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The Effects of Varenicline, Bupropion, Nicotine Patch and Placebo on Smoking Cessation among Smokers with Major Depression: A Randomized Clinical Trial

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Abstract

Importance: Improving treatment outcomes for smokers with Major Depressive Disorder (MDD) can have significant public health implications.

Objective: To evaluate the safety and efficacy of smoking cessation pharmacotherapy among smokers with MDD.

Design: Secondary analysis of a randomized, double-blind, active- (nicotine patch) and placebo-controlled trial of 12 weeks of either varenicline or bupropion with 12-week follow-up.

Participants: Community volunteers 18-75 years of age; smoke 10+ cigarettes/day; with clinically stable MDD(N=2635) or no psychiatric disorder(N=4028), from 140 sites in 16 countries.

Intervention: 12 weeks of pharmacotherapy (placebo, PLA; nicotine replacement therapy, NRT; bupropion, BUP; varenicline, VAR) plus brief cessation counseling.

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Data Sharing Statement. Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Measure(s): Primary safety outcome: the occurrence of ≥ 1 treatment-emergent, moderate to severe Neuropsychiatric Adverse Event (NPSAE). Primary efficacy outcome: biochemically confirmed continuous abstinence (CA) during the final 4 weeks of treatment (Weeks 9–12).

Results: 6,653 participants (56% female; 39% MDD) ~47 years old. Risk of NPSAEs did not differ by medication for MDD. MDD had higher risk ($p<0.0001$) for NPSAEs than the non-psychiatric cohort (NPC). Efficacy (6,653; intent-to-treat): CA rates for MDD vs. NPC respectively were 31.2% vs. 38.0% VAR; 23.0% vs 26.1% BUP; 22.6% vs 26.4% NRT; and 13.4% vs. 13.7% PLA but no differential treatment effect was noted within the cohorts. All active treatments differed from PLA but VAR showed the largest effect.

Conclusions: Results suggest that for MDD smokers, inclusive of those with recurrent episodes (RE), varenicline plus counseling may be the best pharmacological option for the treatment of smoking given its greater efficacy effect size and similar risk of NPSAEs.

Trial Registration: ClinicalTrials.gov Identifier: NCT01456936. https://clinicaltrials.gov/ct2/show/NCT01456936

INTRODUCTION

There is a compelling need to better understand smoking cessation treatment in patients with depressive disorders. In 2014, smoking rates among those with major depressive disorder (MDD) were 1.5 times higher than those without MDD[1]. MDD is one of the most common psychiatric disorders (life-time prevalence of 20.6%)[2,3] and frequently encountered in primary care. Fifty-two percent of these individuals seek assistance from primary care physicians[4], who account for 60% of all antidepressant prescriptions.[5]

Depressive symptom severity is associated with increased risk for persistent nicotine dependence, relapse across time, [6–10] and more frequent [11] and sustained [12] periods of withdrawal. Evidence also suggests that smokers with chronic or recurrent depression may experience poorer cessation outcomes than those with single episode depression[13–16].

The adverse health consequences of smoking among those with MDD includes increased morbidity and mortality from tobacco related illness[17]. Smokers with a psychiatric disorder die 8.4 years earlier from tobacco-related illness than those with no psychiatric disorder [18]. With regard to treatment, MDD smokers have lower abstinence rates than those with no disorders in studies involving quitline interventions and NRT [19,13] and in a large randomized trial involving multiple medications (bupropion, NRT and combinations) [20]. Bupropion and the combination of bupropion and nicotine replacement therapy (NRT) were found to be more effective than placebo in smokers with past MDD, while neither NRT alone, fluoxetine, paroxetine or nortriptyline were noted as effective[21]. Other studies of smokers with past or current (stable) MDD showed similar efficacy for bupropion plus NRT and NRT alone[22] and higher quit rates for varenicline vs. placebo with no differences in neuropsychiatric adverse events[23].

The present study is a secondary data analysis of the largest smoking cessation randomized clinical trial conducted to date involving smokers with psychiatric disorders[24]. The primary aim of this analysis was to evaluate the comparative safety and efficacy of varenicline,

bupropion, NRT, and placebo in smokers with clinically stable MDD versus those with no psychiatric disorder. A secondary aim was to explore differential responses to these medications in smokers with recurrent versus single episode MDD. Prior to this trial, there were no trials evaluating the *comparative* safety and efficacy of these first-line medications in smokers with MDD, nor any examination of differences in outcomes among those with single-episode or recurrent depression.

METHODS

Study Design

The parent study (EAGLES: Evaluating Adverse Events in a Global Smoking Cessation Study, NCT01456936; https://clinicaltrials.gov) was a 24-week randomized, double-blind, triple-dummy, placebo- and active-controlled trial characterizing the neuropsychiatric safety and efficacy of varenicline and bupropion. EAGLES methods have been previously detailed[24]. The population consisted of 8144 current smokers screened between November 30, 2011, and January 13, 2015, ages 18-75 from 140 centers in 16 countries including 4116 with and 4028 participants without a history of psychiatric disorders. The primary safety endpoint consisted of neuropsychiatric symptoms assessed using the Neuropsychiatric Adverse Events Interview (NAEI), a semi-structured interview [24,23] administered at each visit occurring up to 30 days after the last dose of study medication. The main and secondary efficacy endpoints were biochemically confirmed continuous abstinence over the last 4 weeks of treatment and at the 6-month follow-up, respectively.

