevant articles published from January 1983 up to March 2025. Although the review followed a predefined search strategy with explicit inclusion and exclusion criteria and a structured study selection process, it was conceived as a narrative review, as no quantitative synthesis or formal meta-analysis was planned due to marked clinical and methodological heterogeneity across studies.

The search was performed using combinations of MeSH terms and free-text keywords related to BD and smoking cessation, including: 'bipolar disorder,' 'smoking cessation,' 'pharmacological treatment,' 'varenicline,' 'bupropion,' and 'nicotine replacement therapy.' Overlapping terms referring to tobacco use were not used simultaneously to avoid redundancy.

Studies were considered eligible if they met the following criteria: (1) original research articles published between January 1985 and March 2025; (2) peer-reviewed journals; (3) written in English or Spanish; (4) evaluation of pharmacological interventions for smoking cessation; (5) inclusion of patients diagnosed with BD according to Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria (any version); (6) reporting outcomes related to smoking cessation efficacy, including measures of association and confidence intervals when available.

Exclusion criteria were: (1) studies in which BD data were not analyzed separately from other diagnostic groups; (2) non-pharmacological interventions as the primary treatment; (3) reviews, meta-analyses, case reports, opinion articles, protocols, or editorials; (4) studies published in languages other than English or Spanish.

Two reviewers independently screened titles, abstracts, and full texts (JCT and MDR). Discrepancies were resolved by consensus, with the involvement of a third reviewer when necessary (PGD). Data extracted included author, year of publication, country, study design, sample size, diagnostic composition, pharmacological intervention and dosage, follow-up duration, smoking cessation outcomes, and reported adverse effects.

Given the narrative nature of the review and the heterogeneity of study designs, a formal standardized risk-of-bias tool (e.g., Cochrane RoB or ROBINS-I) was not applied. Instead, an overall qualitative appraisal of methodological quality was performed, considering key aspects such as study design (randomized vs. non-randomized), sample size, diagnostic specificity for BD, method of smoking abstinence verification, duration of follow-up, and reporting of adverse events.

