Dextromethorphan/Bupropion: First Approval

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Abstract
An oral, fixed-dose combination of dextromethorphan hydrobromide [an uncompetitive \(N\)-methyl-\(d\)-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist] and the antidepressant bupropion hydrochloride (an aminoketone and CYP2D6 inhibitor that increases dextromethorphan bioavailability) [AUVELITY\textsuperscript{TM}; dextromethorphan/bupropion], is being developed by Axsome Therapeutics, Inc. for the treatment of major depressive disorder (MDD), Alzheimer’s disease agitation and smoking cessation. Dextromethorphan/bupropion was approved in the USA in August 2022 for the treatment of MDD in adults. This article summarizes the milestones in the development of dextromethorphan/bupropion leading to this first approval for the treatment of adults with MDD.

1 Introduction
Depression is a leading cause of disability worldwide, and contributes significantly to the overall global burden of disease \([1, 2]\). While there are many antidepressants available for the treatment of the disorder, efficacy in major depressive disorder (MDD) is limited and new, more effective and rapidly-acting treatment options for MDD are required \([2, 3]\).

In the last two decades, the discovery that subanaesthetic doses of the glutamatergic drug ketamine [a parenterally administered uncompetitive \(N\)-methyl-\(d\)-aspartate (NMDA) receptor antagonist] have rapid antidepressant effects in treatment-resistant depression (TRD) has led to the investigation of other agents in this class, including dextromethorphan (an orally administered, non-selective, uncompetitive NMDA receptor antagonist and sigma-1 receptor agonist), as potential treatments for depression \([2–5]\). One of the limitations of dextromethorphan is that it is rapidly and extensively metabolized in humans, and the plasma concentrations needed for psychotherapeutic effects cannot be achieved without metabolic inhibition \([4, 6]\). The antidepressant bupropion (an aminoketone and competitive CYP2D6 inhibitor) inhibits a major biotransformation pathway for dextromethorphan; consequently, coadministration of the two drugs increases dextromethorphan bioavailability to the level required for psychotherapeutic effects \([6, 7]\).

The biological pathways targeted by dextromethorphan (NMDA receptor binding, sigma-1 agonist activity, inhibition of the serotonin and norepinephrine transporters) and bupropion [norepinephrine and dopamine reuptake inhibition (with absence of monoamine oxidase inhibition and...
reuptake of serotonin]) have been implicated in depressive disorders [4]. Clinical evidence with antidepressants in several pharmacological classes that individually share the mechanisms of action of dextromethorphan and bupropion supports the development of the combination for depressive disorders [4].

The biological pathways targeted by dextromethorphan and bupropion have also been implicated in the neuropsychiatric symptoms of Alzheimer’s disease [4, 8]. Glutamate transmission is thought to play a role in the behavioural and cognitive changes in dementia, and agents that target sigma-1 (e.g., fluvoxamine, donepezil) have shown efficacy in patients with behavioural disorders and Alzheimer’s disease. Dextromethorphan (in the presence of metabolic inhibition) and drugs affecting serotonergic neurotransmission (including selective serotonin reuptake inhibitors) have shown efficacy in Alzheimer’s disease agitation in clinical trials [4, 9, 10]. Agitation is prevalent in up to 50% of patients with Alzheimer’s disease and is associated with accelerated cognitive decline, increased mortality risk and earlier admission to institutional care [9-13]; however, there are no approved pharmacological agents to treat behavioural and psychiatric symptoms that can develop in the moderate and severe stages of Alzheimer’s dementia [9, 10].

As well as use as an antidepressant [14], bupropion is approved as a treatment for smoking cessation [15] and is currently being investigated in combination with dextromethorphan for this indication [16].

Dextromethorphan/bupropion (AUVELITY™), a fixed-dose combination tablet, is the first oral NMDA receptor antagonist approved for use in MDD [7, 17]. Dextromethorphan/bupropion is approved for use in adults with MDD in the USA under the 505(b)(2) regulatory development pathway [18]. Each tablet of dextromethorphan/bupropion contains 45 mg dextromethorphan hydrobromide (equivalent to 32.98 mg dextromethorphan base) in an immediate-release formulation and 105 mg bupropion hydrochloride (equivalent to 91.14 mg bupropion base) in an extended-release formulation. The recommended starting dosage is one tablet once daily in the morning with or without food. After 3 days, the dosage should be increased to one tablet twice daily, taken at least 8 h apart (maximum dosage; should not exceed two doses within the same day) [7]. A reduced dosage of dextromethorphan/bupropion (one tablet once daily in the morning) is recommended for patients with moderate kidney impairment (eGFR 30–59 mL/min/1.73 m²), those known to be poor CYP2D6 metabolizers and where dextromethorphan/bupropion is coadministered with strong CYP2D6 inhibitors. Concomitant use with strong CYP2B6 inducers should be avoided. Dextromethorphan/bupropion can cause increased blood pressure and hypertension; blood pressure should be assessed regularly prior to and after initiating treatment [7].

