Review
https://doi.org/10.9758/cpn.23.1081 pISSN 1738-1088 / eISSN 2093-4327
Clinical Psychopharmacology and Neuroscience 2023;21(4):609-616

Dextromethorphan-bupropion (Auvelity) for the Treatment of Major Depressive Disorder

Brian McCarthy[1], Hannah Bunn[2], Morgan Santalucia[2], Charlotte Wilmouth[2], Andrew Muzyk[3], Colin M. Smith[4]

[1]Mood Treatment Center, Winston-Salem, NC, USA
[2]Campbell University College of Pharmacy and Health Sciences, Buies Creek, NC, USA
[3]Department of Pharmacy Practice, Campbell University College of Pharmacy and Health Sciences, Buies Creek, NC, USA
[4]Department of Behavioral Health, Phoenix Indian Medical Center, Indian Health Service, Phoenix, AZ, USA

Depression is a significant cause of morbidity and mortality globally. Although various pharmacologic options exist for depression, treatments are limited by delayed or incomplete therapeutic response, low rates of remission, and adverse effects necessitating effective, fast-acting, and better tolerated alternatives. The purpose of this review is to describe the safety and efficacy of dextromethorphan-bupropion (Auvelity), a Food and Drug Administration approved treatment for major depressive disorder in adults. Dextromethorphan modulates glutamate signaling through uncompetitive antagonism of N-methyl-D-aspartate receptors and sigma-1 agonism, while bupropion increases the bioavailability of dextromethorphan by CYP2D6 inhibition. In a phase 3 trial with dextromethorphan-bupropion 45−105 mg for patients with major depressive disorder saw significant reductions in their Montgomery–Åsberg Depression Rating Scale total scores compared to placebo. A phase 2 trial comparing dextromethorphan-bupropion 45−105 mg to bupropion monotherapy led to significant reduction in Montgomery-Åsberg Depression Rating Scale score. Changes in Montgomery–Åsberg Depression Rating Scale with dextromethorphan-bupropion were seen within two weeks in both clinical trials. Remission and response rates were significantly higher with dextromethorphan-bupropion in both studies. The medication was well-tolerated in both trials, with the most common adverse events being rated as mild-to-moderate. Two long-term, open-label studies with dextromethorphan-bupropion saw large reductions in Montgomery–Åsberg Depression Rating Scale scores that were maintained through 12 and 15 months of treatment. In both long-term studies, remission rates approached 70%, while response rates were greater than 80%. These data suggest that dextromethorphan-bupropion is an effective, fast-acting, and well tolerated option for depression treatment and produced remission in a large percentage of patients.

KEY WORDS: Antidepressant; Ketamine; Treatment outcome; Drug combination; Anhedonia.

INTRODUCTION

Major depressive disorder affects an estimated 280 million people globally and is a leading cause of disability worldwide [1]. Despite numerous pharmacologic options for the management of depression, treatment failure with monotherapy is common [2] and therapeutic response time generally takes weeks-to-months [3]. Given that untreated depression may lead to significant functional impairment and suicide [1], there is a need for effective, rapid-acting oral antidepressants that treat patients' depression into remission [2].

Guidelines for non-psychotic depression management recommend antidepressant monotherapy with agents that rely on directly modulating the monoamine neurotransmitter system, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), or atypical antidepressants such as bupropion and mirtazapine, as first line treatment [4,5]. Antidepressant monotherapies across classes indeed outperform placebo [6]. However, nearly two-thirds of patients fail to remit after initial treatment with an SSRI, and

Received: April 8, 2023 / **Revised:** May 6, 2023
Accepted: May 10, 2023 / **Published online:** July 17, 2023
Address for correspondence: Andrew Muzyk
Department of Pharmacy Practice, Campbell University College of Pharmacy and Health Sciences, Room 237, JP Riddle Pharmacy Center, Buies Creek, NC 27506, USA
E-mail: Andrew.Muzyk@duke.edu
ORCID: https://orcid.org/0000-0002-6904-2466

another two-thirds fail to remit after switching to a different antidepressant [2]. Of those who do reach remission, patients often experience weeks-long delays prior to responding to treatment [3] and untoward side effects during this period from medications [7], highlighting the need for novel treatment options that are effective, rapid-acting, and well tolerated.