Participants

The sample for this analysis consists of 6653 randomized smokers, including 2635 with a primary diagnosis of MDD and 4028 with no lifetime psychiatric disorder, based on a mental health professional's (who were blinded to treatment allocation) review of the Structured Clinical Interview for DSM-IV-TR (SCID-I)[25]. The MDD sample was further analyzed by separating the participants with MDD into a Recurrent Episode (RE) subcohort (n = 1282) and a Single Episode (SE) subcohort (n = 1343). Like the larger psychiatric cohort, MDD participants had to be clinically stable, with no significant worsening of psychiatric status in the prior 6 months and with no changes in treatment over the last 3 months or planned during the study. Potential participants at high risk for suicidal behavior, as assessed by the Suicide Behaviors Questionnaire-revised [26] or the Columbia-Suicide Severity Rating Scale (C-SSRS) [27], or those with active substance use disorder, were excluded. Severity of symptoms was also assessed with the Hospital Anxiety and Depression Scale (HADS)[28]. The CONSORT diagram is provided in Figure 1.

Randomization

Subjects were randomized to 12 weeks of varenicline 1 mg twice daily (BID), bupropion 150 mg BID, nicotine replacement therapy (NRT patch: 21 mg/daily with tapering), or placebo. Participants received brief (≤10 minutes) behavioral counseling at every visit. Randomization was computer generated (1:1:1:1 ratio). Eligibility criteria included smoking >10 cigarettes/day in the previous year, interest in quitting and exhaled carbon monoxide (CO) of ≥10 parts per million (ppm) at screening.

Outcomes

The primary safety outcome was the occurrence of ≥ 1 treatment-emergent (plus 30 days post-medication), all-causality (i.e. regardless of treatment relatedness), moderate to severe NPSAE consisting of 16 event components: anxiety, depression, feeling abnormal, hostility, agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal behavior, suicidal ideation, or completed suicide. To be included as an NPSAE, four components (anxiety, depression, feeling abnormal, and hostility) required a severe event (substantial interference with daily functioning), with the remaining twelve requiring an event of at least moderate severity (some interference with daily functioning). Secondary psychiatric AE safety outcomes included severe-only NPSAE's and those that resulted in discontinuation.

The main efficacy endpoint was carbon monoxide (CO)-confirmed (exhaled CO concentration greater than 10 ppm) continuous abstinence (CA) during the final 4 weeks of treatment (Weeks 9–12). Secondary cessation outcome was CO-confirmed CA at 6-months (Weeks 9–24). Missing abstinence data were coded as smoking [29].

Statistical Analysis

Generalized linear models were used for NPSAE and CA endpoints. The model included treatment, psychiatric cohort, region (US or non-US), and the treatment by psychiatric cohort interaction. Efficacy analyses utilized all randomized participants, while safety analyses utilized participants who took ≥ 1 dose of study medication (MDD n = 2602 [RE, n = 1274; SE n = 1328]; NPC, n = 3984) (also see eFigure 1). Analyses were conducted using SAS® version 9.4 [30]. All tests were two-tailed with $P < 0.05$ for statistical significance. A Tukey-Kramer adjustment was used to control for multiple comparisons within models. Because subgroup analyses are typically underpowered to answer the safety and efficacy research questions of the larger EAGLES trial, we prioritized effect size estimates and confidence intervals over statistical significance in our interpretation and presentation of the safety and efficacy data.

RESULTS

MDD

Baseline Characteristics—Baseline characteristics are presented in eTable 1. MDD cohort participants were more likely to be female, heavier, more nicotine dependent, have smoked longer and made more previous quit attempts, than the NPC group. As expected, smokers in the MDD cohort were also more likely to have a history of past comorbid conditions, higher HADS anxiety and depression scores, be receiving psychotropic medications and higher rates of life-time suicidal ideation and/or behavior on the C-SSRS.

Safety—As shown in Table 1, the observed incidence of moderate to severe treatment-emergent NPSAEs (see Observed NPSAEs-Primary Composite) was higher in all treatment arms in the MDD cohort. Collectively, few of these were rated as severe (see Observed NPSAEs-severe only), with a range of 0.1% for VAR in NPC and 1.5% for NRT in MDD.

There was no significant effect due to treatment, region, or treatment-by-cohort interaction. Thus, the risk of moderate-to-severe NPSAEs did not differ by medication treatment group in either the MDD or the NPC cohort. As shown in eFigure 2, the MDD cohort was at significantly higher risk ($p<0.0001$) for the occurrence of an NPSAE than the NPC (risk difference= 0.032 (95% CI: 0.023, 0.042) but no differences were observed between the three medications and placebo.

Table 1 also shows the frequency of the individual components comprising the composite NPSAE (see NPSAE Component Summary). Individually, these symptoms are highly infrequent, with the vast majority occurring between 0%-.9%. Importantly, we found no treatment related differences in either self-reported suicidal ideation or behaviors (both very low frequency events), or treatment discontinuations within the MDD cohort (see Table 1 Primary endpoint events). As shown in Table 1 (see C-SSRS Treatment emergent) overall ideation was higher in the MDD (2.4%) than the NPC cohort (.7%), consistent with their higher baseline lifetime reports (eTable 1). Suicidal behavior did not differ across cohorts (both .1%) or medications.

The incidence of AE's from the Psychiatric Disorders SOC in the Medical Dictionary for Regulatory Activities (MedDRA), occurring at a rate of ≥ 1% is shown in eTable2. Overall, these were similar across all medications, including those on placebo (25.9%-37.2%). The most common category of AEs was sleep disorders and disturbances.

Efficacy

Main Efficacy Endpoint (CA weeks 9-12): Results for continuous abstinence from weeks 9-12 across cohorts and treatments are shown in eFigure3. Though abstinence for active treatments were slightly lower in the MDD vs. NPC cohorts, only the main effect of Treatment was significant ($p < 0.001$). Neither the main effect of Cohort ($p=0.101$) nor the Cohort X Treatment interaction were significant ($p = 0.489$), indicating that treatments did not have a differential effect within cohorts.