As with other antidepressants, the US prescribing information for dextromethorphan/bupropion contains a boxed warning regarding an increased risk of suicidal thoughts and behaviours in paediatric and young adult patients; dextromethorphan/bupropion is not approved for use in paediatric patients. Dextromethorphan/bupropion has not been evaluated in patients aged ≥ 65 years in clinical studies of MDD [7]. Bupropion can cause seizures, and the risk is dose related; dextromethorphan/bupropion should be discontinued if seizures occur. Dextromethorphan/bupropion is contraindicated in patients with seizure disorders and in those with disorders that have an increased risk of seizure, including a current or prior diagnosis of bulimia or anorexia nervosa, or where there is abrupt discontinuation of alcohol, benzodiazepines, barbiturates or anticonvulsant drugs. Dextromethorphan/bupropion should not be administered with a monoamine oxidase inhibitor (MAOI) or within 14 days of stopping treatment with an MAOI, nor should an MAOI be used within 14 days of stopping treatment with dextromethorphan/bupropion [7]. The risk of serotonin syndrome is increased if dextromethorphan/bupropion is coadministered with serotonergic drugs including selective serotonin reuptake inhibitors or tricyclic antidepressants; dextromethorphan/bupropion and/or concomitant serotonergic drugs should be discontinued if this occurs. Other clinically important drug interactions with dextromethorphan/bupropion include increased risk of seizure when coadministered with drugs that lower seizure threshold, decreased plasma digoxin levels when coadministered with digoxin and CNS toxicity when coadministered with dopaminergic drugs [7].

Patients should be screened for a personal or family history of bipolar disorder, mania or hypomania, as these disorders can be activated by antidepressant treatment. Patients should be made aware that dextromethorphan/bupropion can induce psychosis or other neuropsychiatric reactions [7]. Based on animal studies, dextromethorphan/bupropion may cause foetal harm; treatment should be discontinued in pregnant females and an alternative treatment should be considered in females planning pregnancy. Breastfeeding is not recommended during treatment with dextromethorphan/bupropion. Dextromethorphan/bupropion should be avoided in patients with severe kidney or hepatic impairment [7].

1.1 Company Agreements and Patent Information

In December 2017, Axsome Therapeutics entered into a research collaboration with Duke University to evaluate the impact of dextromethorphan/bupropion on smoking cessation [16].
In December 2012, Axsome Therapeutics entered into an exclusive license agreement with Antecip Bioventures II LLC to develop, manufacture and commercialize Antecip's patents and applications related to the development of dextromethorphan/bupropion. In August 2015, the licensing agreement of Axsome Therapeutics and Antecip Bioventures was amended to update the schedule of patents and applications subject to the license agreement [18].

More than 50 issued US patents and more than 40 issued foreign patents covering dextromethorphan/bupropion have claims covering method of treatment, pharmaceutical composition, drug delivery, and pharmacokinetics with protection extending through 2034 and 2040 [18].

2 Scientific Summary

2.1 Pharmacodynamics

The mechanism of dextromethorphan in the treatment of MDD is unclear [7]. The antidepressant effects of NMDA receptor antagonism are thought to result from alterations to the inhibitory tone of interneurons and/or direct modulation of glutamate neurotransmission action on the postsynaptic NMDA receptor; sigma-1 receptor agonism is thought to modulate glutamate and monoamine signalling [6, 19]. In addition to NMDA receptor antagonism and sigma-1 receptor agonism, dextromethorphan is also an inhibitor of the serotonin transporter and the norepinephrine transporter [4]. The mechanism of action of bupropion in the treatment of MDD is also unclear; however, it may be related to noradrenergic and/or dopaminergic mechanisms [7]. Dextromethorphan and bupropion are also nicotinic acetylcholine receptor antagonists [4, 20] and have anti-inflammatory properties [4].

In the mouse tail suspension test (a model predictive of antidepressant activity) dextromethorphan reduced immobility time to the same extent as ketamine in a dose-dependent manner. Similar outcomes were seen in the mouse forced swim test; however, dextromethorphan did not increase locomotor activity in the mouse model, in contrast to ketamine [4]. In a rat model, dextromethorphan administration resulted in significant, dose-dependent reductions in nicotine self-administration [21].

At the maximum recommended dose (i.e. two tablets), dextromethorphan/bupropion does not prolong the QT interval to any clinically relevant extent [7].

2.2 Pharmacokinetics

When coadministered with bupropion, the pharmacokinetics of dextromethorphan are non-linear at steady state, with greater than proportional changes in exposure (AUC and C_{max}) with varying dextromethorphan doses (60-120 mg; 0.67–1.33 times the maximum recommended dose of dextromethorphan/bupropion) and less than dose-proportional changes with varying bupropion dose. 