Combination therapies with agents from different antidepressant classes have emerged as effective alternatives to monotherapy in acute depression [8,9]. A growing number of second-generation antipsychotics (e.g., aripiprazole [10], brexpiprazole [11], cariprazine [12], olanzapine [combined with fluoxetine] [13], and quetiapine extended release [14]) have also been approved by the Food and Drug Administration (FDA) for adjunctive treatment of depression, although they are associated with extrapyramidal symptoms and metabolic syndrome. While intranasal esketamine, a rapid acting non-competitive N-methyl D-aspartate (NMDA) receptor antagonist, was FDA approved for adjunctive treatment of treatment resistant depressive and depressive symptoms in adults with major depressive disorder and suicidality, it requires strict monitoring due to side effects and abuse potential, and it is not available in an oral formulation [15].

A fixed-dose, extended-release combination of dextromethorphan and bupropion (Auvelity), an antagonist of NMDA receptors and an agonist at sigma-1 receptors, was approved by the FDA in 2022 for the treatment of major depressive disorder in adults [16]. Dextromethorphan-bupropion combination tablet represents a novel rapid-acting oral treatment option for depression in adults. In this article, we describe the efficacy and safety of dextromethorphan-bupropion in the treatment of major depressive disorder in adults.

CLINICAL PHARMACOLOGY

Dextromethorphan's primary potential for MDD treatment is theorized to be due to its uncompetitive antagonism of the ionotropic glutamate receptor NMDA in the central nervous system [17,18]. Previous imaging and clinical postmortem data from clinically depressed patients have demonstrated the involvement of the glutaminergic system in depression with magnetic resonance imagining (MRI) data showing the role that glutamate and glutamine have in regulating learning, memory, and synaptic plasticity. NMDA inhibition leads to downstream activation of AMPA, a suspected target for enhancing neuronal plasticity and by association improved antidepressant effect. In addition to NMDA antagonism, dextromethorphan is a sigma-1 agonist and inhibits serotonin and norepinephrine reuptake [19]. Sigma-1 receptors regulation of both voltage-gated and ligand-gated channels may also contribute to synaptic plasticity. Agonists at the sigma-1 receptor are thought to modulate NMDA receptors, with lower doses leading to excitation, and high doses to inhibition [20].

The therapeutic benefits of dextromethorphan are limited due to rapid metabolism by CYP2D6 leading to a half-life of only 4 hours [16]. Maintaining therapeutic levels of dextromethorphan is essential for sustained antagonism of NMDA receptors. Bupropion, a dopamine and norepinephrine reuptake inhibitor, competitively inhibits CYP2D6, which extends dextromethorphan's half-life to 22 hours [16,17,19]. Additional pharmacokinetic properties are overviewed in Table 1 [16]. Due to the rates of CYP2D6 metabolism and subsequent blockade by bupropion, patient CYPD6 status may impact therapeutic choices. In patients with known poor CYP2D6 metabolism, drug metabolism is reduced [16]. Detailed dosing changes based on CYP2D6 metabolism as well as renal and hepatic adjustments are listed in Table 2.

CLINICAL TRIALS

Phase 2 Trial

Dextromethorphan-bupropion was assessed for efficacy and safety in treating major depressive disorder (MDD) in a phase 2, randomized, double-blind, active-controlled trial (n = 80) [17]. Bupropion was used as the active control. Included patients were between the ages of 18–65, had a diagnosis of MDD without psychotic features, and were experiencing a current depressive episode of moderate severity or greater; confirmed by an independent blinded assessor. The treatment phase of the study lasted for 6 weeks; after the baseline visit, study visits occurred at weeks 1, 2, 3, 4, and 6, along with a safety follow-up at week 7. Patients also completed a daily visual analogue mood scale. Other key baseline demographics can be found in Table 3.