Effect size differences for CA at weeks 9-12 are presented in Figure 2. Collapsing across cohorts, all active treatments differed from placebo although varenicline showed the largest effect. However, comparisons between treatments across cohorts, for weeks 9-12 CA showed that varenicline was superior to NRT and bupropion, whereas bupropion and NRT did not differ from each other. The same pattern was observed within cohorts (see Treatments Within Cohort). The overall comparison of cohorts, collapsing across treatments, was not significant ($p = 0.101$).

Secondary Efficacy Endpoint (CA weeks 9-24): As shown in eFigure 3, the observed proportions of continuous abstinence at weeks 9-24 by treatment condition for the MDD vs. NPC cohorts, respectively, while lower, generally mirror those for weeks 9-12. However, a significant effect was noted for both Treatment ($p<0.001$) and Cohort ($p=0.010$) with no significant Treatment X Cohort Interaction ($p = 0.606$), indicating no differential treatment effect as a function of cohort. As shown in Figure 2, all active treatment comparisons versus placebo are significant, when collapsing across cohorts (see Treatments Overall

Comparisons), with varenicline outperforming bupropion and NRT, while bupropion and NRT did not differ from each other.

Within the MDD cohort, comparisons with placebo are significant for varenicline and bupropion but not NRT. The MDD cohort reported lower abstinence when combining all treatments compared to NPC. Although the interaction of Cohort by Treatment was not significant, it bears noting that within the MDD group, NRT did not differ from placebo for CA at weeks 9-24, while the other two active treatments maintained superiority over placebo.

Recurrent versus Single Episode

Baseline Characteristics—The baseline characteristics of those with recurrent (RE) (n = 1282) or single episode (SE) (n= 1343) depression are presented in eTable3. No substantive differences were observed, though the RE subcohort had relatively higher rates of psychiatric comorbidities, use of psychotropic medication, lifetime suicide-related history and higher HADS anxiety and depression scores.

Safety—Table 2 illustrates the observed incidence of moderate to severe treatment-emergent NPSAEs in the RE and SE subcohorts. Collectively, few NPSAEs were rated as severe (range .6% in SE NRT and placebo, to 2.5% in RE NRT). Neither the main effect of Treatment ($p = 0.751$) or the Treatment by Group (RE/SE/NPC) interaction ($p = 0.203$) were significant. There was a main effect of subcohort (F-value = 32.2; $p < 0.001$), with higher incidence of NPSAEs observed for the RE and SE versus NPC. As shown in eFigure 4, the RE subcohort had higher rates of NPSAEs versus the SE; however, the risk difference was not significant (RD = 0.021; 95% CI: 0.00, 0.041). As shown in Table 2, occurrence of agitation and panic were the most frequently reported symptoms, with somewhat higher rates observed for agitation in the varenicline RE vs SE subcohort.

The incidence of any type of AE in the Medical Dictionary for Regulatory Activities (MedDRA) of any severity (ranging from mild to severe), was slightly higher for the RE vs SE subcohort (see eTable 4) and higher than NPC (see eTable 2 for NPC) but were similar within medication groups. The most common AE was sleep and anxiety disorders.

Efficacy—As shown in eFigure 5, CA abstinence at weeks 9-12 for RE smokers was somewhat lower than the SE group across all medications except varenicline. As shown in Figure 3, only CA between the NPC and RE subcohort was significant; effect sizes between the NPC and SE and RE and SE cohorts were not significant. There was no treatment by cohort interaction (SE, RE, NPC) ($p = 0.646$), and main effects of treatment remain significant ($p < 0.001$), reflecting the findings of the MDD and NPC analysis. When comparing treatments within subcohorts (see Figure 3), the pattern of effects is similar to the MDD cohort as a whole. Active treatments were superior to placebo, with varenicline having the largest effect. While varenicline outperformed both bupropion and NRT for the RE group, there were no treatment differences in the SE group. In addition, bupropion did not differ from NRT for either subgroup.

In the CA for weeks 9-24 (see eFigure 5), the rates for all groups declined but no treatment by cohort interaction was observed. However, Figure 3 indicates that only the varenicline vs placebo contrast was significant across both cohorts for Week 9-24. The bupropion vs. placebo comparison was also significant, but only for the RE subcohort.

DISCUSSION

Effective smoking cessation intervention for smokers with MDD can have a major impact on public health. MDD is one of the most common psychiatric disorders, is associated with increased smoking prevalence and several indicators of nicotine dependence [6–10] , and MDD vs. non-MDD smokers are at greater risk of dying from tobacco related illnesses[17], at an earlier age [18]. Until recently, large-scale studies comparing the safety and efficacy of smoking cessation pharmacotherapies in smokers with MDD were lacking, nor have there been analyses of such differences among those with either recurrent or single episode MDD. Our analysis yielded 4 major conclusions.

The first is that use of smoking cessation medications in smokers with MDD confers little increased risk relative to those with no psychiatric disorder, for a host of adverse events. These adverse events may collectively be more common in smokers with MDD, but not differentially so across medication types. The risk of a pre-defined set of neuropsychiatric serious adverse events (NPSAEs, i.e., anxiety, depression, hostility, aggression, etc.)[31], our primary safety endpoint, did not differ by smoking cessation treatment within the MDD or the NPC cohorts; nor were any of the comparisons between medications and placebo significant. However, the overall risk of NPSAE's was higher for the MDD (5.3%) vs. NPC (2.1%) cohort. Individual components of the composite NPSAE were infrequent (few >1%), with the highest being agitation and aggression, particularly in the MDD cohort; few were rated as severe. No treatment-related differences in other self-reported AE's from any source (MedDRA) were observed. The most common for all smokers were sleep disturbances. There were no differences in discontinuation due to AE's. Moreover, there were no treatment related differences in self-reported suicidal ideation or behavior.