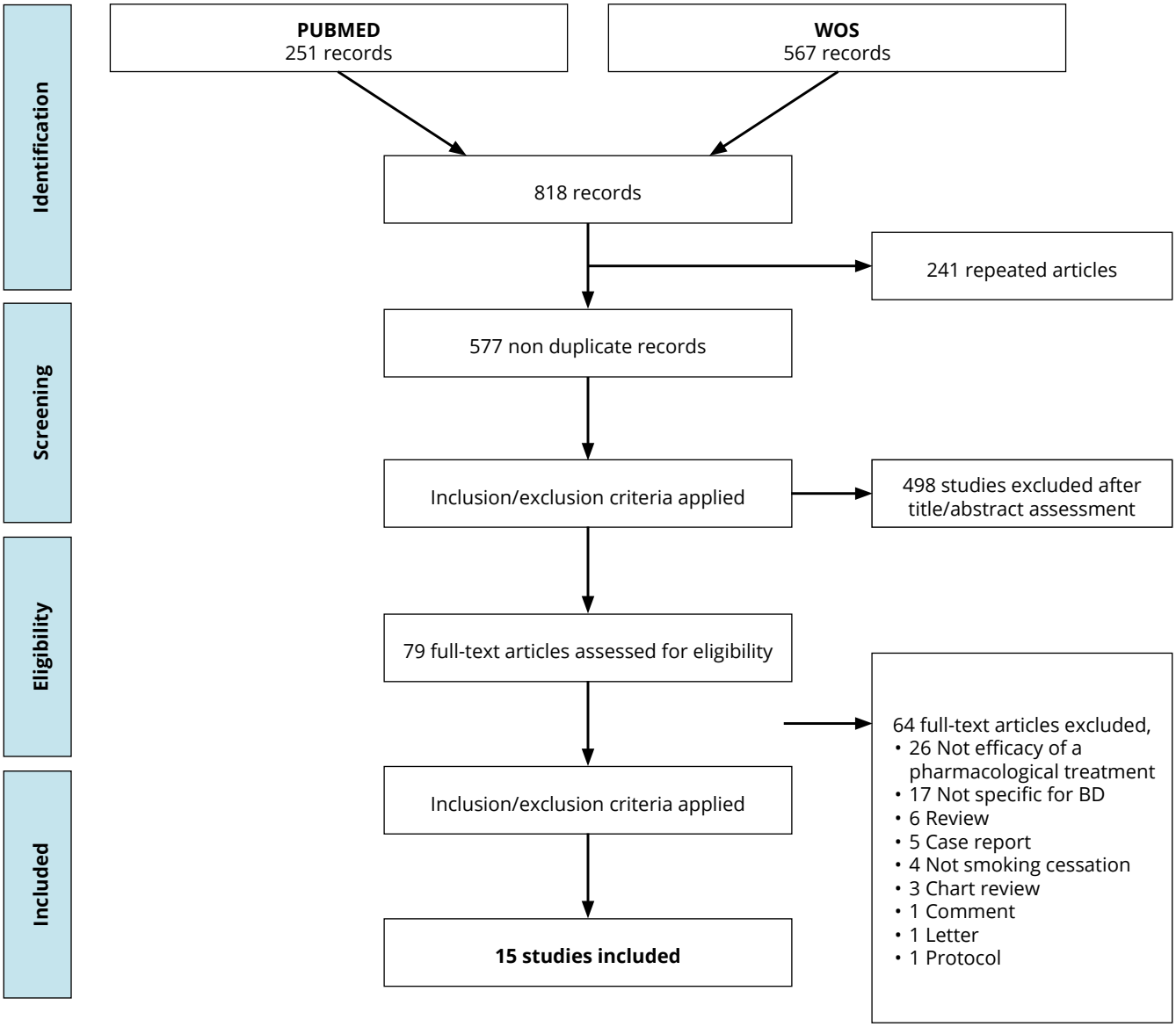
Overall, the quality of evidence ranged from moderate in large randomized controlled trials and post hoc analyses of multicenter studies to low in small pilot trials and open-label studies, which limits the comparability of findings across studies.

Results

Study selection

Figure 1 shows the flow chart of the literature search. Initial search showed 818 records (251 from PubMed database, 567 from Web of Science database). No additional records were identified through The Cochrane Library. From these, 241 were repeated articles, keeping 577 non duplicate records for the screening. After applying the inclusion and exclusion criteria after title and abstract assessment, 498 articles were excluded. 79 full-text were assessed for eligibility, excluding 64 from these. Finally, 15 records were included in the review.

Figure 1
Flow diagram of study selection for the structured narrative review



Characteristics of the studies:

Their characteristics and main findings are presented in *Table 1* (Anthenelli et al., 2016, 2023; Brunette et al., 2018; Chengappa et al., 2014; Daumit et al., 2023; Evins et al., 2014, 2019; Fouz Rosón et al., 2017; Garcia-Portilla et al., 2016; Gilbody et al., 2019; Heffner et al., 2019; Hickman et al., 2015; Prochaska et al., 2014; Weinberger et al., 2008).

Table 1
Published studies about pharmacological smoking cessation treatments in BD patients

