Perception Mapping of Clinicians to Understand an Overview of Dextromethorphan and Bupropion in the Management of Depression

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Introduction

Major Depressive Disorder (MDD) is a pervasive and debilitating mental health condition that significantly affects millions of individuals worldwide. Characterized by persistent low mood, anhedonia, cognitive impairments, and a range of physical symptoms, MDD imposes substantial personal, societal, and economic burdens. According to the World Health Organization (WHO), MDD is among the leading causes of disability globally, with an estimated lifetime prevalence of 15% (1). The disorder not only disrupts the quality of life but also increases the risk of comorbid conditions, including cardiovascular disease, diabetes, and substance abuse disorders (2).

The pathophysiology of MDD is complex and multifactorial, involving genetic, neurobiological, and environmental factors. Dysregulation of monoaminergic neurotransmitters—serotonin, norepinephrine, and dopamine—has long been considered central to its etiology. However, emerging research highlights the importance of additional pathways, including glutamatergic signaling, inflammation, and neuroplasticity deficits (3, 4). These insights underscore the limitations of traditional antidepressants, which primarily target monoaminergic systems, and reveal the need for therapies with novel mechanisms of action

Limitations of Current Treatments

For decades, the treatment of MDD has relied heavily on selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and other classes of antidepressants such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). While these therapies provide symptom relief for many, approximately one-third of patients fail to respond adequately, a condition referred to as treatment-resistant depression (TRD) (5). Even among those who respond, the latency of therapeutic onset—typically weeks to months—poses a significant challenge, especially for patients with severe symptoms or suicidal ideation (6). Furthermore, side effects such as sexual dysfunction, weight gain, and sedation contribute to poor adherence, further limiting treatment efficacy (7).

In recent years, novel therapies have emerged to address these limitations. Ketamine, an NMDA receptor antagonist, demonstrated rapid antidepressant effects, inspiring interest in glutamatergic pathways as therapeutic targets (8). However, ketamine's use is constrained by its dissociative side effects, potential for misuse, and need for intravenous administration. Against this backdrop, the combination of Dextromethorphan and Bupropion represents a promising new approach to MDD treatment.

Dextromethorphan and Bupropion: Mechanism of Action

Dextromethorphan, traditionally known as a cough suppressant, has garnered attention for its antidepressant properties. It acts primarily as an NMDA receptor antagonist, modulating glutamatergic neurotransmission and promoting neuroplasticity (9). Additionally, Dextromethorphan exhibits sigma-1 receptor agonism, which enhances neuroprotection and modulates mood-regulating pathways (10). These mechanisms contribute to its rapid antidepressant effects, akin to ketamine, but with a more favorable safety profile.

Bupropion, a norepinephrine-dopamine reuptake inhibitor (NDRI), complements Dextromethorphan by enhancing dopaminergic and noradrenergic neurotransmission. This dual action not only amplifies the therapeutic effects but also mitigates the risk of serotonin syndrome, a potential complication of monoaminergic therapies (11). By targeting multiple pathways implicated in MDD, the combination offers a multimodal mechanism of action that sets it apart from existing treatments.

Clinical Evidence

Several clinical trials have demonstrated the efficacy and safety of the Dextromethorphan-Bupropion combination in treating MDD. In a pivotal Phase 3 trial, the combination showed statistically significant improvements in depressive symptoms compared to placebo, with rapid onset of action observed within one week of treatment initiation (12). Patients reported substantial reductions in core symptoms, including mood disturbances, anhedonia, and cognitive impairments. Importantly, the combination was well-tolerated, with a low incidence of adverse effects such as dizziness and dry mouth (13).

Another notable advantage of this therapy is its applicability to diverse patient populations, including those with TRD or comorbidities that preclude the use of vasoconstrictive agents like Triptans. Unlike ketamine or electroconvulsive therapy (ECT), the combination can be administered orally, enhancing its feasibility for widespread use (14).

Addressing Unmet Needs in MDD Treatment

The introduction of the Dextromethorphan-Bupropion combination marks a significant advancement in the treatment landscape of MDD. However, several questions remain unanswered regarding its real-world effectiveness, safety, and acceptability. Clinical trials, while rigorous, often involve controlled settings that may not fully capture the complexities of routine practice. For instance, patients in clinical trials are typically screened for specific characteristics, which may not reflect the heterogeneity of real-world populations (15).

Rationale of The Study

MDD continues to pose a significant global health challenge, with many patients experiencing inadequate relief from traditional antidepressant therapies. The need for innovative treatments is underscored by the growing recognition of the limitations of monoaminergic-based approaches. The Dextromethorphan-Bupropion combination represents a paradigm shift in MDD management by targeting glutamatergic and dopaminergic systems, offering potential benefits for patients with TRD or partial responders to existing treatments.

While clinical trials have demonstrated its efficacy and safety, real-world data on its use are crucial to understanding its broader applicability, identifying patient subgroups most likely to benefit, and addressing barriers to adoption. This study seeks to provide these insights, contributing to evidence-based advancements in MDD treatment.

Study Objective

The primary objective of this study is to evaluate the real-world usage, effectiveness, and safety of the Dextromethorphan-Bupropion combination therapy for MDD treatment. Specifically, the study aims to:

- **Assess Clinician Awareness and Familiarity:** Evaluate healthcare providers' understanding of the novel mechanism of action and therapeutic potential of this combination.
- **Evaluate Prescribing Patterns:** Identify how frequently and under what conditions this therapy is prescribed compared to traditional antidepressants.
- **Analyze Effectiveness and Safety:** Assess clinicians' perceptions of the combination's efficacy in alleviating depressive symptoms and its safety profile in clinical practice.
- **Explore Patient Demographics:** Determine which patient populations are most prescribed this therapy, including those with TRD or specific comorbidities.
- **Identify Barriers and Opportunities:** Investigate challenges to its adoption, such as concerns about cost, side effects, or clinical guidelines, and identify opportunities for broader integration.

Methods

The study employed a survey-based design targeting healthcare professionals managing patients with Major Depressive Disorder (MDD). A structured 15-question was developed to explore clinicians' clinical experience, prescribing patterns, perceived effectiveness, safety, and patient demographics associated with the use of Dextromethorphan and Bupropion combination therapy.

- **Survey Design:** A structured questionnaire was developed to address key areas such as clinician familiarity with the combination therapy, prescribing patterns, perceived effectiveness, safety, and patient demographics. Experts in psychiatry reviewed and validated the questionnaire to ensure relevance and accuracy.

- **Participant Recruitment:** The survey was distributed to a targeted sample of psychiatrists, general practitioners, and mental health specialists across diverse regions. Participants were selected based on their experience in treating MDD and their willingness to provide insights into the use of the Dextromethorphan-Bupropion combination.

- **Data Collection:** Responses were collected over a three-month period through physical and electronic means. The data were anonymized to ensure confidentiality, promoting honest and unbiased feedback from participants.

- **Data Analysis:** Quantitative methods were used to analyze the collected data, identifying trends and patterns in prescribing practices, effectiveness ratings, and safety concerns. Descriptive statistics summarized the data, while comparative analyses evaluated variations based on clinician specialty, patient demographics, and treatment settings.

- **Ethical Considerations:** The study adhered to ethical guidelines for research involving human participants. Informed consent was obtained from all participants, and confidentiality was maintained throughout the study.