Patients were excluded if they had a concurrent psychiatric diagnosis such as bipolar disorder, obsessive com-

Table 1. Pharmacodynamic and pharmacokinetic properties

Class	Dextromethorphan: NMDA receptor antagonist & sigma-1 receptor agonist Bupropion: dopamine and norepinephrine reuptake inhibitor and CYP2D6 inhibitor
Formulation	45 mg dextromethorphan/105 mg bupropion ER tablets
Route	Oral
Metabolism	Dextromethorphan: CYP2D6 de-methylation Bupropion: CYP2B6 hydroxylation and reduction
Half-life	Dextromethorphan/bupropion: 22 hours
Steady state	8 days
Elimination	Dextromethorphan: CYP2D6 extensive metabolizers: 37−52% urine, 2% unchanged CYP2D6 poor metabolizers: 45−83% urine, 26% unchanged Bupropion: 87% urine, 10% feces, 0.5% unchanged
Drug interactions	MAOIs, serotonergic agents, dopaminergic agents, strong CYP2D6 inhibitors, strong CYP2B6 inducers, agents metabolized by CYP2D6, agents which lower seizure threshold, digoxin, alcohol

NMDA, N-methyl D-aspartate; ER, extended release; MAOIs, monoamine oxidase inhibitors.

Table 2. Dosing in adults and special populations [16]

Patient population	Initial dosing	Maintenance dosing
Adults	45/105 mg daily × 3 days	45/105 mg twice daily[a]
Hepatic impairment		
Child Pugh A−B	45/105 mg daily × 3 days	45/105 mg twice
Child Pugh C	Not recommended, no data studied	
Renal impairment		
eGFR 30−59	45/105 mg daily	45/105 mg daily
eGFR < 30	Not recommended, no data studied	
Poor CYP2D6 metabolizers	45/105 mg daily	45/105 mg daily
Concomitant strong CYP2D6 inhibitor use	45/105 mg daily	45/105 mg daily

eGFR, estimated glomerular filtration rate.
[a]Dosing should be at least 8 hours apart. Do not exceed 2 tablets in 24 hours.

Table 3. Key baseline demographics for the clinical trials

Demographic	Phase 2 trial		Phase 3 trial	
	Dextromethorphan-bupropion (n = 43)	Bupropion (n = 37)	Dextromethorphan-bupropion (n = 156)	Placebo (n = 162)
Age (yr)	37.3 ± 12.0	37.7 ± 11.9	42.1 ± 12.8	41.2 ± 13.8
Female	25 (58.1)	26 (70.3)	95 (60.9)	117 (72.2)
Race				
White	30 (69.8)	20 (54.1)	84 (53.8)	92 (56.8)
Black or African American	12 (27.9)	14 (37.8)	58 (37.2)	54 (33.3)
Asian	1 (2.3)	0	9 (5.8)	8 (4.9)
Other	0	3 (8.1)	2 (1.3)	6 (3.7)
Hispanic or Latino	6 (14.0)	11 (29.7)	-	-
MADRS total score	31.8 ± 4.0	32.2 ± 4.5	33.6 ± 4.4	33.2 ± 4.4

Values are presented as mean ± standard deviation or number (%).
MADRS, Montgomery–Åsberg Depression Rating Scale.

pulsive disorder, panic disorder, or a lifetime history of psychotic disorder. Patients were also excluded if they had treatment-resistant depression (at least two failed treatments in the current depressive episode), substance use disorder within the past year, clinically significant suicide risk, or history of seizure disorder. Patients could not be on any other antidepressant medications for the duration of the trial; if they were on an antidepressant at

screening, they had to complete a washout of at least one week or 5 half-lives of the medication before the baseline visit.

The primary endpoint was the change from baseline to week 6 in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score. Patients were randomized 1:1 to receive either dextromethorphan-bupropion 45/105 mg or sustained-release bupropion 105 mg once daily for the first 3 days, then twice daily for the remainder of the study. At the end of the 6-week treatment period, patients in the dextromethorphan-bupropion group had significantly larger reductions from baseline in their MADRS total score, with a statistically significant effect beginning as early as week 2. Remission (MADRS total score ≤ 10) and response rates (≥ 50% decrease in MADRS total score), key secondary endpoints, were significantly higher in the dextromethorphan-bupropion group. This outcome also had a significant separation beginning at week 2. Table 4 contains the results for the primary outcome and key secondary outcomes. Adherence was evaluated by tablet counts and plasma levels of bupropion at the last study visit on week 7. For both groups, adherence based on tablet counts was ≥ 90%, and 93.1% of the 72 patients with plasma samples had measurable bupropion levels at the last study visit.