Author, year and country	Participants	Design and follow-up	Assessment	Pharmacological Smoking cessation treatment	Other Smoking cessation treatment	Main findings
Anthenelli *et al*. 2016 USA	N = 8144 Psychiatric cohort (n=4116) MDD and BD (n=2882) AD (n=782) SSD (n=386) BPD (n=24) Non-psychiatric cohort (n= 4028)	Multi center, randomized, double-blind, triple-dummy, placebo-controlled and active-controlled trial 12 weeks follow-up	**BD diagnosis:** SCID-I (DSM-IV-TR) **Abstinence:** Self-reported and CO level ≤10 ppm	Varenicline (n=731) 1 mg twice daily Bupropion (n=716) 150 mg twice daily NRT (n=722) 21 mg daily with taper	Quitline counseling (all participants, each visit)	- Higher abstinence rates with varenicline vs: Placebo (OR 3.61, 95% CI 3.07 to 4.24); Nicotine patch (OR 1.68, 95% CI 1.46 to 1.93); and Bupropion (OR 1.75, 95% CI 1.52 to 2.01) - Higher abstinence rates with bupropion vs placebo (OR 2.07, 95% CI 1.75 to 2.45) - Higher abstinence rates with nicotine patch vs placebo (OR 2.15, 95% CI 1.82 to 2.54)
Anthenelli *et al*. 2023 USA	N = 28 BD (n=15) SSD (n= 13)	Randomized, double-blind, placebo-controlled clinical trial 12 weeks follow-up	**BD diagnosis:** MINI (DSM-V) **Abstinence:** CO level ≤4 ppm and Urine cotinine (-)	Varenicline Low dose (0.5 mg twice daily) Standard dose (1 mg twice daily)	ACT (all participant, up to 10 sessions)	Higher abstinence rates in BD participants (37.5%) than SSD participants (16.7%) for standard dose
Brunette *et al.* 2018 USA	N= 661* AD/Other (n= 205) MDD (n= 158) BD (n=150) SSD (n=148) *n=231 participants discontinued	Randomized, clinical trial 1 year follow-up	**BD diagnosis:** DSM-IV-TR **Abstinence:** CO level ≤ 4 ppm and Urine cotinine <10 ng/ml	Varenicline/ Bupropion NRT (doses not reported)	CBT Quitline counseling	- There was no significant effect of intervention (medication only, medication + Quitline counseling, and medication + CBT) - Higher abstinent for who received monetary incentives (AOR=1.77, p=.009) - No differences between diagnostic groups
Chengappa *et al*. 2014 USA	N= 60 euthymic BD participants	Randomized, double-blind, placebo-controlled clinical trial 3 months follow-up + 3 (extra) months	**BD diagnosis:** DSM-IV **Abstinence:** Self-reported and CO level ≤10 ppm	Varenicline (1 mg twice daily)	Quitline counselling (all participants)	- Higher abstinence with varenicline vs placebo (OR= 8.1; 95% CI, 2.0-32.5; p<.002) - At 6 months, varenicline-treated subjects remained more abstinent compared to placebo
Daumit *et al*. 2023 USA	N= 192 SSD (n=82) BD (n=62) MDD (n= 48)	Randomized, double-blind, clinical trial (intervention Vs control groups) 18 months follow-up	**BD diagnosis:** BPRS **Abstinence:** Self-reported (FTCD) CO level Urine cotinine	Intervention group: Varenicline (+/- NRT) or Bupropion + NRT	Motivational interview (all participants) Quitline counselling (all participants) Group exercise class, 50 minutes, 2-3 x/week (all participants)	- 62% reported interest in quitting immediately (within 1 month) - At 18 months, 26.4% of participants in the intervention group and 5.7% of participants in the control group achieved abstinence (AOR 5.9; 95% CI, 2.3-15.4; p < .001). - No differences at weight gain between groups
Evins *et al*. 2014 USA	N = 203 SSD (n=185) BD (n=18)	Randomized, double-blind, placebo-controlled, parallel-group, relapse-prevention clinical trial 19 months follow-up	**BD diagnosis:** BPRS YMRS MADRS **Abstinence:** Self-reported and CO level<9 ppm	Varenicline 1 mg twice daily	CBT (varenicline group)	- Weeks 12-52: abstinence rates: 60% varenicline vs 19% placebo (OR 6.2; 95%CI, 2.2-19.2; p < .001) - Weeks 12-64: abstinence rates: 45% varenicline vs 15% placebo (OR, 4.6; 95%CI, 1.5-15.7; p = .004); - Weeks 12-76: abstinence rates: 30% varenicline vs 11% placebo (OR, 3.4; 95%CI, 1.02-13.6; p = .03)