Results

A total of 88 HCPs participated in the survey. Below is the summary of the responses.

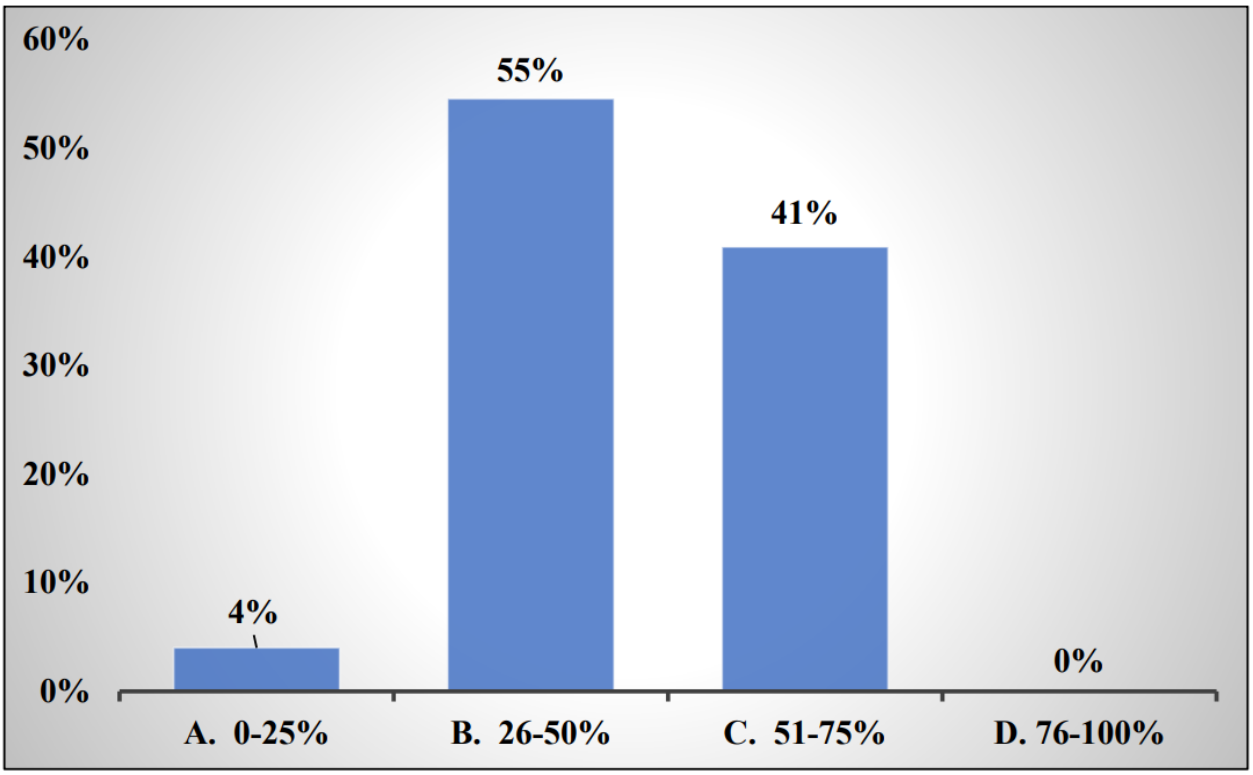
1. In your clinical practice, of the total OPD patient load what percentage of patients do you encounter with depression?

A. 0-25%

B. 26-50%

C. 51-75%

D. 76-100%



- 55% of clinicians encounter depression in 26-50% of their patients.
- 41% report that 51-75% of their patients suffer from depression.
- 4% encounter depression in 0-25% of their patients.
- 0% report encountering depression in 76-100% of their patients.

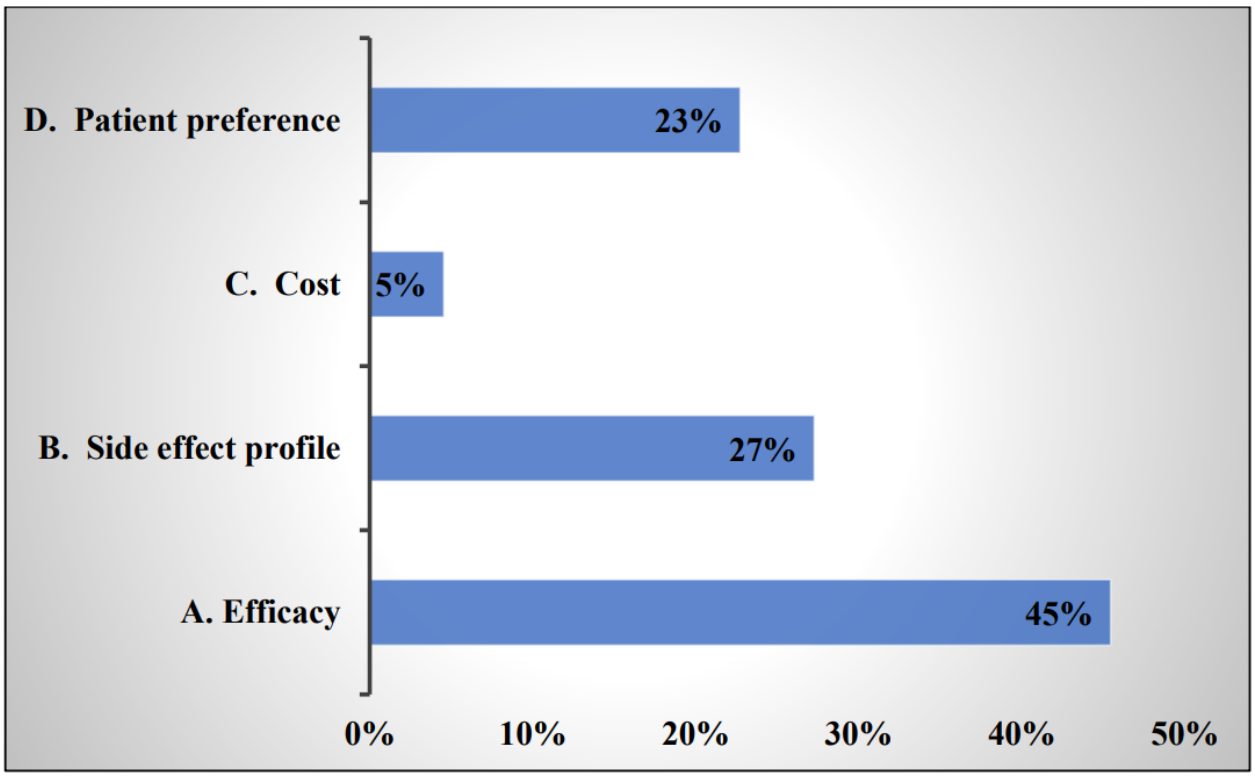
2. **In your clinical practice, what is your primary consideration when choosing between antidepressants for treating depression?**