Adverse events were assessed from the time of the first dose of study medication until 7 days after the last dose. Overall, dextromethorphan-bupropion was well-tolerated, with the most common adverse events being dizziness, nausea, dry mouth, decreased appetite, and anxiety. Most of these adverse events were determined to be mild-to-moderate. Adverse events reported as severe intensity occurred in three patients in the dextromethorphan-bupropion group (two patients with dizziness; one patient each with nausea, somnolence, and anxiety) and one patient in the bupropion group (psychotic disorder). Adverse events with an incidence of greater than 5% are summarized in Table 5. No change on the Columbia-Suicide Severity Rating Scale (C-SSRS) from baseline to week 6 were seen. Withdrawals due to adverse events were equivalent between the two study groups. Notably, dextromethorphan-bupropion did not lead to adverse events such as abuse, weight gain, sexual dysfunction, or psychotomimetic effects.

Phase 3 Trial

The GEMINI trial was a phase 3, double-blind, randomized controlled trial (n = 327) that evaluated the safety and efficacy of dextromethorphan-bupropion versus placebo over 6 weeks [18]. Eligible patients were aged 18−65 years old with a diagnosis of MDD experiencing a major depressive episode for at least 4 weeks, a MADRS score of 25 or greater, and a Clinician Global Impression Severity (CGI-S) of 4 or higher. Patients with treatment-resistant depression (at least two failed treatments in the current depressive episode) were excluded along with any diagnosis of psychotic disorder, bipolar disorder, panic disorder, obsessive compulsive disorder, seizure disorder, alcohol or substance abuse disorder within the past year, and any patients that were at high risk of suicide. Patients were randomly assigned in a 1:1 ratio to receive dextromethorphan-bupropion (n = 163) or placebo (n = 164) for 6 weeks. Patients received dextromethorphan-bupropion

Table 4. Study outcomes for phase 2 trial

Outcome	Dextromethorphan-bupropion (n = 43)	Bupropion (n = 37)	Difference
Overall change from baseline in MADRS total score[a]	−13.7 ± 0.6	−8.8 ± 0.7	−4.9 (−3.1, −6.8)[d,*]
Change from baseline in MADRS total score, week 2	−12.5 ± 1.4	−7.8 ± 1.5	−4.7 (−0.6, −8.8)[d,*]
Change from baseline in MADRS total score, week 6	−17.3 ± 1.4	−12.1 ± 1.5	−5.2 (−1.1, −9.3)[d,*]
Remission at week 2[b]	11 (25.6)	1 (2.7)	22.9 (8.8, 36.9)[e,*]
Remission at week 6	20 (46.5)	6 (16.2)	30.3 (11.2, 49.4)[e,*]
Clinical response at week 2[c]	16 (37.2)	10 (27.0)	10.2 (−10.2, 30.5)[e]
Clinical response at week 6	26 (60.5)	15 (40.5)	19.9 (−1.6, 41.5)[e]

Values are presented as least-squares mean ± standard error or number (%).
[a]MADRS: Montgomery-Åsberg Depression Rating Scale; 10-item clinician-rated questionnaire with scores ranging from 0−60. A higher score corresponds to more severe depression. [b]Remission defined as MADRS total score ≤ 10. [c]Clinical response defined as ≥ 50% reduction in MADRS total score from baseline. [d]Least-squares mean (95% confidence interval). [e]% (95% confidence interval).
*$p < 0.05$.