Author, year and country	Participants	Design and follow-up	Assessment	Pharmacological Smoking cessation treatment	Other Smoking cessation treatment	Main findings
Evins *et al*. 2019 USA United Kingdom	N = 4092 MDD and BD (n=2910) AD (n=792) SSD (n=390)	Randomized, double-blind, triple-dummy, placebo-controlled and active-controlled trial 12 weeks follow-up	**BD diagnosis:** SCID-I (DSM-IV-TR) **Abstinence:** Self-reported and CO level ≤10 ppm	Varenicline 1 mg twice daily Bupropion 150 mg twice a day NRT 21 mg per day with taper		- Higher abstinence rates with varenicline vs placebo (OR 4.57, 95% CI 2.59 to 8.06) - Higher abstinence rates with bupropion vs placebo (OR 2.22, 95% CI 1.21 to 4.06) - Higher abstinence rates with NRT vs placebo (OR 2.76, 95% CI 1.53 to 4.97)
Garcia-Portilla *et al*. 2016 Spain	N = 75 SSD (n=54) BD (n=21)	Multi center, non-randomized, open-label, prospective trial 12 weeks follow-up	**BD diagnosis:** DSM-IV **Abstinence:** Self-reported and CO level ≤9 ppm	Varenicline 1 mg twice daily Bupropion 150 mg twice daily NRT 21, 28 or 35 mg depending on tobacco use	Motivational therapy	- 12-week abstinence rates: 49,3% (NRT 50.0%; varenicline 48.6%) - Week 24 abstinence rates:41,3% (no treatments differences) - Week 36 abstinence rates:37,3% (no treatments differences)
Fouz Rosón *et al.* 2007 Spain	N= 109 AD, MDD, SSD, BD (not specified)	Open-label, randomized, parallel-group, controlled trial 1-year follow-up	**BD diagnosis:** Not reported **Abstinence:** Not reported	Varenicline 1 mg twice daily or 0.5 mg twice daily (both during 8 weeks)		- Better results (not significative; p=0.094) with the low dose (44.3%) vs the standard dose (37.5%) - Patients with BD or SSD had more difficulties to stop smoking - Patients with addiction to other drugs had a tendency (not significative; p=0.078) to quit smoking less than those without drug addiction (34,3% vs 48,2%)
Gilbody *et al.* 2015 USA United Kingdom	N = 97 BD (not specified) SSD (not specified)	Randomized controlled trial 12 months follow-up	**BD diagnosis:** ICD 10 **Abstinence*:** CO level < 10 ppm *Self-reported if CO level couldn´t obtained	Intervention group: A bespoke, structured, smoking cessation program (tailored assessment) that include varenicline and NRT	Free telephone Quitline (for all participants)	Higher smoking cessation ([36%] vs [23%]; adjusted OR 2.9, 95% CI 0.8–10.5) if received bespoke intervention 16% participants stopped smoking in the control group vs 26% from the intervention group (OR 2.5, 95% CI 0.8–7.7).
Gilbody *et al*. 2019 United Kingdom	N= 524 SSD (n= 343) BD (n= 115) SAD (n= 66)	Multi center randomized controlled trial 12 months follow-up	**BD diagnosis:** ICD 10 **Abstinence*:** CO level < 10 ppm *Self-reported if CO level couldn´t obtained	Intervention group: Bespoke smoking cessation intervention (behavioral support and pharmacological aids for smoking cessation*, with adaptations for people with SMI) *Include vareniciline and NRT (not dosage reported)	Usual care by NHS (all participants)	- 6 months: Higher smoking cessation rates in the intervention (14%) vs control (6%) OR 2.4, 95% CI 1.2 to 4.6; p=0.010) - 12 months: Higher smoking cessation rates in the intervention (15%) vs control (13%), but non-significantly (OR 1.6, 95% CI 0.9 to 2.9; p=0·10)
Heffner *et al*. 2019 USA United Kingdom	N = 3041* BD I/II sub cohort (n=280) (81.4% with BD I) Non-psychiatric cohort (n= 2761) *Post hoc analyses of Anthenelli *et al*, 2016 with BD	Multi center, randomized, double-blind, triple-dummy, placebo-controlled and active-controlled trial 12 weeks follow-up	**BD diagnosis:** SCID-I (DSM-IV-TR) **Abstinence:** Self-reported and CO level ≤10 ppm	Varenicline (n=75) 1 mg twice daily Bupropion (n=84) 150 mg twice daily NRT (n=64) 21 mg per day with tapering	Placebo (n=57)	- Higher abstinence rates with varenicline vs: Placebo (OR, 3.36; 95% CI: 1.68 to 6.74; P<0.001); Nicotine patch (OR, 2.45; 95% CI: 1.18 to 5.06; P=0.002); and Bupropion (OR, 1.93; 95% CI: 1.07 to 3.48; P=0.005) - OR for bupropion vs placebo: 1.29 (95% CI: 0.31 to 5.37) - OR for NRT vs placebo: 0.71 (95% CI: 0.14 to 3.74) The Non-psychiatric cohort had significantly higher abstinence rates than the BD sub cohort