A. Efficacy

B. Side effect profile

C. Cost

D. Patient preference



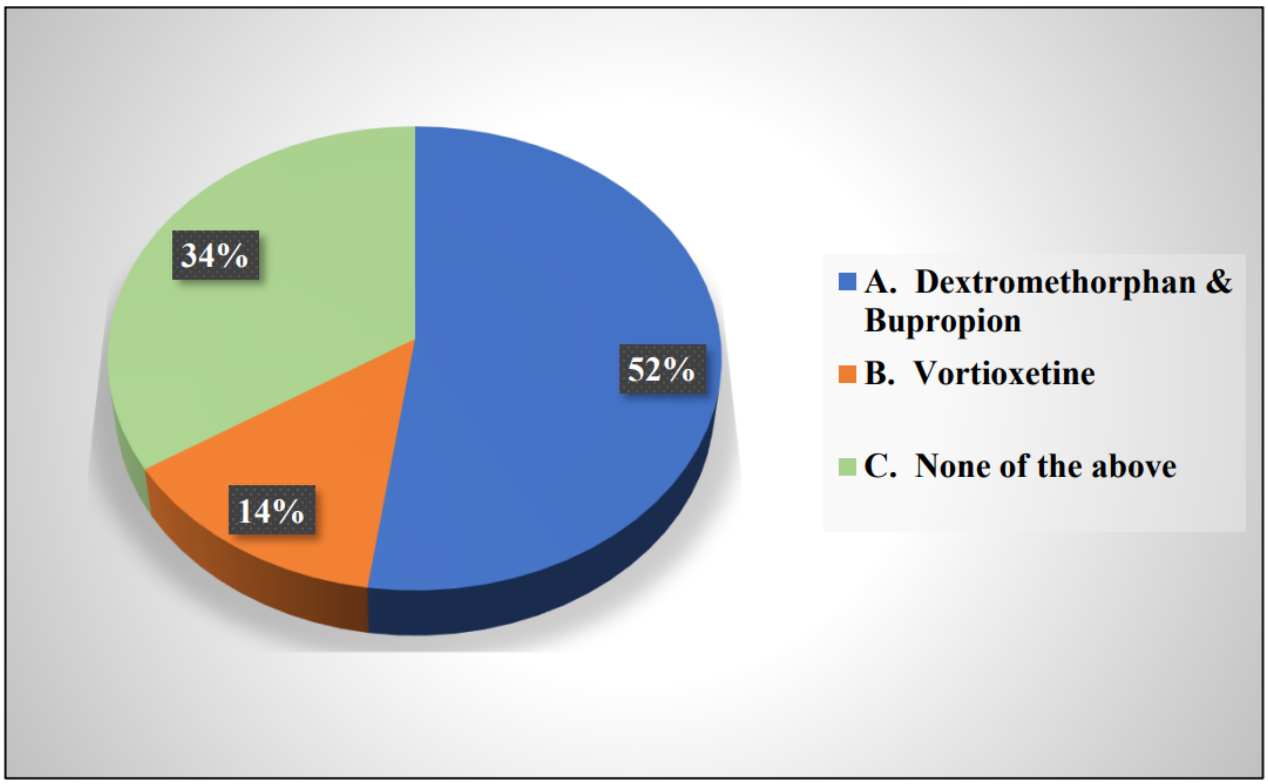
- 45% of clinicians prioritize efficacy when selecting antidepressants, focusing on achieving the best clinical outcomes.
- 27% of clinicians consider the side effect profile as the key factor to ensure safety and tolerability for patients.
- 23% of clinicians emphasize patient preference, reflecting the importance of shared decision-making in treatment.
- Only 5% of clinicians cite cost as their primary consideration, indicating that financial factors are less influential in decision-making.

3. In your clinical practice, which medication do you prescribe more frequently for depression?

A. Dextromethorphan & Bupropion

B. Vortioxetine

C. None of the above



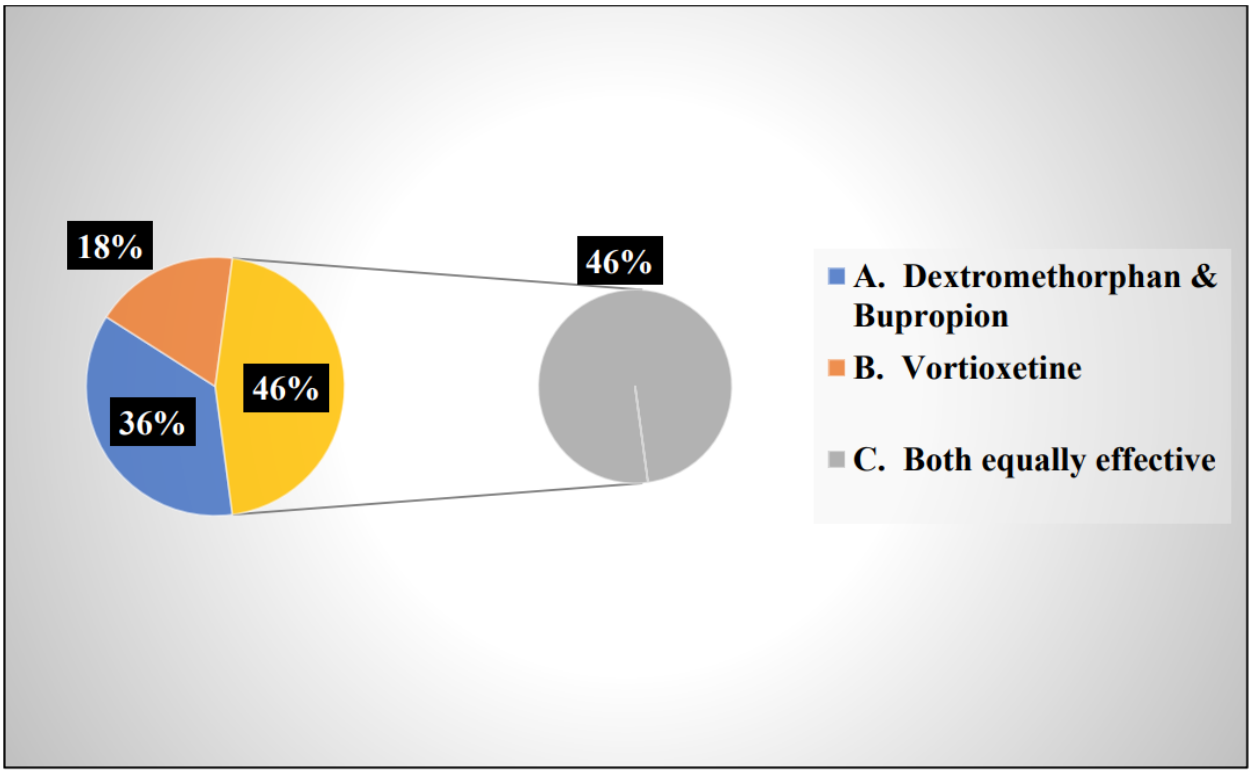
- In clinical practice, 52% of clinicians report prescribing Dextromethorphan and Bupropion more frequently for treating depression, making it the most commonly chosen medication.
- Vortioxetine is prescribed by 14% of clinicians.
- While 34% opt for neither, indicating the use of other treatment options or approaches.