The second major conclusion is that among smokers with MDD, varenicline plus smoking cessation behavioral counseling may represent the best option of the three active monotherapies given its greater efficacy effect size and similar AE risk profile. Within the MDD cohort, varenicline produced higher continuous abstinence rates at the primary endpoint (Weeks 9-12) compared to all other treatments (OR~1.6), an effect only slightly lower than that observed in the nonpsychiatric cohort (OR~1.7). No differences were observed between NRT and bupropion for either group, consistent with previous meta-analyses[32]. Treatment effects for all medications were lower for continuous abstinence at 6 months (Week 9-24).

The third conclusion is that while smokers in the recurrent vs. single episode of major depression cohort reported more frequent NPSAEs, the difference in risk was not significant (2.1%) and did not differ by medication. Among the individual components of the NPSAE composite, agitation was the most common, though all were relatively low in frequency and

few were rated as severe. Self-reports of any AE among RE and SE smokers, regardless of severity, did not differ, with the most common being sleep disorders and anxiety.

Fourth, although there was no significant difference in the primary efficacy endpoint of CA Week 9-12 between the RE and SE sub-cohorts, the RE smokers were somewhat less likely to be abstinent than the NPC smokers (OR=1.23), whereas SE smokers were not. Within the RE and SE cohorts, all active treatments differed from placebo, but varenicline produced higher abstinence rates for RE smokers than either bupropion or NRT. The same was not true for the SE group. Interestingly, this means that while overall abstinence was somewhat lower in the RE subgroup, RE participants seemed to respond better to varenicline than the other medications, whereas the response of SE smokers across medications was similar. These effects diminished by Week 9-24. Efficacy between bupropion and NRT did not differ in either subgroup. Nevertheless, given the RE group's lower probability of quitting, but similar AE profile across medications, varenicline would appear the better choice to optimize end of treatment outcomes.

Limitations

While it is the largest study completed to date on smokers with MDD, and the first with sufficient numbers to compare single episode vs. recurrent depression, this study has several limitations. First, MDD smokers were required to be psychiatrically stable at baseline and hence our findings may not generalize to smokers with unstable or more severe MDD. Second, combination NRT (e.g., patch/lozenge/gum), which had become more standard after this study was undertaken, was not included among the treatments so its comparative safety and efficacy could not be evaluated. Third, though MDD comprised the largest psychiatric subgroup in the parent study, the study was not specifically powered to detect differences in outcomes for the MDD cohort or the RE and SE subgroups. Our results should be interpreted with that caveat.

Conclusions:

Results suggest that varenicline plus behavioral counseling may be the best treatment option for MDD smokers, including those with RE, given its greater CA effect size and similar risk of NPSAEs. MDD smokers are less likely to quit and more likely to experience NPSAE's than those with no psychiatric illness, regardless of which pharmacotherapy they receive. Given the epidemiological evidence that continued smoking may itself be depressogenic[33–36], future studies are needed that target those with untreated current depression with concurrent treatment of both their depression and nicotine dependence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question:

Are medications for treating smoking safe and effective for smokers with Major Depressive Disorder (MDD)?

Findings:

The risk of moderate to severe neuropsychiatric adverse events among smokers with MDD treated with varenicline, bupropion, or nicotine patch did not differ compared to those without MDD. Varenicline produced the highest abstinence rates at the end of treatment and was especially effective for those with recurrent MDD.

Meaning:

Among smokers with MDD, varenicline plus smoking cessation counseling may represent the best treatment option given its greater efficacy effect size and similar risk profile.