![Chemical structure of dextromethorphan hydrobromide (left) and bupropion hydrochloride (right)](image-url)
doses (150–300 mg; 0.71–1.43 times the maximum recommended dose of dextromethorphan/bupropion) [7]. After repeat administration of dextromethorphan/bupropion, steady state plasma concentrations of the individual agents are achieved within 8 days. The accumulation ratios for dextromethorphan at steady state based on $C_{\text{max}}$ and AUC$_{12}$ are 20 and 32, respectively, when administered as dextromethorphan/bupropion and are 1.3 and 1.4, respectively, when administered without bupropion. The accumulation ratios for bupropion at steady state when administered as dextromethorphan/bupropion and are 1.1 and 1.5 ($C_{\text{max}}$ and AUC$_{12}$). The $C_{\text{max}}$ of dextromethorphan and bupropion was achieved at a median 3 h and 2 h, respectively, after administration of dextromethorphan/bupropion. Administration of dextromethorphan/bupropion with food had minimal effects on dextromethorphan and bupropion exposure ($C_{\text{max}}$ and AUC$_{12}$), and the combination can be taken with or without food. Dextromethorphan is $\approx 60$–$70\%$ bound to plasma protein and bupropion is 84% plasma protein bound [7].

Dextromethorphan is primarily metabolized by CYP2D6 to dextrorphan. Bupropion is extensively metabolized, and has three active metabolites (hydroxybupropion, threohydroxybupropion and erythrohydroxybupropion). Hydroxybupropion is primarily formed through CYP2B6 metabolism; CYP isoenzymes are not involved in the formation of the other active metabolites. A mouse model of antidepressant activity found that hydroxybupropion is half as potent as bupropion, while threohydroxybupropion and erythrohydroxybupropion are five times less potent than bupropion [7]. The $C_{\text{max}}$ of hydroxybupropion occurs $\approx 3$ h after administration of dextromethorphan/bupropion and is $\approx 14$ times higher than that of bupropion; AUC$_{12}$ is $\approx 19$ times higher than that of bupropion. The $C_{\text{max}}$ of threohydroxybupropion occurs $\approx 4$ h post-dose and is $\approx 5$ times higher than that of bupropion; AUC$_{12}$ is $\approx 7$ times higher than that of bupropion. The $C_{\text{max}}$ of erythrohydroxybupropion also occurs $\approx 4$ h post-dose; AUC$_{12}$ is 1.2 times higher than that of bupropion. The plasma protein binding of hydroxybupropion is similar to that of bupropion, while that of threohydroxybupropion is approximately half that of bupropion. A glycine conjugate of meta-chlorobenzoic acid, which is excreted as the major urinary metabolite, is formed through oxidation of the bupropion side chain [7].

The mean $t_{1/2}$ of dextromethorphan and bupropion after 8 days’ administration of dextromethorphan/bupropion was 22 h and 15 h, respectively [7]. In CYP2D6 extensive metabolizers, the mean $t_{1/2}$ of dextromethorphan was increased $\approx 3$-fold compared with dextromethorphan administered without bupropion. The apparent $t_{1/2}$ of hydroxybupropion, threohydroxybupropion and erythrohydroxybupropion is $\approx 35$ h, 33 h and 44 h, respectively. In CYP2D6 extensive metabolizers, $\approx 37$–$52\%$ of the administered dose of dextromethorphan is recovered in urine, with $< 2\%$ as the unchanged drug. In contrast, in CYP2D6 poor metabolizers, $\approx 45$–$83\%$ of the administered dose is recovered in the urine, with $\approx 26\%$ as the unchanged drug. After oral administration of a 200 mg dose of $^{14}$C-bupropion, 87% of the radioactive dose was recovered in urine and 10% in faeces, predominantly as metabolites (0.5% of the oral dose was excreted as the unchanged drug) [7].

Exposure to dextromethorphan/bupropion is increased by kidney impairment and CYP2D6 poor metabolizer status; dosage reductions are required in patients with moderate kidney impairment and in CYP2D6 poor metabolizers [dosage adjustments are not required in patients with mild or moderate hepatic impairment (Child-Pugh A and Child-Pugh B)] [7]. The pharmacokinetics of dextromethorphan/bupropion has not been studied in patients with severe kidney (eGFR 15–29 mL/min/1.73 m$^3$) or hepatic (Child-Pugh C) impairment and use of dextromethorphan/bupropion in these patients is not recommended [7].

At therapeutically relevant concentrations in in vitro studies, dextromethorphan is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 or an inducer of CYP1A2, CYP3A4, or CYP2B6. Dextromethorphan is a substrate of P-glycoprotein but does not inhibit transporters. Bupropion, hydroxybupropion, threohydroxybupropion and erythrohydroxybupropion are inhibitors of CYP2D6 in vitro.