4. In your clinical practice, which medication do you consider more effective in treating depression?

A. Dextromethorphan & Bupropion

B. Vortioxetine

C. Both equally effective



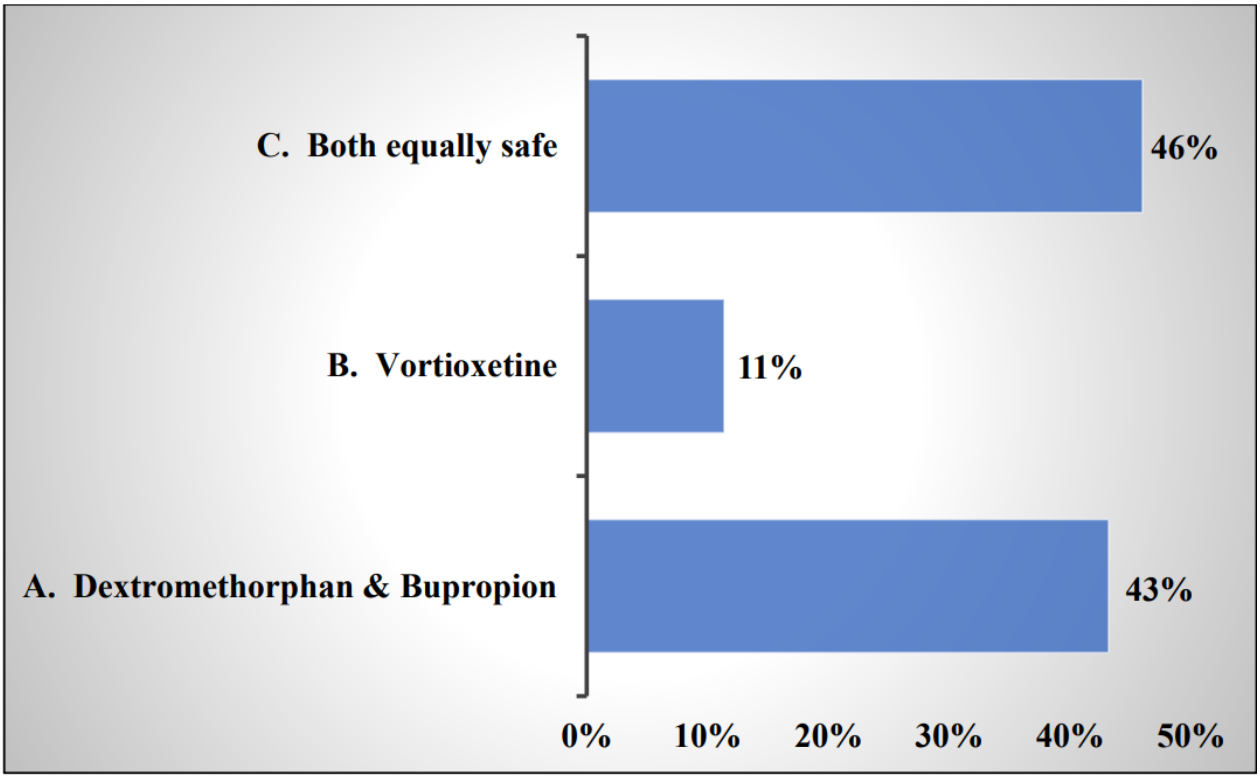
- In clinical practice, 36% of clinicians consider Dextromethorphan and Bupropion more effective in treating depression.
- While 18% believe Vortioxetine offers comparable efficacy.
- However, the majority (46%) perceive both medications to be equally effective in managing depressive symptoms. This suggests that while Dextromethorphan and Bupropion are preferred by a significant portion, there is also substantial confidence in Vortioxetine's ability to achieve similar therapeutic outcomes.

5. In your clinical practice, which medication do you consider safer in terms of side effects?

A. Dextromethorphan & Bupropion

B. Vortioxetine

C. Both equally effective



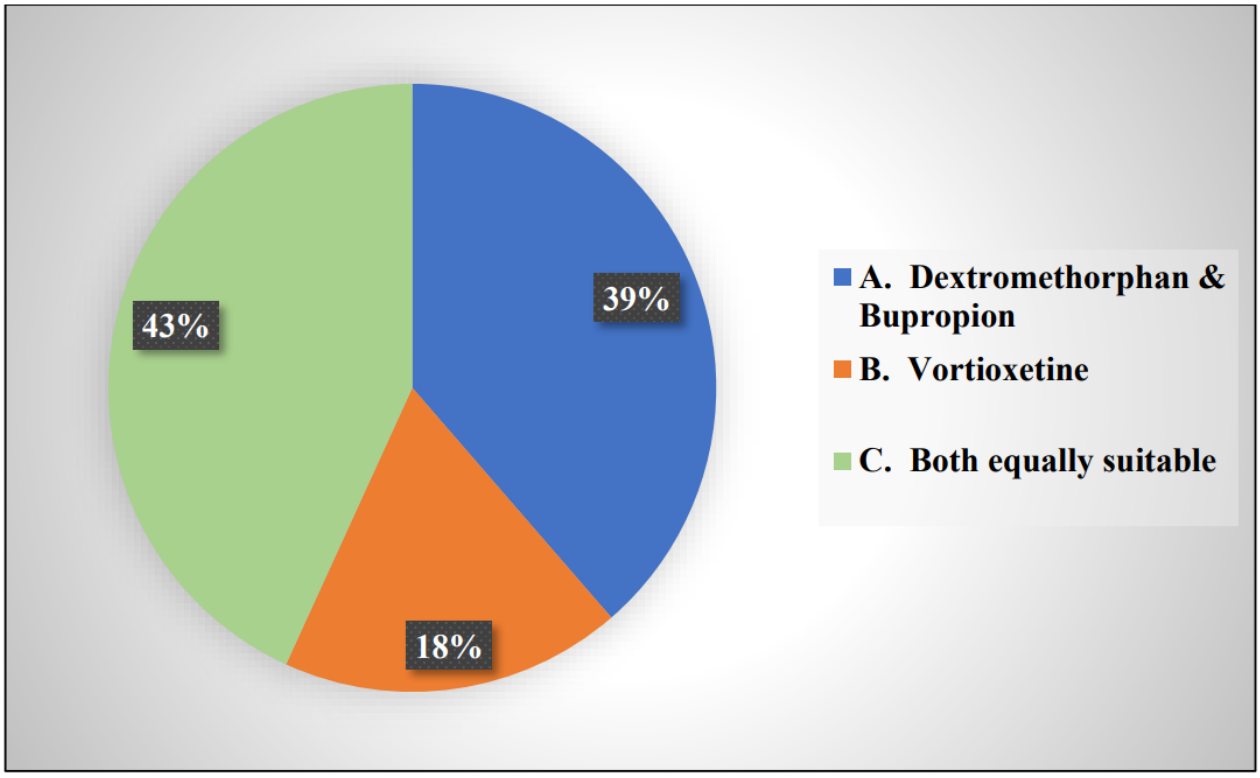
- In clinical practice, 43% of clinicians consider Dextromethorphan and Bupropion safer in terms of side effects.
- While 11% believe Vortioxetine offers better safety.
- The majority, 46%, feel both medications are equally safe, indicating that side effect profiles are a significant factor in prescribing decisions.

6. In your clinical practice, do you consider Escitalopram or Desvenlafaxine more suitable for patients with comorbid anxiety disorders?