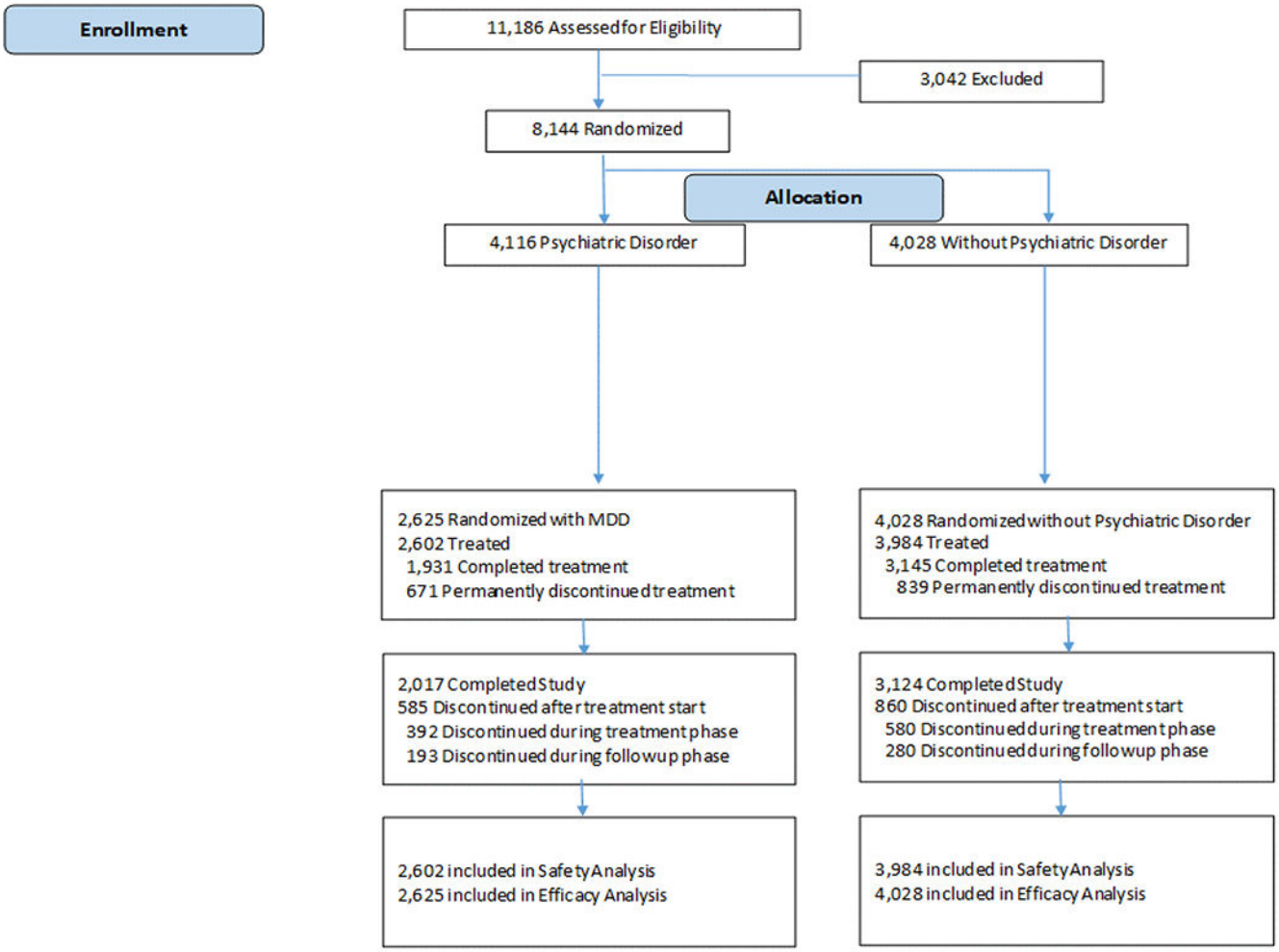

Figure 1.
Consort Flow Diagram for Patient Ascertainment

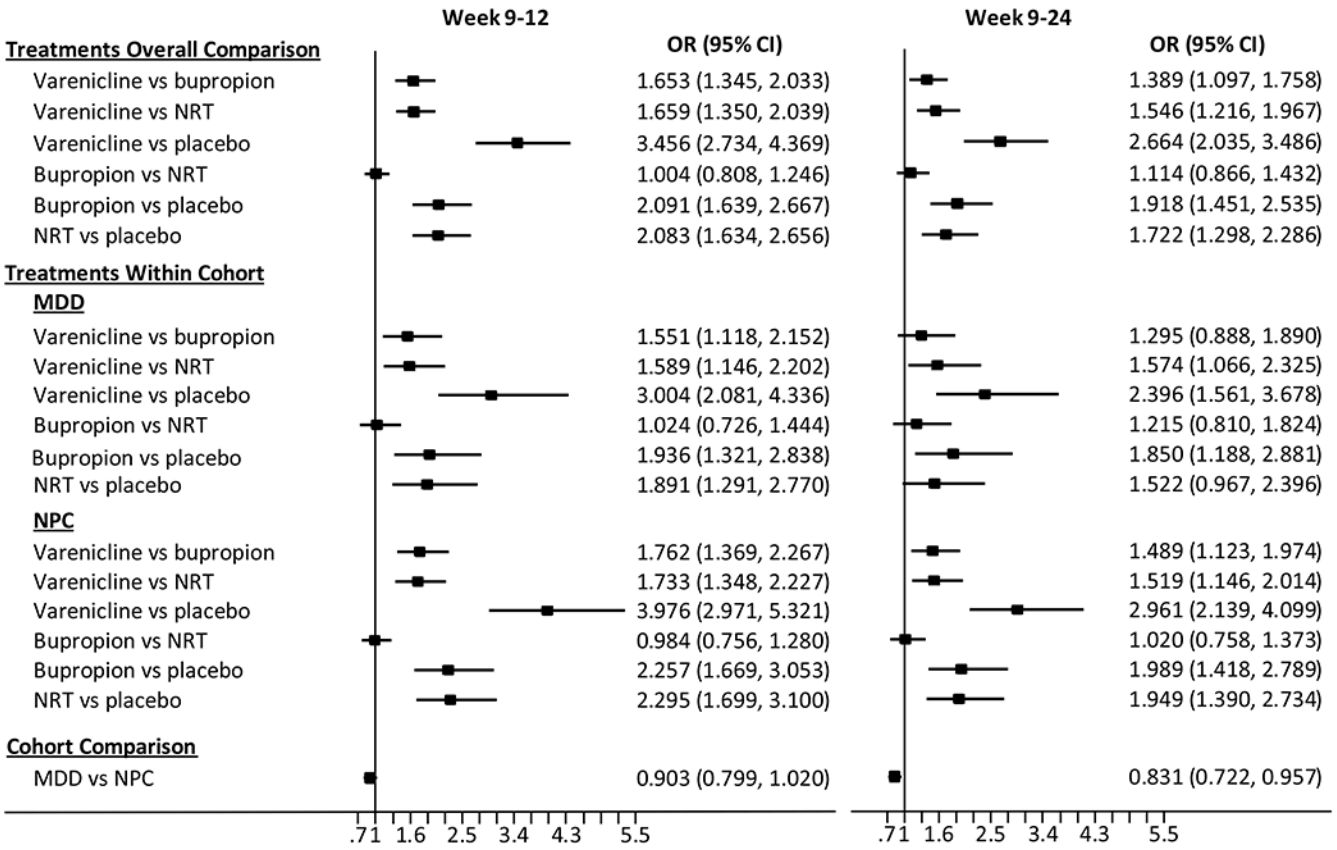

Figure 2.

Odds Ratios for continuous abstinence rates for Weeks 9–12 & 9-24 for the MDD and NPC cohorts.