Table 5. Summary of AEs from the clinical trials

AE	Phase 2 trial		Phase 3 trial	
	Dextromethorphan-bupropion (n = 48)	Bupropion (n = 48)	Dextromethorphan-bupropion (n = 162)	Placebo (n = 164)
Any AE	35 (72.9)	31 (64.6)	100 (61.7)	74 (45.1)
Serious AE[a]	0	0	1 (0.6)	0
Severe AE[b]	3 (6.3)	1 (2.1)	1 (0.6)	2 (1.2)
AE leading to discontinuation	6 (12.5)	6 (12.5)	10 (6.2)	1 (0.6)
Dizziness	10 (20.8)	2 (4.2)	26 (16.0)	10 (6.1)
Nausea	8 (16.7)	6 (12.5)	21 (13.0)	14 (8.5)
Headache	NR	NR	13 (8.0)	6 (3.7)
Diarrhea	NR	NR	11 (6.8)	5 (3.0)
Somnolence	1 (2.1)	NR	11 (6.8)	5 (3.0)
Dry mouth	5 (10.4)	4 (8.3)	9 (5.6)	4 (2.4)
Anxiety	5 (10.4)	1 (2.1)	7 (4.3)	2 (1.2)
Decreased appetite	5 (10.4)	4 (8.3)	6 (3.7)	1 (0.6)
Change in body weight at week 6 (kg)	−0.6 ± 2.4	0.1 ± 2.1	−0.2 ± 7.8	0.4 ± 2.3

Values are presented as number (%) or mean ± standard deviation.
AE, adverse event; NR, not reported.
[a]Any AE that results in death, was life threatening, led to hospitalization or prolongation of hospitalization, or caused significant disability or incapacity. [b]A severe AE that interrupted usual daily activities, significantly affected clinical status, or requires intensive therapeutic intervention.

Table 6. Study outcomes for phase 3 trial

Outcome	Dextromethorphan-bupropion (n =156)	Placebo (n = 162)	Difference
Overall change from baseline at week 6 in MADRS total score[a]	−15.9 ± 0.9	−12.0 ± 0.9	−3.9 (1.4, −6.4)[d,*]
Change from baseline in MADRS total score, week 1[a]	−7.2 ± 0.6	−5 ± 0.6	−2.2 (−0.6, −3.9)[d,*]
Change from baseline in MADRS total score, week 2[a]	−11.1 ± 0.7	−7.7 ± 0.7	−3.4 (−1.4, −5.5)[d,*]
Remission at week 2[b]	24 (16.9)	12 (7.5)	9.4 (1.9, 16.8)[e,*]
Remission at week 6[b]	49 (39.5)	26 (17.3)	22.2 (11.7, 32.7)[e,*]
Clinical response at week 2[c]	40 (28.2)	27 (17.0)	11.2 (1.8, 20.6)[e,*]
Clinical response at week 6[c]	67 (54.0)	51 (34.0)	20 (8.4, 31.6)[e,*]

Values are presented as least-squares mean ± standard error or number (%).
[a]MADRS: Montgomery-Åsberg Depression Rating Scale; 10-item clinician-rated questionnaire with scores ranging from 0−60. A higher score corresponds to more severe depression. [b]Remission defined as MADRS total score ≤ 10. [c]Clinical response defined as ≥ 50% reduction in MADRS total score from baseline. [d]Least-squares mean (95% confidence interval). [e]% (95% confidence interval).
*$p < 0.05$.

45−105 mg or placebo once daily for 3 days, then twice daily thereafter. Following the baseline visit, study visits were at weeks 1, 2, 3, 4, and 6 and a safety follow-up visit occurred at week 7. Baseline characteristics (Table 3) were similar among both arms except the dextromethorphan-bupropion arm included more men than the placebo group (39.1% vs. 27.8%; $p = 0.033$).

The primary endpoint was the change from baseline in the MADRS total score at 6 weeks. Dextromethorphan-bupropion demonstrated statistically significant reductions in MADRS scores starting as early as week 1 and at every time point thereafter. Remission (MADRS total score < 10) was achieved by 39.5% of patients in the dextromethorphan-bupropion group versus 17.3% in the placebo group at week 6 and a statistically significant difference was seen starting at week 2. At week 6, 54.0% of patients receiving dextromethorphan-bupropion had a statistically significant clinical response (≥ 50% reduction in MADRS total score) versus 34.0% with placebo. Table 6 contains the results for the primary outcome and key secondary outcomes.