Concomitant use of dextromethorphan/bupropion with strong CYP2D6 inhibitors increases plasma concentrations of dextromethorphan; dosage adjustment of dextromethorphan/bupropion is required during coadministration and patients should be monitored for adverse reactions potentially attributable to dextromethorphan. Concomitant use of dextromethorphan/bupropion with strong CYP2B6 inducers decreases plasma concentrations of dextromethorphan and bupropion and may decrease efficacy; avoid coadministration of dextromethorphan/bupropion and strong inducers of CYP2B6 and consider alternative agents if needed. Coadministration of dextromethorphan/bupropion with drugs that are metabolized by CYP2D6 can increase the exposures of drugs that are substrates of CYP2D6; a decrease in the dose of these drugs may be required, particularly if they have a narrow therapeutic index. Drugs that require metabolic activation by CYP2D6 to be effective could have reduced efficacy when administered concomitantly with dextromethorphan/bupropion and increased dosages of drugs that require activation by CYP2D6 may be required [7].

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Dextromethorphan/Bupropion: First Approval

Features and properties of dextromethorphan/bupropion

Alternative names
AUVELITY; AXS-05; Dextromethorphan HBr-bupropion HCl

Class
Anti-inflammatories; Antidementias; Antidepressants; Behavioural disorder therapies; Morphinans; Propionophenones; Small molecules; Smoking cessation therapies

Mechanism of action
Dextromethorphan: NMDA receptor antagonists; sigma-1 receptor agonists; serotonin plasma membrane transport protein inhibitors; norepinephrine plasma membrane transport protein inhibitors; nicotinic receptor antagonists;
Bupropion: dopamine reuptake inhibitors; norepinephrine reuptake inhibitors; nicotinic receptor antagonists

Formulation
Fixed-dose combination tablet

Route of administration
Oral

Pharmacodynamics
Mechanism of dextromethorphan in MDD is unclear; NMDA receptor antagonism antidepressant effects may result from modulation of glutamate signalling; sigma-1 receptor agonism modulates glutamate and monoamine signalling. Animal models indicate that dextromethorphan has antidepressant activity similar to that of the NMDA receptor antagonist ketamine
Mechanism of bupropion in the treatment of MDD is unclear; it may be related to noradrenergic and/or dopaminergic mechanisms.

Pharmacokinetics
Bupropion increases plasma dextromethorphan concentrations by inhibiting metabolism
At steady state (after 8 days’ administration of dextromethorphan/bupropion), accumulation ratios for dextromethorphan based on Cmax and AUC12 are 20 and 32, respectively, compared with 1.3 and 1.4 when administered without bupropion
Peak plasma concentrations of dextromethorphan and bupropion are achieved at a median 3 h and 2 h
Steady state mean t1/2 of dextromethorphan is 22 h and that of bupropion is 15 h

Adverse events
Most frequent (incidence ≥ 5% and > twice as frequent as placebo)
Dizziness, headache, diarrhoea, somnolence, dry mouth, sexual dysfunction, hyperhidrosis

ATC codes
WHO ATC code
N07X-X59 (Dextromethorphan, combinations); N06A-X12 (Bupropion); N06B (Psychostimulants, agents used for ADHD and nootropics)

EphMRA ATC code
N5A (Antipsychotics); N6A9 (Antidepressants, all others); N6B (Psychostimulants)

Chemical name
(1S,9S,10S)-4-methoxy-17-methyl-17-azatetracyclo[7.5.3.01,10.02,7]heptadeca-2(7),3,5-triene;hydrobromide / 2-(tert-butylamino)-1-(3-chlorophenyl)propan-1-one;hydrochloride

2.3 Therapeutic Trials

2.3.1 In Major Depressive Disorder

2.3.1.1 Phase 3 Trials
Treatment with dextromethorphan/bupropion significantly improved depressive symptoms in patients with MDD in the 6-week, randomized, double-blind, placebo-controlled, phase 3 GEMINI trial (NCT04019704) [6]. The least squares mean (LSM) change from baseline to week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score (primary endpoint) was significantly greater in dextromethorphan/bupropion recipients (n = 156) than in placebo recipients (n = 162) [−15.9 vs −12.0; LSM difference −3.87; 95% CI −1.39 to −6.36; p = 0.002] [6]. Dextromethorphan/bupropion was more effective than placebo in improving MADRS at week 1 (LSM change from baseline in MADRS total score of −7.20 vs −4.97; LSM difference −2.23; 95% CI −3.86 to −3.86; p = 0.007), week 2 (LSM change from baseline in MADRS total score of −11.09 vs −7.66; LSM difference −3.44; 95% CI −1.40 to −5.47; p < 0.001) and at subsequent assessments [i.e. week 3 (p < 0.001), week 4 (p < 0.001) and week 6 (p = 0.002)]; changes at weeks 1 and 2 were prespecified key secondary endpoints [7]. Clinical response (≥ 50% improvement in MADRS total score) was seen in significantly more dextromethorphan/bupropion than placebo recipients at all assessments; at week 6 more than half of the dextromethorphan/bupropion recipients had achieved a clinical response (54% vs 34.0%; p < 0.001). Remission (MADRS total score ≤10) was evident in significantly more dextromethorphan/bupropion...
bupropion than placebo recipients from week 2 onwards (16.9% vs 7.5%; p = 0.013); at week 6, the remission rate in the dextromethorphan/bupropion group was more than double that in the placebo group (39.5% vs 17.3%; p < 0.001) [6]. Improvements in Clinician Global Impression-Improvement (CGI-I) scores paralleled improvements in MADRS and favoured dextromethorphan/bupropion; for instance, at week 6, a marked/moderate improvement was seen in 57.6% of dextromethorphan/bupropion recipients versus 43.0% of placebo recipients (p = 0.016) and the LSM change from baseline to week 6 in Clinical Global Impression-Severity (CGI-S) score was greater with dextromethorphan/bupropion than with placebo (– 1.69 vs – 1.29; LSM difference – 0.48; 95% CI – 0.48 to – 0.79; p = 0.002). In GEMINI, eligible patients with a DSM-5 diagnosis of MDD, a MADRS score ≥ 25 and a CGI-S score ≥ 4 were randomized to either dextromethorphan/bupropion or placebo once daily for 3 days, then twice daily for the remainder of the trial. Patients with TRD were excluded from the trial. At baseline, the mean MADRS total score was 33.6 in the dextromethorphan/bupropion group and 33.2 in the placebo group and the CGI-S score was 4.6 in each group [6].