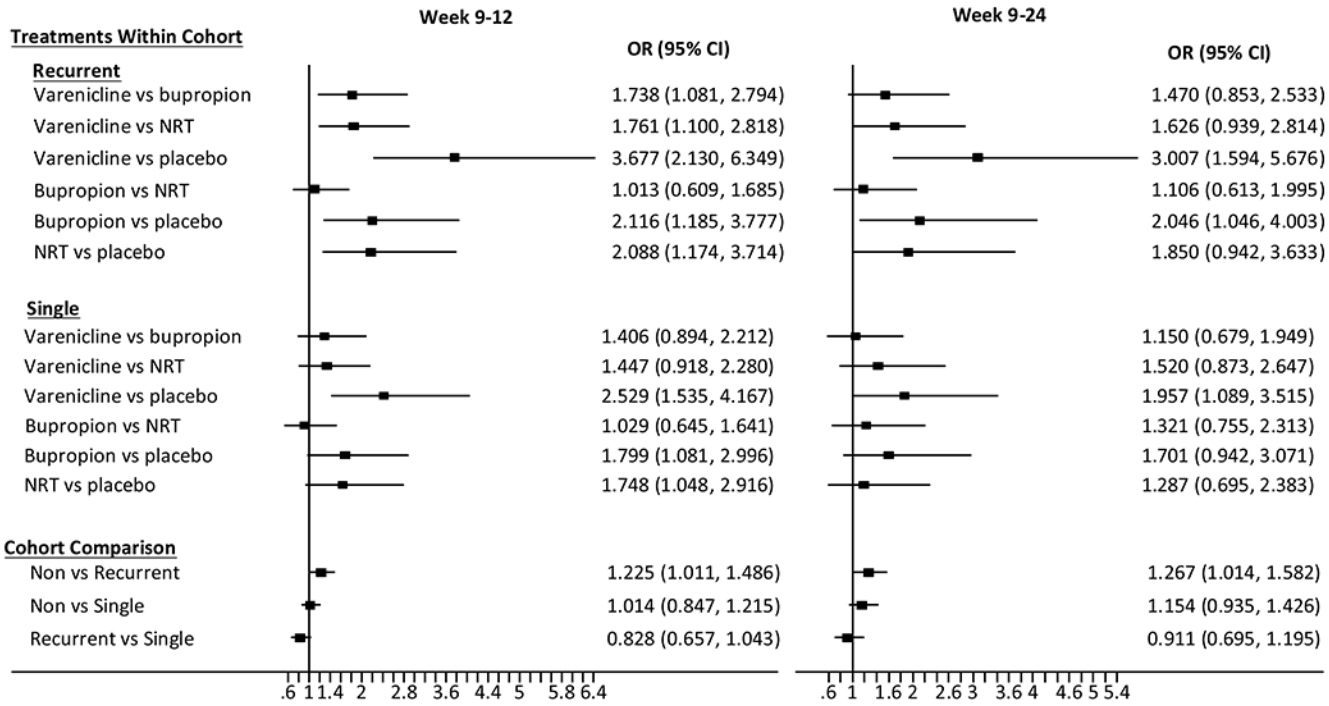

Figure 3.

Odds Ratios for continuous abstinence rates for Weeks 9–12 & 9-24 for the MDD and RE and SE subcohorts.

Table 1.

Incidence of treatment-emergent neuropsychiatric adverse events (NPSAE, the primary endpoint) and treatment-emergent C-SSRS among treated participants by 2-level cohort (MDD or NPC)

		MDD disorders subcohort					Nonpsychiatric cohort				
		ALL	**VAR**	**BUP**	**NRT**	**PBO**	**ALL**	**VAR**	**BUP**	**NRT**	**PBO**
Treated Subjects		**2602**	657	632	649	664	**3984**	990	989	1006	999
Observed NPSAE[a]:											
Primary Composite	*n* (%)	**138 (5.3)**	39 (5.9)	35 (5.5)	36 (5.5)	28 (4.2)	**84 (2.1)**	13 (1.3)	22 (2.2)	25 (2.5)	24 (2.4)
Severe-Only	*n* (%)	**33 (1.3)**	7 (1.1)	7 (1.1)	10 (1.5)	9 (1.4)	**13 (0.3)**	1 (0.1)	4 (0.4)	3 (0.3)	5 (0.5)
Estimated NPSAE[b]:											
Primary Composite	% (95% CI)	**5.3 (4.5, 6.2)**	5.9 (4.1, 7.7)	5.6 (3.8, 7.4)	5.6 (3.8, 7.3)	4.2 (2.7, 5.7)	**2.1 (1.6, 2.5)**	1.2 (0.5, 1.9)	2.3 (1.4, 3.3)	2.4 (1.4, 3.3)	2.4 (1.5, 3.4)
NPSAE Component Summary, n (%):											
Anxiety											
	Severe	**10 (0.4)**	4 (0.6)	1 (0.2)	3 (0.5)	2 (0.3)	**4 (0.1)**	0 (0.0)	1 (0.1)	0 (0.0)	3 (0.3)
Depression											
	Severe	**16 (0.6)**	3 (0.5)	3 (0.5)	6 (0.9)	4 (0.6)	**1 (0.0)**	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Feeling Abnormal											
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hostility											
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**2 (0.1)**	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)
Agitation											
	Moderate/Severe	**63 (2.4)**	16 (2.4)	17 (2.7)	17 (2.6)	13 (2.0)	**51 (1.3)**	10 (1.0)	11 (1.1)	19 (1.9)	11 (1.1)
	Severe	**7 (0.3)**	1 (0.2)	1 (0.2)	4 (0.6)	1 (0.2)	**2 (0.1)**	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)
Aggression											
	Moderate/Severe	**21 (0.8)**	9 (1.4)	4 (0.6)	5 (0.8)	3 (0.5)	**11 (0.3)**	3 (0.3)	3 (0.3)	2 (0.2)	3 (0.3)