Safety was assessed based on reported adverse events, changes in vital signs, physical examinations, laboratory measurements, electrocardiograms, and assessment of

suicidal ideation and behavior. The safety population included all patients who received at least 1 dose of the study medication. Adverse events were defined as any adverse event occurring from the first dose of treatment until 7 days after the last dose. Dextromethorphan-bupropion was safe and well-tolerated with the most common adverse being dizziness, nausea, headache, diarrhea, somnolence, and dry mouth. Psychomimetic effects, weight gain, and increased sexual dysfunction were not reported with dextromethorphan-bupropion. One severe adverse event of a migraine was reported in the dextromethorphan-bupropion group. Table 5 provides a summary of adverse events. There were no reported suicide-related adverse events based on the C-SSRS.

POSTER PRESENTATIONS

Two posters detailing long-term, open-label studies with dextromethorphan-bupropion have been presented at annual meetings. The first of these posters presented the results from the COMET Phase 3 Trial at the 2021 American Society of Clinical Psychopharmacology Annual Meeting. Patients in this trial were treated with dextromethorphan-bupropion 45−105 mg twice daily for up to 12 months [21]. Inclusion/exclusion criteria were like previously mentioned studies. This trial found a rapid reduction in MADRS total score that was maintained through month 12, with a mean reduction from baseline of 23 points at the end of the study period (n = 611). Clinical response (≥ 50% reduction in MADRS total score) was achieved by 82.8% of patients at month 12, and clinical remission (MADRS total score ≤ 10) was achieved by 69.0% of patients at month 12. The main adverse events (n = 876) experienced were dizziness (12.7%), nausea (11.9%), headache (8.8%), dry mouth (7.1%), and decreased appetite (6.1%). No serious adverse events were reported.

The second poster presented the results from the EVOLVE open-label, long-term study at the 2022 American College of Neuropsychopharmacology Annual Meeting. One hundred and forty-five patients in this trial were treated with dextromethorphan-bupropion 45−105 mg twice daily for up to 15 months, with similar inclusion and exclusion criteria as mentioned previously [22]. Significant improvements were reported on MADRS total scores, Cognitive and Physical Functioning Questionnaire, Sheehan Disability Scale, and the Hamilton Anxiety Rating Scale. Significant robust findings on each of these assessment scales were seen by week 1. Similar to the COMET trial, clinical response and remission were achieved at month 12 by 81.9% and 67.5% of patients, respectively. The most common adverse events (n = 146) were COVID-19 infection (8.9%), nausea (8.9%), headache (7.5%), dry mouth (6.2%), dizziness (5.5%), and insomnia (5.5%). The poster reported serious adverse events in 5 patients (3.4%) but did not specify what these adverse events were.

PLACE IN THERAPY

Combination dextromethorphan-bupropion represents the first FDA approved rapidly acting oral medication for major depressive disorder in adults. Compiling evidence suggests that this novel medication may fill a unique role in the management of acute depression.

Dextromethorphan-bupropion's novel pharmacologic properties provide several advantages over other antidepressants. First, antidepressants affecting primarily monoamine neurotransmitters often take 4−8 weeks to result in a clinically meaningful depression response or remission [3], while dextromethorphan-bupropion has demonstrated efficacy after only one week of treatment [19]. Second, dextromethorphan-bupropion has a relatively favorable side-effect profile compared with other fast-acting antidepressants, such as intranasal esketamine, which is only available through a restricted drug program due to serious adverse outcomes resulting from sedation, dissociation, and abuse potential [23]. Finally, unlike other fast-acting antidepressants, brexanolone [24] and esketamine [15], dextromethorphan-bupropion is an oral formulation, available from pharmacies, and able to be self-administered by a patient without assistance or observation from a healthcare provider.