Author, year and country	Participants	Design and follow-up	Assessment	Pharmacological Smoking cessation treatment	Other Smoking cessation treatment	Main findings
Hickman *et al*. 2015 USA	N = 100* MDD (n= 52) SSD (n= 29) BD (n= 15) Non diagnosis (n=4) *Extension and replication of Prochaska *et al*, 2014	Two-arms randomized clinical trial 12 months follow-up	**BD diagnosis:** DSM-IV **Abstinence:** CO level ≤10 ppm	Intervention group: Transtheoretical-model tailored, computer-assisted intervention, stage-matched manual, brief counseling, and 10-week post-hospitalization NRT	Usual care group: On-unit NRT + quit advice while hospitalized	- 3 months abstinence: intervention (12.5%) vs usual care (7.3%) - 6 months abstinence: intervention (17.5%) vs usual care (8.5%) - 12 months abstinence: intervention (26.2%) vs usual care (16.7%)
Prochaska *et al.* 2014 USA	N = 224* MDD (n= 105) BD (n= 56) SSD (n= 34) Other (n=29) *Inpatient psychiatry	Randomized controlled trial 18 months follow-up	**BD diagnosis:** DSM-IV **Abstinence*:** Collateral reports (67%) CO level ≤10 ppm (33%) *No difference by groups for type of verification	Intervention group: Transtheoretical-model tailored, computer-assisted intervention, stage-matched manual, brief counseling, and 10-week post-hospitalization NRT* *NRT were delivered in 4 and 6 weeks supplies to prevent loss or misuse	Usual care group: On-unit NRT + quit advice while hospitalized	- Higher rates of abstinence in intervention group (OR 3.15; 95% CI 1.22 to 8.14; p=.018) - 6 months abstinence: intervention (3.9%) vs usual care (3.2%) - 12 months abstinence: intervention (19.4%) vs usual care (10.9%) - 18 months abstinence: intervention (20.0%) vs usual care (7.7%) - More rehospitalization in usual care group (adjusted OR=1.92; 95% CI =1.06, 3.49).
Weinberger *et al*. 2008	N = 5 BD I	Pilot placebo-controlled trial 10 weeks follow-up	**BD diagnosis:** DSM-IV **Abstinence:** CO level <10 ppm	Bupropion (n=2) 75-300 mg daily Placebo (n=3)		- No participant receiving placebo medication quit smoking during the trial - 2 participants receiving bupropion reported smoking cessation but only one was CO-confirmed abstinent.