Dextromethorphan/bupropion was effective in rapidly improving symptoms of depression in patients with MDD, including in those with TRD or suicidal ideation in the up to 12-month open-label, phase 3 COMET trial (NCT04039022) [22] and its phase 2 sub-studies (COMET-TRD [23], COMET-AU [24] and COMET-SI [25]). COMET (n = 876) included patients who had either participated in an earlier study of dextromethorphan/bupropion or were newly enrolled [22]. In newly enrolled patients (n = 609), the mean change in MADRS total score from baseline to week 6 of treatment with dextromethorphan/bupropion twice daily was substantial (– 21.1); reductions were seen as early as week 1 (– 9.1) and week 2 (– 14.0) of treatment and were maintained at month 12 (– 23.0). By week 6 of treatment, 73.2% of patients had a clinical response, increasing to 82.8% at month 12. By week 6, 52.5% of patients were in remission, increasing to 69.0% at month 12. CGI-I scores correlated with MADRS scores, with 83.1% of patients showing a response (marked or moderate improvement on the CGI-I scale) at week 6 and 93.1% at month 12. Functioning [assessed by the Sheehan Disability Scale (SDS)], improved rapidly with dextromethorphan/bupropion administration; a clinical response (SDS score of ≤ 12) was seen in 55.1% of patients at week 2, 70.7% of patients at week 6 and 75.9% of patients at month 12 [22]. Improvements in MADRS total score and the proportions of patients achieving a MADRS clinical response or clinical remission in the COMET-AU (n = 115; patients had ongoing symptoms despite previous treatment with one antidepressant) and COMET-TRD (n = 70; patients had received ≥ 2 prior antidepressants in the current major depressive episode) sub-studies were consistent with outcomes in the overall COMET population and were similarly rapid and durable [23, 24]. In the COMET-SI trial [n = 37; patients had a mean MADRS-Suicidal Ideation (SI) score of 3.4 at baseline], a rapid reduction in suicidal ideation (i.e., a reduction in the MADRS-SI score) was observed with dextromethorphan/bupropion from week 1 of treatment. At week 4, the mean MADRS-SI score had reduced from baseline by 2.8 and resolution of suicidal ideation (MADRS-SI score ≤ 1) was seen in 78% of patients [25]. At baseline in COMET, for newly enrolled patients the mean MADRS total score was 32.7 and the mean SDS total score was 20.0. Eligible patients had a DSM-5 diagnosis of MDD and a MADRS total score ≥ 25 [22].

Although there was no significant difference between the dextromethorphan/bupropion and bupropion treatment groups in terms of the primary endpoint (mean change in MADRS total score from baseline at week 6) in the phase 3 STRIDE-1 trial (NCT02741791) in 312 patients with TRD [26], significant between-group differences were seen in mean MADRS total score changes at week 1 and week 2 and the mean MADRS total score averaged over the 6-week treatment period (key secondary endpoints). At 6 weeks, in the mITT population the mean reduction from baseline in MADRS total score in the dextromethorphan/bupropion arm (n = 154) was 11.6 and that in the bupropion arm (n = 155) was 9.4. Mean reductions from baseline in MADRS total score favoured dextromethorphan/bupropion over bupropion at week 1 (5.2 vs 3.6; p = 0.02), week 2 (8.0 vs 6.1; p = 0.035) and when averaged over the 6-week period (8.6 vs 6.7; p = 0.031) [26]. In STRIDE-1, patients with TRD (defined as treatment failure with two or more prior antidepressants, including a prospective failure of bupropion during an open-label lead-in period) were treated with sustained release bupropion 150 mg twice daily in a 6-week lead-in period. Those who failed to respond to bupropion were then randomized to treatment with bupropion at the same daily dose or dextromethorphan/bupropion (45 mg/105 mg) twice daily for 6 weeks [26].
### Key clinical trials of dextromethorphan/bupropion (AXS-05)