While dextromethorphan-bupropion is a promising treatment for depression, there are several issues that may limit its clinical utility. First, as is the case with esketamine, dextromethorphan does have abuse potential [25] and no studies have evaluated its utility in patients with depression and comorbid substance use disorders, though abuse and misuse were not reported in clinical trials of the combination product. It should be noted that the abuse of dextromethorphan is believed to be due to its rapid conversion to the metabolite dextrophan by the cytochrome

450 enzyme 2D6, which is inhibited by bupropion [26]. Second, in an unpublished randomized clinical trial, dextromethorphan-bupropion was compared to bupropion for treatment resistant depression but failed to separate at week 6 despite separating at weeks 1 and 2 [27]. Lastly, the cost of the newly patented product limits its use as a first line drug for depression.

Taken together, the available data indicate that dextromethorphan-bupropion is a safe and effective treatment for major depressive disorder and stands alone as a fast-acting oral treatment option for depression without the requirement for a restricted treatment setting or the risk of serious adverse events. Available data with dextromethorphan-bupropion not only demonstrated reduction in depressive symptoms but substantial benefit in achieving remission and response. The EVOLVE study provides evidence that dextromethorphan-bupropion may benefit cognition and anxiety associated with depression; two findings that need further exploration in clinical trials. Future studies should assess the long-term effectiveness of combination dextromethorphan-bupropion and further clarify its utility in people with substance use disorders and treatment resistant depression.

DISCLAIMER

The views expressed are those of the authors and do not necessarily represent those of the United States Government or the Indian Health Service.

■ **Funding**

None.

■ **Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

■ **Author Contributions**

Brian McCarthy, Hannah Bunn, Morgan Santalucia, Charlotte Wilmouth, Andrew Muzyk, and Colin M. Smith were involved in the conceptualization, analysis, writing, reviewing, and editing of this manuscript.

■ **ORCID**

Hannah Bunn https://orcid.org/0009-0000-8373-9916
Morgan Santalucia https://orcid.org/0009-0000-2941-5224
Andrew Muzyk https://orcid.org/0000-0002-6904-2466
Colin M. Smith https://orcid.org/0000-0002-5758-4698

REFERENCES

1. World Health Organization. *Depression [Internet]. World Health Organization; 2021 [cited at 2023 Mar 9]. Available from: https://www.who.int/news-room/fact-sheets/detail/depression*
2. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, *et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. Am J Psychiatry 2006;163:1905-1917.*
3. Cheng Q, Huang J, Xu L, Li Y, Li H, Shen Y, *et al. Analysis of time-course, dose-effect, and influencing factors of antidepressants in the treatment of acute adult patients with major depression. Int J Neuropsychopharmacol 2020;23:76-87.*
4. American Psychiatric Association. *Practice Guideline for the treatment of patients with major depressive disorder, third edition [Internet]. American Psychiatric Association; 2010 [cited at 2023 Mar 9]. Available from: https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf*
5. National Institute for Health and Care Excellence. *Depression in adults: Treatment and management [Internet]. National Institute for Health and Care Excellence; 2022 [cited at 2023 Mar 9]. Available from: https://www.nice.org.uk/guidance/ng222/resources/depression-in-adults-treatment-and-management-pdf-66143832307909*
6. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, *et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. Lancet 2018;391:1357-1366.*
7. Anderson HD, Pace WD, Libby AM, West DR, Valuck RJ. *Rates of 5 common antidepressant side effects among new adult and adolescent cases of depression: A retrospective US claims study. Clin Ther 2012;34:113-123.*
8. Henssler J, Alexander D, Schwarzer G, Bschor T, Baethge C. *Combining antidepressants vs antidepressant monotherapy for treatment of patients with acute depression: A systematic review and meta-analysis. JAMA Psychiatry 2022;79:300-312.*
9. Blier P, Ward HE, Tremblay P, Laberge L, Hébert C, Bergeron R. *Combination of antidepressant medications from treatment initiation for major depressive disorder: A double-blind randomized study. Am J Psychiatry 2010;167:281-288.*
10. Otsuka America Pharmaceutical, Inc. *Aripiprazole. Tokyo: Otsuka America Pharmaceutical, Inc.;2013. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021436s037,021713s029,021729s021,021866s022lbl.pdf*
11. Otsuka Pharmaceutical Co., Ltd. *Brexpiprazole. Tokyo: Otsuka Pharmaceutical Co., Ltd..;2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/205422s007lbl.pdf*
12. AbbVie. *U.S. FDA approves VRAYLAR® (cariprazine) as an*

adjunctive treatment for major depressive disorder [Internet]. AbbVie; 2022 [cited at 2023 Mar 9]. Available from: https://news.abbvie.com/news/press-releases/us-fda-approves-vraylar-cariprazine-as-an-adjunctive-treatment-for-major-depressive-disorder.htm#:~:text=Cariprazine%20is%20marketed%20as%20VRAYLAR,disorder%2C%20as%20well%20as%20schizophrenia