		MDD disorders subcohort					Nonpsychiatric cohort				
		ALL	**VAR**	**BUP**	**NRT**	**PBO**	**ALL**	**VAR**	**BUP**	**NRT**	**PBO**
	Severe	**1 (0.0)**	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	**2 (0.1)**	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Delusions											
	Moderate/Severe	**1 (0.0)**	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	**1 (0.0)**	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hallucination											
	Moderate/Severe	**5 (0.2)**	1 (0.2)	2 (0.3)	1 (0.2)	1 (0.2)	**1 (0.0)**	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Severe	**1 (0.0)**	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mania											
	Moderate/Severe	**7 (0.3)**	1 (0.2)	3 (0.5)	2 (0.3)	1 (0.2)	**5 (0.1)**	0 (0.0)	1 (0.1)	2 (0.2)	2 (0.2)
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Panic											
	Moderate/Severe	**26 (1.0)**	6 (0.9)	9 (1.4)	6 (0.9)	5 (0.8)	**8 (0.2)**	0 (0.0)	4 (0.4)	1 (0.1)	3 (0.3)
	Severe	**2 (0.1)**	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	**3 (0.1)**	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.1)
Paranoia											
	Moderate/Severe	**1 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	**1 (0.0)**	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychosis											
	Moderate/Severe	**4 (0.2)**	3 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)	**1 (0.0)**	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
	Severe	**1 (0.0)**	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Homicidal Ideation											
	Moderate/Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.0)**	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suicidal Behavior											
	Moderate/Severe	**3 (0.1)**	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	**2 (0.1)**	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)
	Severe	**3 (0.1)**	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	**1 (0.0)**	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

	MDD disorders subcohort					Nonpsychiatric cohort				
	ALL	**VAR**	**BUP**	**NRT**	**PBO**	**ALL**	**VAR**	**BUP**	**NRT**	**PBO**
Suicidal Ideation										
Moderate/Severe	**6 (0.2)**	2 (0.3)	0 (0.0)	2 (0.3)	2 (0.3)	**6 (0.2)**	0 (0.0)	1 (0.1)	2 (0.2)	3 (0.3)
Severe	**1 (0.0)**	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	**1 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Suicide										
Moderate/Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Primary endpoint events, n (%):										
Serious adverse event	**8 (0.3)**	2 (0.3)	1 (0.2)	3 (0.5)	2 (0.3)	**6 (0.2)**	0 (0.0)	1 (0.1)	2 (0.2)	3 (0.3)
Led to permanent treatment discontinuation	**26 (1.0)**	8 (1.2)	2 (0.3)	8 (1.2)	8 (1.2)	**17 (0.4)**	1 (0.1)	5 (0.5)	7 (0.7)	4 (0.4)
Serious, severe, OR led to either treatment discontinuation or treatment intervention	**47 (1.8)**	13 (2.0)	7 (1.1)	14 (2.2)	13 (2.0)	**27 (0.7)**	2 (0.2)	7 (0.7)	8 (0.8)	10 (1.0)
C-SSRS[c] (Treatment-emergent) n (%):										
Suicidal ideation and/or behavior	**63 (2.4)**	20 (3.0)	11 (1.7)	14 (2.2)	18 (2.7)	**27 (0.7)**	9 (0.9)	5 (0.5)	5 (0.5)	8 (0.8)
Ideation	**63 (2.4)**	20 (3.0)	11 (1.7)	14 (2.2)	18 (2.7)	**26 (0.7)**	9 (0.9)	5 (0.5)	5 (0.5)	7 (0.7)
Behavior	**3 (0.1)**	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	**3 (0.1)**	0 (0.0)	1 (0.1)	1 (0.1)	(0.1)

[a] The primary safety endpoint, NPSAE, was defined as the occurrence of at least one adverse event from a pre-specified list of 261 MedDRA preferred terms, spanning 16 components, that were of moderate or severe intensity for 12 components (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal behavior, suicidal ideation; or completed suicide) and of severe intensity for 4 components (anxiety, depression, feeling abnormal, hostility) while on-treatment or up to 30 days post-treatment (referred to as treatment-emergent) and included all causalities.

[b] Estimation was via LS Means.

[c] Not all C-SSRS-captured reports of suicidal ideation were considered adverse events or met criteria as moderate to severe neuropsychiatric adverse events. Reported here are positive reports of any intensity.

Abbreviations: NPSAE, neuropsychiatric adverse event (as per definition), CI, confidence interval; C-SSRS, Columbia Suicide Severity Rating Scale[27]; NRT, nicotine replacement therapy (transdermal nicotine patch).

Table 2.

Incidence of treatment-emergent neuropsychiatric adverse events (NPSAE, the primary endpoint) and treatment-emergent C-SSRS among treated participants by MDD subcohort classification: recurrent (RE) single episode (SE)