| Drug(s)     | Indication     | Phase | Status      | Location(s)   | Sponsor/Collaborator                        | Identifier                  |
|-------------|----------------|-------|-------------|---------------|---------------------------------------------|-----------------------------|
| AXS-05, placebo | MDD           | 3     | Completed   | USA           | Axsome Therapeutics                         | NCT04019704; GEMINI; AXS-05-MDD-301 |
| AXS-05      | MDD            | 3     | Completed   | USA           | Axsome Therapeutics                         | NCT04039022; COMET; AXS-05-303 |
| AXS-05, bupropion SR | TRD       | 3     | Completed   | USA           | Axsome Therapeutics                         | NCT02741791; STRIDE-1; AXS-05-301 |
| AXS-05, bupropion SR | MDD       | 2     | Completed   | USA           | Axsome Therapeutics                         | NCT03595579; ASCEND; AXS-05-MDD-201 |
| AXS-05, placebo | MDD           | 2     | Completed   | USA           | Axsome Therapeutics                         | NCT04608396; MERIT; AXS-05-TRD-201 |
| AXS-05      | TRD            | 2     | Completed   | USA           | Axsome Therapeutics                         | NCT04634669; EVOLVE; AXS-05-TRD-202 |
| AXS-05, bupropion SR | TRD       | 2     | Completed   | USA           | Axsome Therapeutics                         | NCT04971291; TARGET; AXS-05-TRD-203 |
| AXS-05, placebo | ADA           | 3     | Recruiting  | USA           | Axsome Therapeutics                         | ADVANCE-2                   |
| AXS-05      | ADA            | 3     | Ongoing     | USA           | Axsome Therapeutics                         | NCT04947553; AXS-05-AD-303  |
| AXS-05, placebo | ADA           | 3     | Ongoing     | USA, Canada   | Axsome Therapeutics                         | NCT04797715; ACCORD; AXS-05-AD-302 |
| AXS-05, placebo, bupropion | 2/3     | Completed | USA, Australia | Axsome Therapeutics | NCT03226522; ADVANCE-1; AXS-05-AD-301          |
| AXS-05, bupropion SR 105 mg | Smoking cessation | 2     | Completed   | USA           | Duke University, Axsome Therapeutics         | NCT03471767                  |

**ADA** Alzheimer’s disease agitation, **MDD** major depressive disorder, **SR** sustained release, **TRD** treatment-resistant depression

*COMET includes three phase 2 substudies: COMET-TRD (in TRD), COMET-AU (in antidepressant unresponsive MDD) and COMET-SI (in MDD with suicidal ideation)*

### 2.3.1.2 Phase 2 Trials

Treatment with dextromethorphan/bupropion significantly improved depressive symptoms in patients with MDD in the 6-week, randomized, double-blind, active-comparator-controlled, phase 2 ASCEND trial (NCT03595579) [27]. Dextromethorphan/bupropion recipients ($n = 43$) showed a significantly greater overall treatment effect on the MADRS total score (LSM change from baseline over weeks 1–6; primary endpoint) than bupropion recipients ($n = 37$) [−13.7 vs −8.8; LSM difference −4.9; 95% CI −3.1 to −6.8; Cohen’s d −1.2; $p < 0.001$] [27]. A significant between-group difference favouring dextromethorphan/bupropion was seen at week 2 (LSM difference −4.7; 95% CI −0.6 to −8.8; vs $p = 0.024$) and at all subsequent assessments; at week 6, the mean change in MADRS total score from baseline was −17.3 in the dextromethorphan/bupropion arm compared with −12.1 in the bupropion arm (LSM difference −5.2; 95% CI −1.1 to −9.3; Cohen’s d = 0.6; $p = 0.013$). At week 6, a clinical response was seen in 60.5% of dextromethorphan/bupropion recipients versus 40.5% of bupropion recipients, but this difference was not statistically significant. Remission rates were significantly greater with dextromethorphan/bupropion than bupropion from week 2 (25.6% vs 2.7%; $p = 0.004$) and at all subsequent timepoints; at week 6, 46.5% of dextromethorphan/bupropion recipients achieved remission compared with 16.2% of bupropion recipients ($p = 0.004$). CGI-S scores correlated with MADRS total scores; the overall treatment effect (mean improvement from baseline over weeks 1–6) on the CGI-S was −1.6 in the dextromethorphan/bupropion group versus −1.0 in the bupropion group (LSM difference −0.5; 95% CI −0.3 to −0.8; $p < 0.001$). Significant between-group differences were seen from week 2 of treatment onwards. In ASCEND, patients with a DSM-5 diagnosis of MDD were randomized to either dextromethorphan/bupropion or sustained release bupropion 105 mg once daily for 3 days, then twice daily for the remainder of the trial. At baseline, the mean MADRS total score was 32 [27].