A. Dextromethorphan & Bupropion

B. Vortioxetine

C. Both equally effective



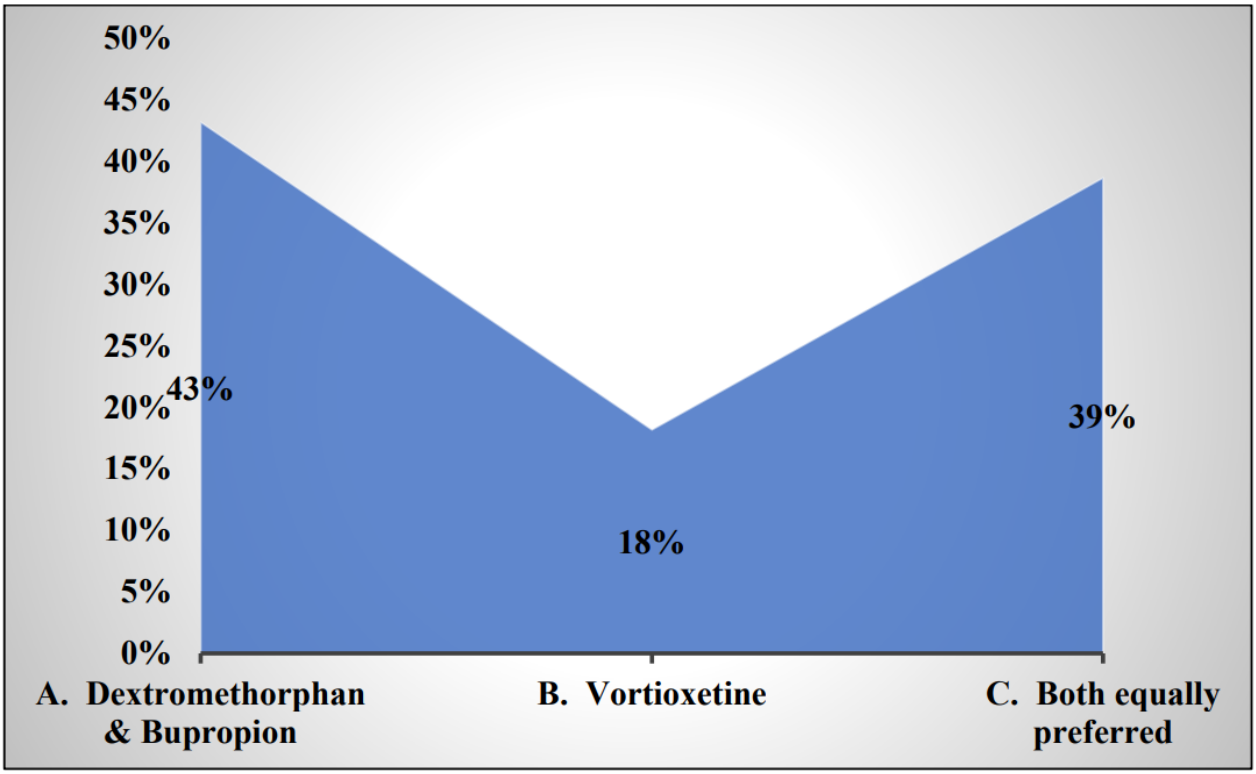
- 39% of clinicians consider Escitalopram or Desvenlafaxine more suitable for patients with comorbid anxiety disorders.
- 18% prefer Vortioxetine for such patients.
- 43% believe both medications are equally suitable.

7. In your clinical practice, which medication do you prefer for patients with treatment-resistant depression?

A. Dextromethorphan & Bupropion

B. Vortioxetine

C. Both equally preferred



- In clinical practice, 43% of clinicians prefer using Dextromethorphan & Bupropion for patients with treatment-resistant depression.
- Another 18% opt for Vortioxetine.
- While 39% believe both options are equally suitable for such cases.
- This reflects varying approaches depending on individual patient needs and response to previous treatments.

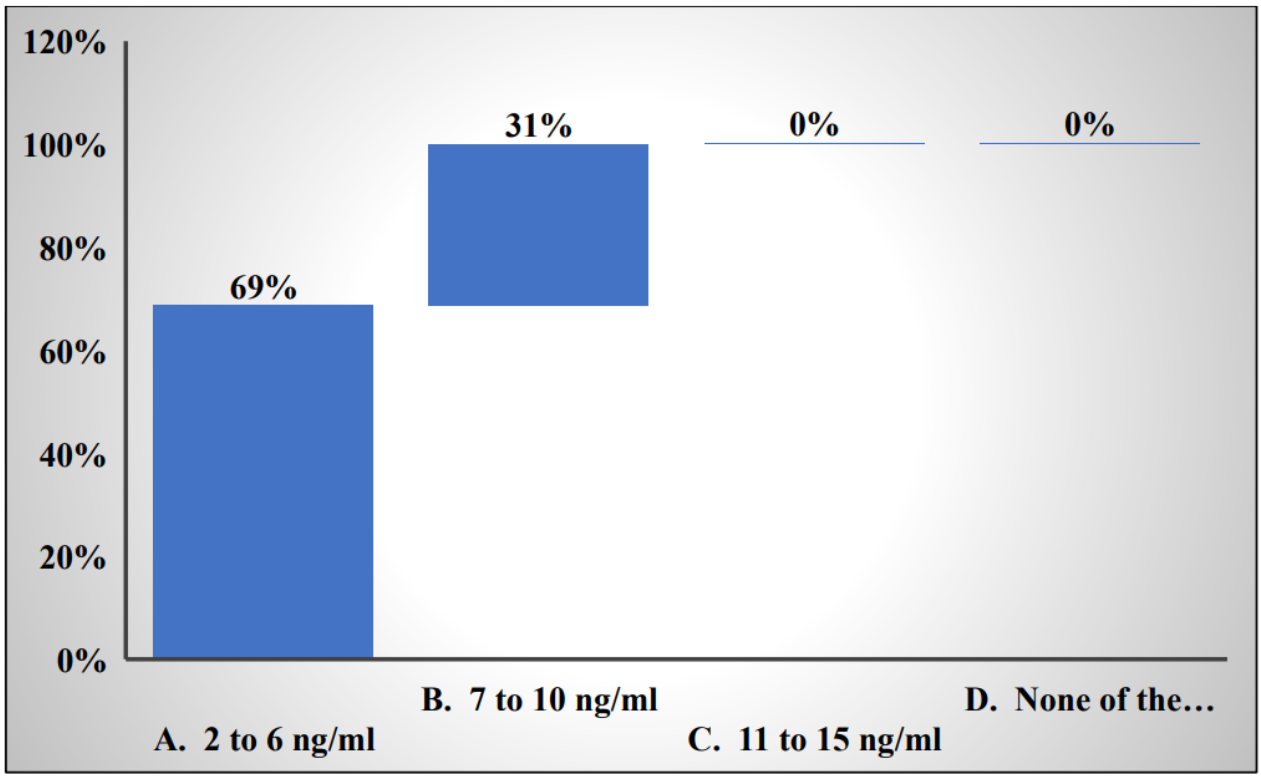
8. In your clinical practice, Dextromethorphan & Bupropion is more commonly associated with which side effect?

A. Insomnia

B. Sedation

C. Nausea

D. Diarrhea



- In clinical practice, 45% of clinicians associate Dextromethorphan & Bupropion more commonly with sedation,
- While 41% report nausea as a side effect.
- Only 12% note insomnia, and 2% mention diarrhea.
- This highlights the primary side effects observed with this combination.