Note. Acceptance and Commitment Therapy (ACT); Anxiety disorder (AD); Adjusted odds ratio (AOR); Bipolar disorder (BD); Border-line personality disorder (BPD); Brief Psychiatric Rating Scale (BPRS); Cognitive behavioral therapy (CBT); Confidence interval (CI); Continuous abstinence rate (CAR); Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR); Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); Fagerström Test for Cigarette Dependence (FTCD); Intermediate-release (IR); Major depression disorder (MDD); Milligrams (mg); Mini-International Neuropsychiatric Interview (MINI) for DSM-5; Montgomery-Asberg Depression Rating Scale (MADRS); Nicotine replacement therapy (NRT); Nonpsychiatric cohort (NPC); Odds ratio (OR); Parts per million (ppm); Severe mental illness (SMI); Sustained-release (SR); Schizoaffective disorder (SAD); Schizophrenia spectrum disorder (SSD); Structured Clinical Interviews for DSM-IV-TR Axis I (SCID-I); Transdermal nicotine patches (TNP); Transtheoretical model (TTM); United States of America (USA); Young Mania Rating Scale (YMRS).

Pharmacological interventions for smoking cessation

Globally, the findings of the studies included in this review showed that pharmacological smoking cessation treatments are effective in BD patients. According to Anthenelli et al. (2016) and Evins et al. (2019), varenicline reached higher abstinence rates than placebo (odds ratio [OR] 3.61, 95% CI 3.07 to 4.24 and 3.03, 95% CI 2.13 to 4.32, respectively), nicotine patch (odds ratio [OR] 1.68, 95% CI 1.46 to 1.93 and 1.68, 95% CI 1.23 to 2.32, respectively) and bupropion (odds ratio [OR] 1.75, 95% CI 1.52 to 2.01 and 1.59, 95% CI 1.16 to 2.18, respectively), and these two were more useful than placebo too. Similar outcomes were found by Heffner and collaborators (Heffner et al., 2019), but in this cases nicotine replacement therapy (NRT) was less effective than placebo (odds ratio [OR] 0.71, 95% CI 0.14 to 3.74). Nevertheless, García-Portilla et al. (2016) did not find significant differences between varenicline and nicotine patch (12-week 7-day smoking cessation of varenicline 48.6% vs nicotine patch 50.0%, chi-square=0.015, p=1.000). Evins et al. (2014) have found out that varenicline combined with cognitive behavioral therapy (CBT) increases abstinence rates. Besides, Gilbody et al. (2019) observed a higher efficacy in those patients who, apart from receiving the usual treatment by local National Health Service (NHS) for smoking cessation, also participated in a personalized intervention consisted of behavioural support from a mental health smoking cessation practitioner and pharmacological aids for smoking cessation, with adaptations for people with severe mental illness—such as, extended pre-quit sessions, cut down to quit, and home visits. Access to pharmacotherapy was via primary care after discussion with the smoking cessation specialist. Weinberger et al. (2008) studied the efficacy of bupropion versus placebo through 10 week trial and all the patients who received it reported efficacy in smoking cessation, although the sample was small (n=5).

Some of these papers have also researched about the possible adverse effects caused by these drugs. The most frequent adverse events found by Anthenelli et al. (2016) were nausea in the 25% of patients under varenicline, insomnia for 12% of patients under bupropion, abnormal dreams for 12% patients under nicotine patch and headache for 10% of patients under placebo. However, these adverse

effects were not significant, and the interventions were well tolerated. According to Evins et al. (2019), varenicline and bupropion were not associated with a significant increase of neuropsychiatric adverse events relative to nicotine patch or placebo in their psychiatric cohort. Female and previous substance use disorders were related with the presence of neuropsychiatric adverse events. This study shows that the most common adverse effects were insomnia and anxiety with bupropion and nicotine patch and abnormal dreams with varenicline and nicotine patch. García-Portilla et al. (2016) point that patient who used varenicline experienced nausea with more frequency and those who used nicotine patches suffered skin reactions with more frequency. Another study showed that neuropsychiatric adverse events incidence for BD smokers was: 14.7% for varenicline, 11.9% for bupropion, 6.3% for NRT and 8.8% for placebo, being sleep disorders the most common (Heffner et al., 2019). In this sense, Chengappa´s group showed that the use of hypnotic drugs was different between quitters and non-quitters (50% vs 21%). Also, Varenicline/placebo, (β = 2.23, p = 0.003) and hypnotics/no-hypnotics (β= 1.5, p = 0.032) were significant independent predictors of quit status, with the OR – (β) of 9.3 (95% CI = 2.1, 40.9) and 4.5 (95% CI = 1.1, 17.6), respectively (Forrest et al., 2015).