		MDD Recurrent					MDD Single				
		ALL	**VAR**	**BUP**	**NRT**	**PBO**	**ALL**	**VAR**	**BUP**	**NRT**	**PBO**
Treated Subjects		**1274**	334	301	317	322	**1328**	323	331	332	342
Observed NPSAE[a]:											
Primary Composite	*n* (%)	**81 (6.4)**	24 (7.2)	17 (5.6)	20 (6.3)	20 (6.2)	**57 (4.3)**	15 (4.6)	18 (5.4)	16 (4.8)	8 (2.3)
Severe-Only	*n* (%)	**21 (1.6)**	4 (1.2)	2 (0.7)	8 (2.5)	7 (2.2)	**12 (0.9)**	3 (0.9)	5 (1.5)	2 (0.6)	2 (0.6)
Estimated NPSAE[b]:											
Primary Composite	% (95% CI)	**6.4 (5.0, 7.7)**	7.1 (4.4, 9.9)	5.8 (3.1, 8.4)	6.4 (3.7, 9.0)	6.2 (3.6, 8.8)	**4.3 (3.2, 5.4)**	4.6 (2.3, 6.9)	5.4 (3.0, 7.9)	4.8 (2.5, 7.1)	2.4 (0.8, 4.0)
NPSAE Component Summary, n (%):											
Anxiety											
	Severe	**7 (0.5)**	3 (0.9)	1 (0.3)	3 (0.9)	0 (0.0)	**3 (0.2)**	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.6)
Depression											
	Severe	**10 (0.8)**	1 (0.3)	0 (0.0)	5 (1.6)	4 (1.2)	**6 (0.5)**	2 (0.6)	3 (0.9)	1 (0.3)	0 (0.0)
Feeling Abnormal											
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hostility											
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Agitation											
	Moderate/Severe	**38 (3.0)**	13 (3.9)	9 (3.0)	8 (2.5)	8 (2.5)	**25 (1.9)**	3 (0.9)	8 (2.4)	9 (2.7)	5 (1.5)
	Severe	**6 (0.5)**	1 (0.3)	1 (0.3)	3 (0.9)	1 (0.3)	**1 (0.1)**	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Aggression											
	Moderate/Severe	**10 (0.8)**	5 (1.5)	2 (0.7)	1 (0.3)	2 (0.6)	**11 (0.8)**	4 (1.2)	2 (0.6)	4 (1.2)	1 (0.3)

		MDD Recurrent					MDD Single				
		ALL	**VAR**	**BUP**	**NRT**	**PBO**	**ALL**	**VAR**	**BUP**	**NRT**	**PBO**
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.1)**	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Delusions											
	Moderate/Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.0)**	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hallucination											
	Moderate/Severe	**1 (0.1)**	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	**4 (0.3)**	1 (0.3)	2 (0.6)	1 (0.3)	0 (0.0)
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.1)**	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Mania											
	Moderate/Severe	**5 (0.4)**	0 (0.0)	2 (0.7)	2 (0.6)	1 (0.3)	**2 (0.2)**	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Panic											
	Moderate/Severe	**17 (1.3)**	4 (1.2)	5 (1.7)	4 (1.3)	4 (1.2)	**9 (0.7)**	2 (0.6)	4 (1.2)	2 (0.6)	1 (0.3)
	Severe	**1 (0.1)**	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	**1 (0.1)**	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Paranoia											
	Moderate/Severe	**1 (0.1)**	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychosis											
	Moderate/Severe	**2 (0.2)**	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	**2 (0.2)**	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.1)**	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Homicidal Ideation											
	Moderate/Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suicidal Behavior											
	Moderate/Severe	**1 (0.1)**	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	**2 (0.2)**	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
	Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	MDD Recurrent					MDD Single				
	ALL	**VAR**	**BUP**	**NRT**	**PBO**	**ALL**	**VAR**	**BUP**	**NRT**	**PBO**
Suicidal Ideation										
Moderate/Severe	**4 (0.3)**	1 (0.3)	0 (0.0)	2 (0.6)	1 (0.3)	**2 (0.2)**>	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Suicide										
Moderate/Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Primary endpoint events, n (%):										
Serious adverse event	**5 (0.4)**	0 (0.0)	0 (0.0)	3 (0.9)	2 (0.6)	**3 (0.2)**	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)
Led to permanent treatment discontinuation	**17 (1.3)**	3 (0.9)	1 (0.3)	8 (2.5)	5 (1.6)	**9 (0.7)**	5 (1.5)	1 (0.3)	0 (0.0)	3 (0.9)
Serious, severe, OR led to either treatment discontinuation or treatment intervention	**29 (2.3)**	6 (1.8)	2 (0.7)	12 (3.8)	9 (2.8)	**18 (1.4)**	7 (2.2)	5 (1.5)	2 (0.6)	4 (1.2)
C-SSRS[c] (Treatment-emergent) n (%):										
Suicidal ideation and/or behavior	**46 (3.6)**	16 (4.8)	6 (2.0)	10 (3.2)	14 (4.3)	**17 (1.3)**	4 (1.2)	5 (1.5)	4 (1.2)	4 (1.2)
Ideation	**46 (3.6)**	16 (4.8)	6 (2.0)	10 (3.2)	14 (4.3)	**17 (1.3)**	4 (1.2)	5 (1.5)	4 (1.2)	4 (1.2)
Behavior	**1 (0.1)**	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	**2 (0.2)**	0 (0.0)	1 (0.3)	1 (0.3)	(0.0)

a. The primary safety endpoint, NPSAE, was defined as the occurrence of at least one adverse event from a pre-specified list of 261 MedDRA preferred terms, spanning 16 components, that were of moderate or severe intensity for 12 components (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal behavior, suicidal ideation; or completed suicide) and of severe intensity for 4 components (anxiety, depression, feeling abnormal, hostility) while on-treatment or up to 30 days post-treatment (referred to as treatment-emergent) and included all causalities.

b. Estimation was via LS Means.

c. Not all C-SSRS-captured reports of suicidal ideation were considered adverse events or met criteria as moderate to severe neuropsychiatric adverse events. Reported here are positive reports of any intensity.

Abbreviations: NPSAE, neuropsychiatric adverse event (as per definition), CI, confidence interval; C-SSRS, Columbia Suicide Severity Rating Scale[27]; NRT, nicotine replacement therapy (transdermal nicotine patch).