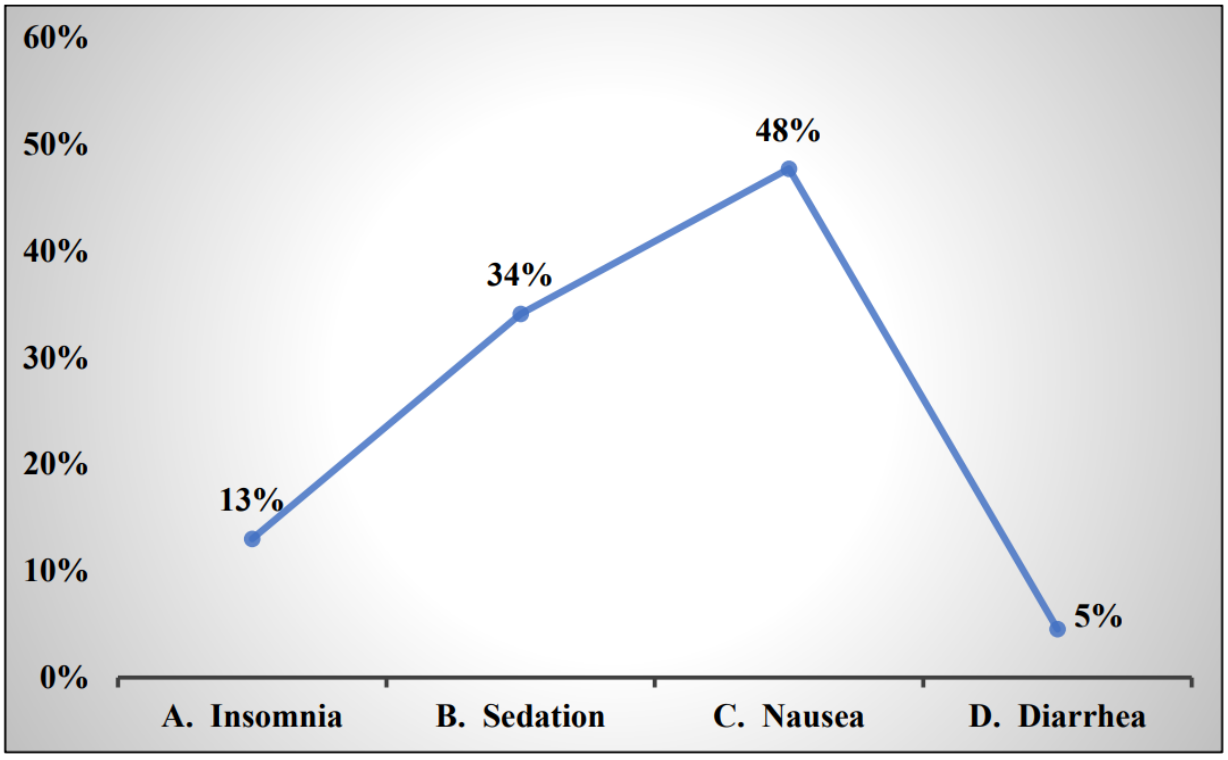
9. In your clinical practice, Vortioxetine is more commonly associated with which side effect?

A. Insomnia

B. Sedation

C. Nausea

D. Diarrhea



- Vortioxetine, a commonly prescribed antidepressant, is most frequently linked to nausea, with 48% of clinicians identifying it as a common side effect.

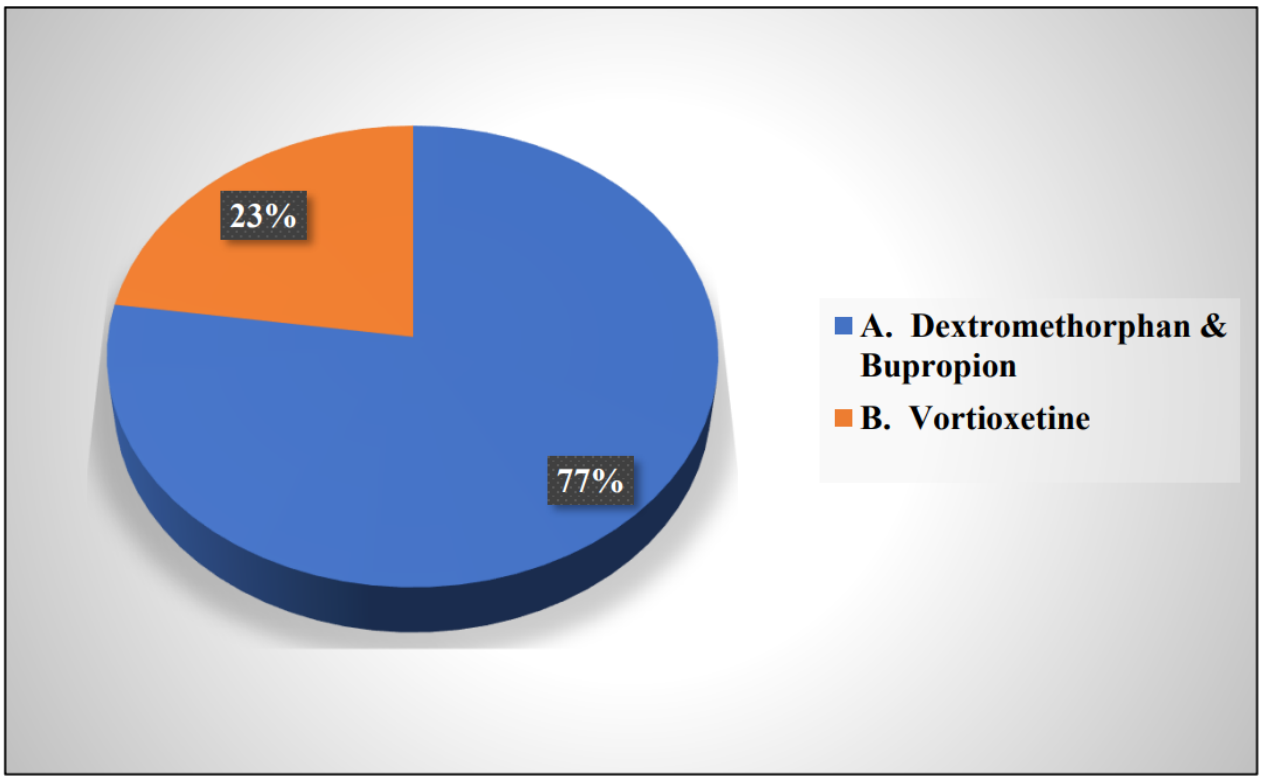
- About 34% of clinicians report sedation as another frequent side effect. A smaller proportion, 13%, associate Vortioxetine with insomnia, while only 5% recognize diarrhea as a typical side effect.

- This distribution suggests that nausea and sedation are the most prominent side effects clinicians observe in patients using Vortioxetine.

10. In your clinical practice, regarding side effects, which medication do you perceive to have a more favorable side effect profile?