Dextromethorphan/bupropion was effective in rapidly improving symptoms of depression in patients with MDD in the up to 15-month, open-label, phase 2 EVOLVE trial (NCT04634669), which included patients who had either participated in an earlier study of dextromethorphan/bupropion ($n = 35$) or were directly enrolled ($n = 146$) [28, 29]. In the directly enrolled population, the mean change in MADRS total score from baseline (score of 32.2) at week 6 of treatment with dextromethorphan/bupropion twice daily
was significant (-20.4; \( p < 0.001 \)) [primary timepoint], and significant reductions were seen as early as week 1 (-9.1; \( p < 0.001 \)) and week 2 (-13.3; \( p < 0.001 \)) of treatment [28]. By week 6 of treatment, 74.2% of patients had a clinical response; clinical responses were evident as early as weeks 1 and 2 (in 17.7% and 39.0% of patients, respectively). By week 6, 46% of patients were in remission, increasing from 5.7% and 16.2% of patients at weeks 1 and 2. Improvements in MADRS total score were sustained through month 12. CGI-S scores correlated with MADRS total scores, with 71.0% of patients showing a response at week 6 and 79.5% at month 12. Functioning (assessed by SDS), improved rapidly with dextromethorphan/bupropion administration; significant reductions in SDS total scores were seen at weeks 1, 2 and 6 (all \( p < 0.001 \) vs baseline) and 39.5% of patients achieved remission (score of \( \leq 6 \)) at week 6. Improvements in SDS were sustained through month 12 [28]. Hamilton Anxiety Rating Scale (HAM-A) scores also improved significantly (\( p < 0.001 \)) from baseline as early as week 1 and were durable through month 12. Response (\( \geq 50\% \) improvement) and remission (HAM-A score \( \leq 7 \)) rates increased during treatment with dextromethorphan/bupropion and were durable through month 12 (77.1% of patients showed a response and 78.3% achieved remission at month 12) [29]. Eligible patients in EVOLVE had a DSM-5 diagnosis of MDD, a MADRS total score \( \geq 25 \) and had received \( \geq 1 \) prior antidepressant in the current major depressive episode [28, 29].

Treatment with dextromethorphan/bupropion was effective in delaying relapse of depressive symptoms in patients with TRD who were in stable remission in the randomized, double-blind, placebo-controlled, phase 2 MERIT trial (NCT04608396) [30]. The time to relapse of depressive symptoms was significantly delayed with dextromethorphan/bupropion (\( n = 22 \)) compared with placebo (\( n = 22 \)) \( [p = 0.002; \) primary endpoint]. No relapses occurred in the dextromethorphan/bupropion treatment arm during double-blind treatment compared with 36.4% of placebo recipients (\( p = 0.004 \)) [30]. The MERIT trial enrolled patients with TRD who had experienced a stable remission (defined as at least two consecutive MADRS total scores of \( \leq 12 \), separated by at least 4 weeks) after up to 12 months of open-label treatment with dextromethorphan/bupropion twice daily in the phase 3 COMET trial (NCT04039022). Patients were randomized to either continue dextromethorphan/bupropion or switch to placebo for up to 52 weeks or until a relapse of depressive symptoms occurred. Relapse was defined in the study by one or more of the following: MADRS total score \( \geq 18 \) for two consecutive assessments; a \( \geq 2 \)-point increase from randomization in CGI-S score, with a minimum CGI-S score of 4, for two consecutive assessments; hospitalization due to worsening of depression or risk of suicide; investigator determination of relapse or need for additional antidepressant or treatment switch [30].

### 2.3.2 Alzheimer's Disease Agitation

Treatment with dextromethorphan/bupropion was effective in reducing agitation symptoms in Alzheimer’s disease in the 5-week randomized, double-blind, placebo- and active comparator-controlled phase 2/3 ADVANCE-1 trial (NCT03226522) [8]. A significantly greater change from baseline in the Cohen-Mansfield Agitation Inventory (CMAI) total score at week 5 (primary endpoint) was seen with dextromethorphan/bupropion (\( n = 152 \)) than with bupropion (\( n = 49 \)) or placebo (\( n = 156 \)) \(-15.4 \text{ vs } -10.0 \text{ and } -11.5; \ p < 0.001 \); \( p < 0.01 \) vs bupropion and \( p = 0.01 \) vs placebo]. A greater reduction in the CMAI total score from baseline with dextromethorphan/bupropion compared with placebo was first seen at week 3 of treatment (\( p = 0.007 \)). A clinical response (defined as reduction of \( \geq 30\% \) from baseline in CMAI) was evident in significantly more dextromethorphan/bupropion than placebo recipients at week 5 (73.2% vs 57.1%; \ p < 0.005 \) [8]. Eligible patients in ADVANCE-1 received either a titrated dose of dextromethorphan/bupropion (week 1: dextromethorphan 30 mg/bupropion 105 mg once daily; week 2 dextromethorphan 30 mg/bupropion 105 mg twice daily; weeks 3–5: dextromethorphan 45 mg/bupropion 105 mg twice daily) \( n = 152 \) or sustained release bupropion (week 1: bupropion 105 mg once daily; weeks 2–5: bupropion 105 mg twice daily \( n = 49 \) or matching placebo \( n = 156 \)) [8]. Baseline characteristics were similar across the three treatment arms. The mean age at study entry was 75.1–76.4 years, 82.1–89.5% were White and the mean baseline CMAI score was 59.4–66.1. All trial participants were community dwelling and had a diagnosis of probable Alzheimer’s disease (based on 2011 NIA-AA criteria) and a diagnosis of agitation (based on the IPA provisional definition of agitation) [8].