Discussion

This structured narrative review suggests that pharmacological interventions can facilitate smoking cessation in patients with BD, particularly when combined with structured behavioral support. Among available treatments, varenicline appears to be associated with higher abstinence rates compared with placebo and, in several studies, with bupropion and NRT (Anthenelli et al., 2016; Evins et al., 2019; Heffner et al., 2019). However, the magnitude and consistency of these effects vary across studies, requiring cautious interpretation.

A major limitation of the existing literature is that most studies were not specifically designed for BD, but rather included patients with BD as part of broader psychiatric or severe mental illness cohorts (Anthenelli et al., 2016; Gilbody et al., 2019). Consequently, much of the evidence derives from subgroup or post hoc analyses, which may be underpowered and prone to selection bias.

In addition, sample sizes varied substantially, ranging from small pilot studies with very limited numbers of BD participants (Weinberger et al., 2008) to large multicenter randomized trials (Anthenelli et al., 2016; Evins et al., 2019). This heterogeneity limits the comparability of effect sizes and precludes direct quantitative synthesis.

Although varenicline demonstrated superior efficacy in several randomized controlled trials, not all studies reported consistent results. For example, García-Portilla et al. (2016) did not observe significant differences between varenicline and nicotine patch in a pragmatic clinical trial, and a BD subgroup analysis by Heffner et al. (2019) found that NRT did not outperform placebo. These discrepancies may reflect differences in study design, diagnostic composition, baseline nicotine dependence, follow-up duration, and the intensity of accompanying behavioral interventions (Evins et al., 2014; Gilbody et al., 2015).

Several studies suggest that pharmacological treatments are more effective when integrated into structured psychosocial interventions, such as CBT, motivational interviewing, or tailored smoking cessation programs (Evins et al., 2014; Gilbody et al., 2019). This highlights the importance of understanding medication effects within a broader therapeutic context, particularly in patients with BD, who often present with complex clinical needs.

Across studies, pharmacological smoking cessation treatments were generally well tolerated in patients with BD, with no significant increase in severe neuropsychiatric adverse events compared with placebo (Anthenelli et al., 2016; Evins et al., 2019). Reported adverse effects were consistent with known safety profiles, including nausea with varenicline, insomnia with bupropion, and sleep disturbances or skin reactions with NRT (García-Portilla et al., 2016; Heffner et al., 2019). Nevertheless, potential drug interactions and individual vulnerability such as seizure risk with bupropion should be carefully considered in clinical practice (Pesola et al., 2002).

Patients with BD exhibit substantially higher smoking rates and cumulative tobacco exposure, which likely contributes to the increased prevalence of respiratory disease, including COPD, observed in this population (Callaghan et al., 2014; Jaén-Moreno et al., 2023; Laguna-Muñoz et al., 2025). Shared neurobiological mechanisms—particularly alterations in dopaminergic reward pathways and impulse control—may underlie both nicotine dependence and mood dysregulation, and merit further investigation (Heffner et al., 2011; Qiu et al., 2024).

The present review has limitations, including the absence of a formal quantitative synthesis and standardized risk-of-bias assessment. Moreover, most studies focused on clinically stable or euthymic patients, limiting generalizability to acute mood episodes. Future research should prioritize randomized controlled trials specifically designed for BD, with stratification by mood phase, longer follow-up, and systematic assessment of adverse events.

Overall, the available evidence supports the use of pharmacological smoking cessation treatments in patients with BD, particularly varenicline, when delivered as part of comprehensive and structured cessation programs. However, the heterogeneity and indirect nature of current evidence underscore the need for bipolar-specific studies to better inform clinical decision-making.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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