A. Dextromethorphan & Bupropion

B. Vortioxetine



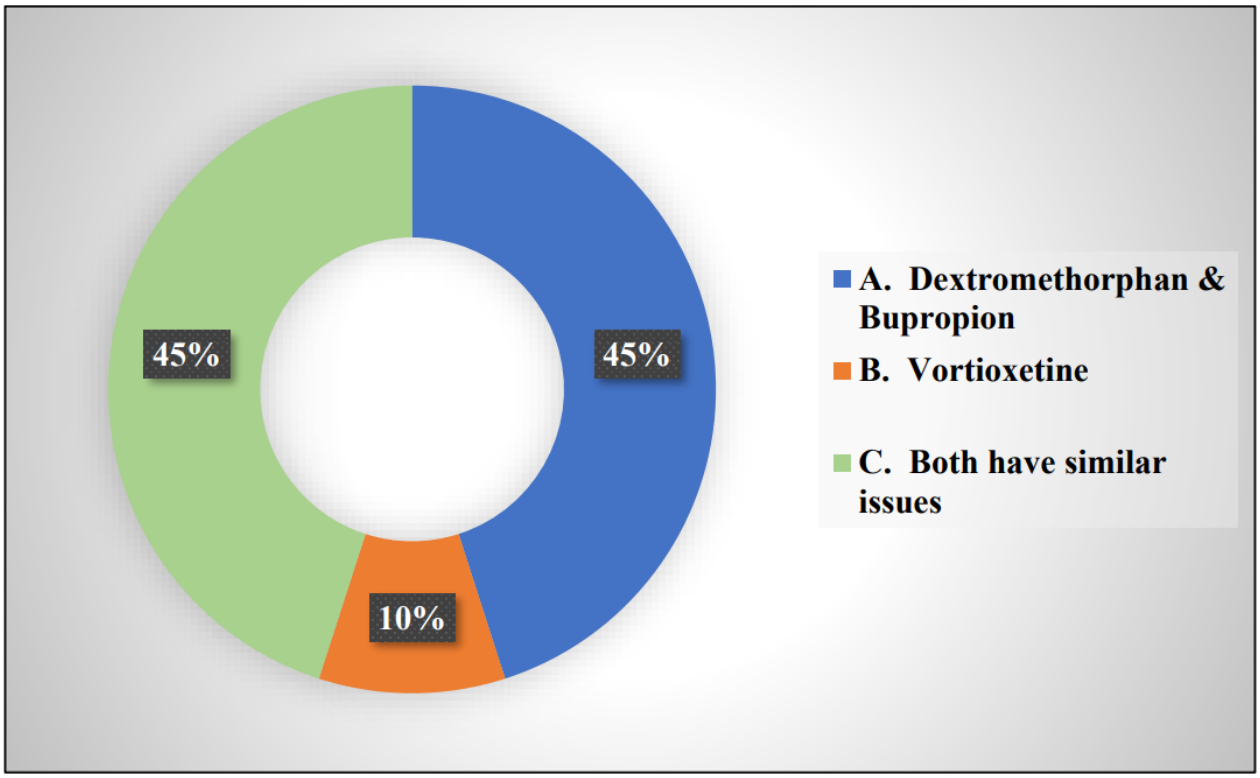
- In clinical practice, 77% of clinicians perceive Dextromethorphan & Bupropion as having a more favorable side effect profile, compared to 23% who feel Vortioxetine offers better tolerability.
- This indicates that most clinicians find the combination of Dextromethorphan and Bupropion to be associated with fewer or more manageable side effects.

11. In terms of sexual side effects, which medication do your patients report fewer issues with?

A. Dextromethorphan & Bupropion

B. Vortioxetine

C. Both have similar issues

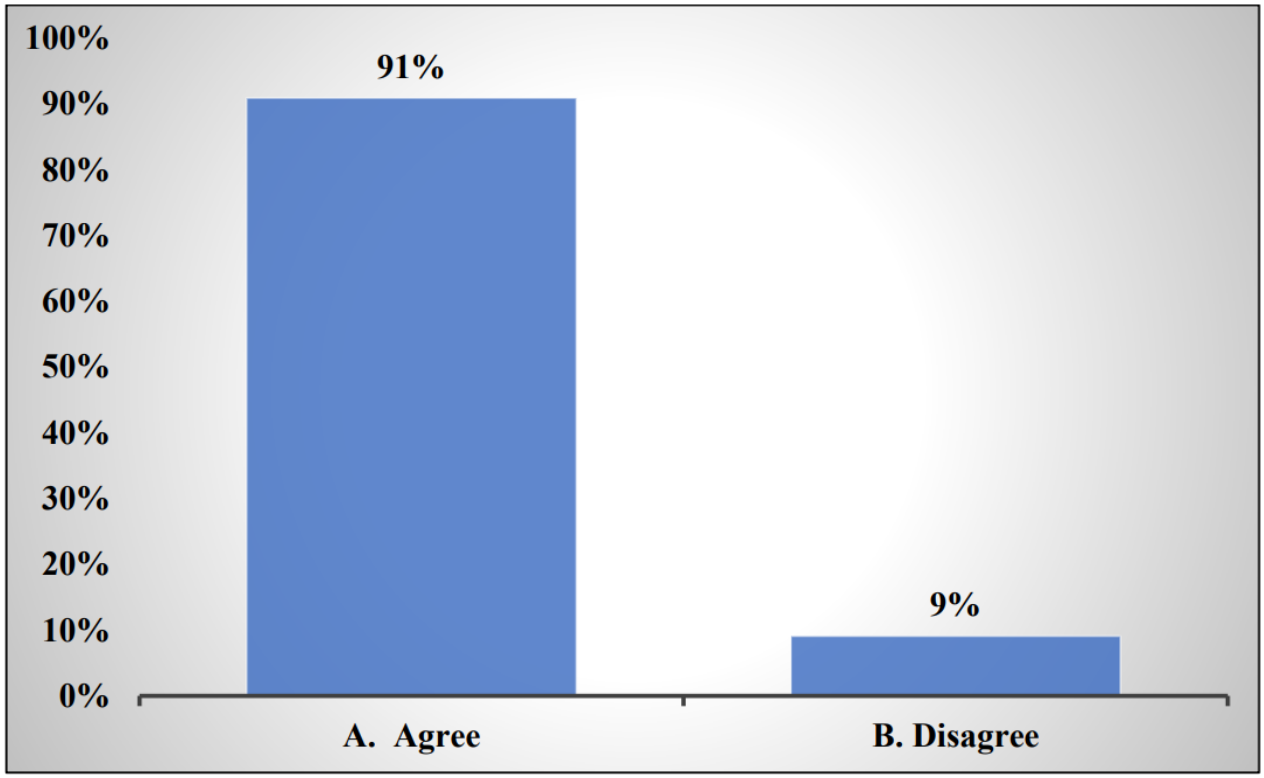


- 45% of clinicians report that Dextromethorphan & Bupropion is associated with fewer sexual side effects.
- 10% report that Vortioxetine has fewer sexual side effects.
- 45% believe that both medications have similar sexual side effect profiles.

12. Dextromethorphan & Bupropion combination and Vortioxetine have similar efficacy in the treatment of depression.

A. Agree

B. Disagree



- Dextromethorphan & Bupropion combination and Vortioxetine have similar efficacy in the treatment of depression was agreed upon by 91% of clinicians, while only 9% disagreed.