### 2.3.3 Smoking Cessation

Dextromethorphan/bupropion was significantly more effective than bupropion as a smoking cessation treatment in a phase 2 randomized, double-blind trial (NCT03471767) [31]. In this trial in 58 adult smokers who were treated with either dextromethorphan/bupropion (\( n = 31 \)) or sustained release bupropion 105 mg (\( n = 27 \)) twice daily, those in the dextromethorphan/bupropion arm had a 25% greater reduction in the average number of cigarettes smoked per day over the 3-week assessment period (primary endpoint) compared with those in the bupropion arm (mean reduction of 8.49 vs 6.79 cigarettes/day; \ p = 0.0016 \). A > 50% reduction in expired carbon monoxide levels (a biochemical marker of smoking intensity) was observed in 52.0% of
Dextromethorphan/bupropion recipients and 30.4% of bupropion recipients. Treatment adherence was similar in either study arm for both the morning (97.1% vs 96.6%) and evening (76.3% vs 79.4%) doses. At baseline, the average number of cigarettes smoked/day was 20 in the dextromethorphan/bupropion arm and 17 in the bupropion arm [31].

2.4 Adverse Events

Dextromethorphan/bupropion was generally well-tolerated in clinical trials. In the phase 3 GEMINI trial in patients with MDD (n = 162 dextromethorphan/bupropion recipients and 164 placebo recipients) [6], adverse events were reported in 61.7% of dextromethorphan/bupropion recipients and 45.1% of placebo recipients. A serious adverse event was reported in one patient (in the dextromethorphan/bupropion arm), but it was not considered to be related to treatment [6]. The most common (incidence ≥ 5% for dextromethorphan/bupropion and more than twice as frequently as placebo) adverse reactions were dizziness (16% vs 6% with placebo), headache (8% vs 4%), diarrhoea (7% vs 3%), somnolence (7% vs 3%), dry mouth (6% vs 2%), sexual dysfunction (6% vs 0%), and hyperhidrosis (5% vs 0%) [7]. Few patients (4% of dextromethorphan/bupropion recipients and 0% of placebo recipients) discontinued GEMINI because of an adverse reaction. The adverse reaction that led to study discontinuation in ≥1% of dextromethorphan/bupropion recipients was anxiety (2%) [7]. The adverse events profile of dextromethorphan/bupropion seen in longer term, open-label studies in patients with MDD (COMET) [22] or TRD (EVOLVE) [28] was consistent with that seen in GEMINI [6].

In the phase 2/3 ADVANCE-1 trial in patients with Alzheimer’s disease agitation, TEAEs were reported in 44.0% of dextromethorphan/bupropion recipients, 61.2% of bupropion recipients and 32.9% of placebo recipients [8]. The most common TEAEs in the dextromethorphan/bupropion arm were somnolence (8.2% vs 4.1% and 3.2% in the bupropion and placebo arms) dizziness (6.3% vs 10.2% and 3.2%), and diarrhoea (4.4% vs 6.1% and 4.4%) [8].

In the phase 2 smoking cessation trial in which dextromethorphan/bupropion was compared with bupropion, the incidences of the most frequent adverse events (headache, dry mouth and insomnia/vivid dreams) in both treatment arms were comparable [31].

2.5 Ongoing Clinical Trials

Three phase 3 clinical trials of dextromethorphan/bupropion in the treatment of Alzheimer’s disease agitation are ongoing: the randomized, double-blind, placebo-controlled ACCORD trial (NCT04797715), an open-label safety trial (NCT04947553) and the randomized, double-blind, placebo-controlled ADVANCE-2 trial, which has recently enrolled the first patient [32]. Based on discussions with the US FDA following the completion of a phase 2 trial of dextromethorphan/bupropion in smoking cessation, a phase 2/3 trial is planned [18].

3 Current Status

Dextromethorphan/bupropion received its first approval on 18 August 2022 for the treatment of MDD in adults in the USA [7, 17].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40263-022-00968-4.

Declarations

Funding The preparation of this review was not supported by any external funding.

Authorship and conflict of interest During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the authors on the basis of scientific completeness and accuracy. Susan J. Keam is a contracted employee of Adis International Ltd/Springer Nature, and declares no relevant conflicts of interest. All authors contributed to the review and are responsible for the article content.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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