13. Eli Lilly and Company. *Olanzapine-Fluoxetine. Indianapolis (IN): Eli Lilly and Company.;2003. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021520s33lbl.pdf*
14. AztraZeneca. *Quetiapine Extended-Release. Wilmington (DE): AztraZeneca.;2009. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022047s011s016s017s019s022lbl.pdf*
15. Janssen Pharmaceuticals, Inc. *Esketamine. Titusville (NJ): Janssen Pharmaceuticals, Inc.;2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211243s004lbl.pdf*
16. AXSOME Therapeutics, Inc. *Dextromethorphan-bupropion. New York (NY): AXSOME Therapeutics, Inc.;2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215430s000lblCorrect3.pdf*
17. Tabuteau H, Jones A, Anderson A, Jacobson M, Iosifescu DV. *Effect of AXS-05 (Dextromethorphan-Bupropion) in major depressive disorder: A randomized double-blind controlled trial. Am J Psychiatry 2022;179:490-499.*
18. Iosifescu DV, Jones A, O'Gorman C, Streicher C, Feliz S, Fava M, *et al. Efficacy and safety of AXS-05 (Dextromethorphan-Bupropion) in patients with major depressive disorder: A phase 3 randomized clinical trial (GEMINI). J Clin Psychiatry 2022;83:21m14345.*
19. Stahl SM. *Dextromethorphan/bupropion: a novel oral NMDA (N-methyl-d-aspartate) receptor antagonist with multimodal activity. CNS Spectr 2019;24:461-466. Erratum in: CNS Spectr 2020;25:803.*
20. Kourrich S, Su TP, Fujimoto M, Bonci A. *The sigma-1 receptor: roles in neuronal plasticity and disease. Trends Neurosci 2012;35:762-771.*
21. O'Gorman C, Jones A, Tabuteau H. *Sustained efficacy with long-term treatment with AXS-05: Results from the COMET phase 3 trial, a long-term, open-label study evaluating the efficacy and safety of AXS-05 for the treatment of MDD. In: American Society of Clinical Psychopharmacology Annual Meeting; June, 2021; virtual.*
22. Jones A, Fava M, Thomas Z, Streicher C, Alter S, Tabuteau H. *Improvements in cognitive and physical functioning outcomes in depressed patients treated with AXS-05 (dextromethorphan-bupropion): Results from the EVOLVE open-label, long-term study. In: American College of Neuropsychopharmacology Annual Meeting; December, 2022; Phoenix, AZ.*
23. Spravato. *Spravato REMS [Internet]. Spravato; 2020 [cited at 2023 Mar 9]. Available from: https://www.spravatorems.com/*
24. SAGE Therapeutics. Brexanolone. *Cambridge (MA): SAGE Therapeutics.;2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211371lbl.pdf*
25. Romanelli F, Smith KM. *Dextromethorphan abuse: Clinical effects and management. J Am Pharm Assoc (2003) 2009;49:e20-25; quiz e26-27.*
26. Nicholson KL, Hayes BA, Balster RL. *Evaluation of the reinforcing properties and phencyclidine-like discriminative stimulus effects of dextromethorphan and dextrorphan in rats and rhesus monkeys. Psychopharmacology (Berl) 1999;146:49-59.*
27. Biospace. *Axsome Therapeutics [Internet]. Biospace; 2020 [cited at 2023 Mar 9]. Available from: https://www.biospace.com/article/releases/axsome-therapeutics-announces-top-line-results-of-the-stride-1-phase-3-trial-in-treatment-resistant-depression-and-expert-call-to-discuss-clinical-implications/*