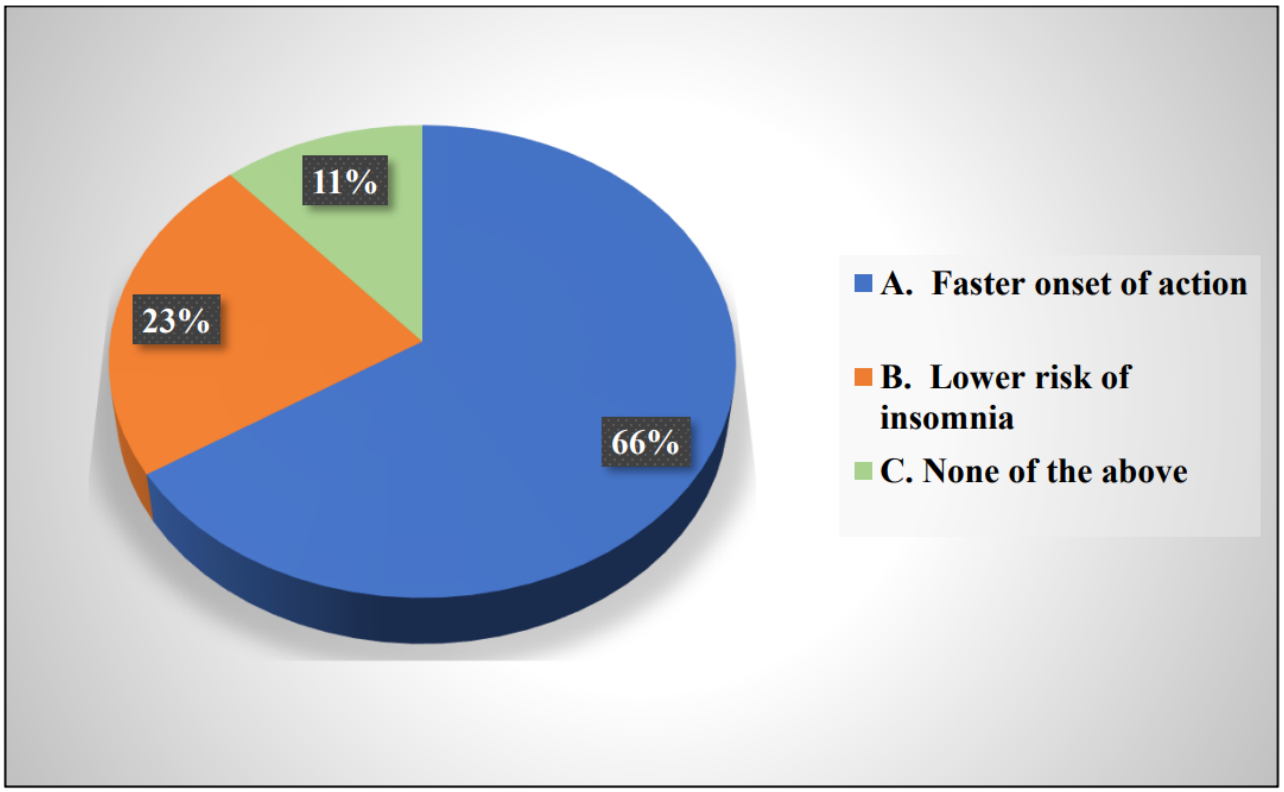
- This suggests that a majority of healthcare providers believe these two medications offer comparable effectiveness when used to treat depression.

13. In your clinical experience, which of the following is a potential advantage of Dextromethorphan & Bupropion over escitalopram?

A. Faster onset of action

B. Lower risk of insomnia

C. None of the above



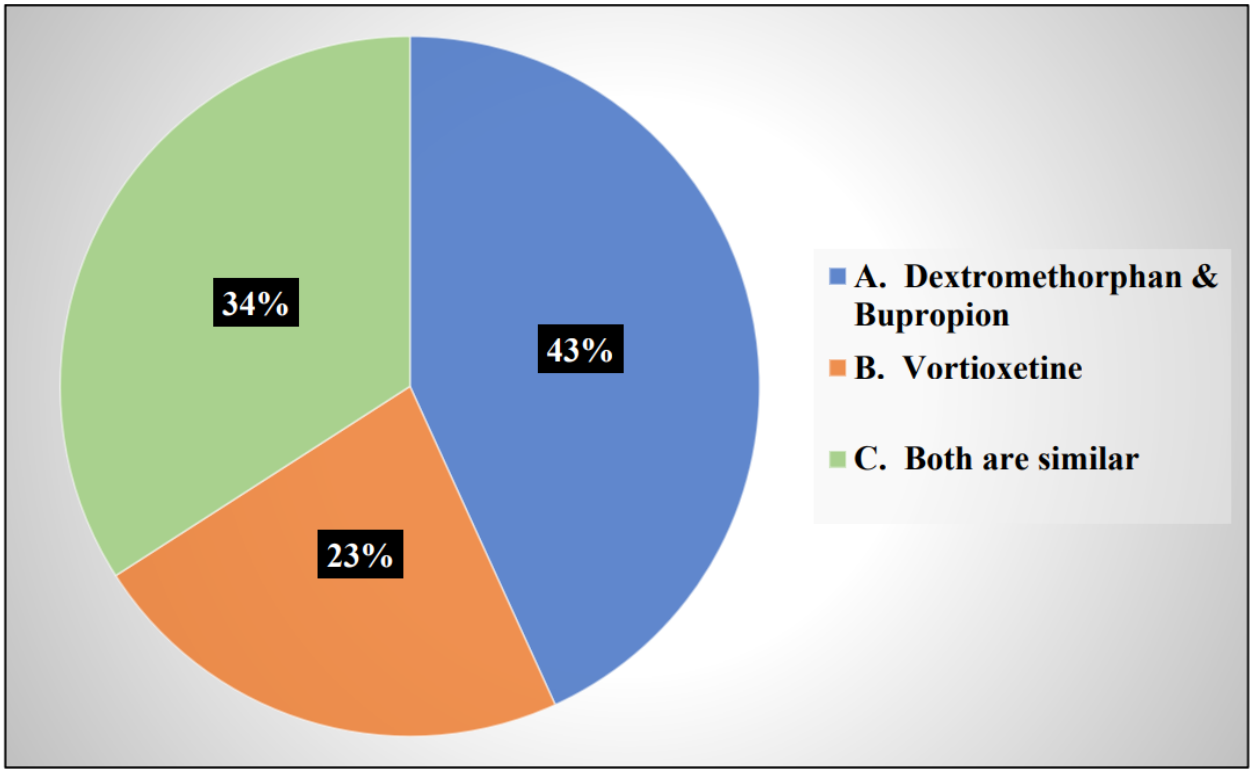
- 66% of clinicians believe that the combination of Dextromethorphan & Bupropion offers a faster onset of action compared to escitalopram, making it a preferred option for patients seeking quicker symptom relief.
- 23% think that this combination has a lower risk of inducing insomnia, which can be a significant advantage for patients with depression who are sensitive to sleep disturbances.
- 11% of clinicians did not find any particular advantage over escitalopram, implying that they do not perceive this combination as significantly better in this regard.

14. In your experience, which medication has a better patient adherence rate?

A. Dextromethorphan & Bupropion

B. Vortioxetine

C. Both are similar



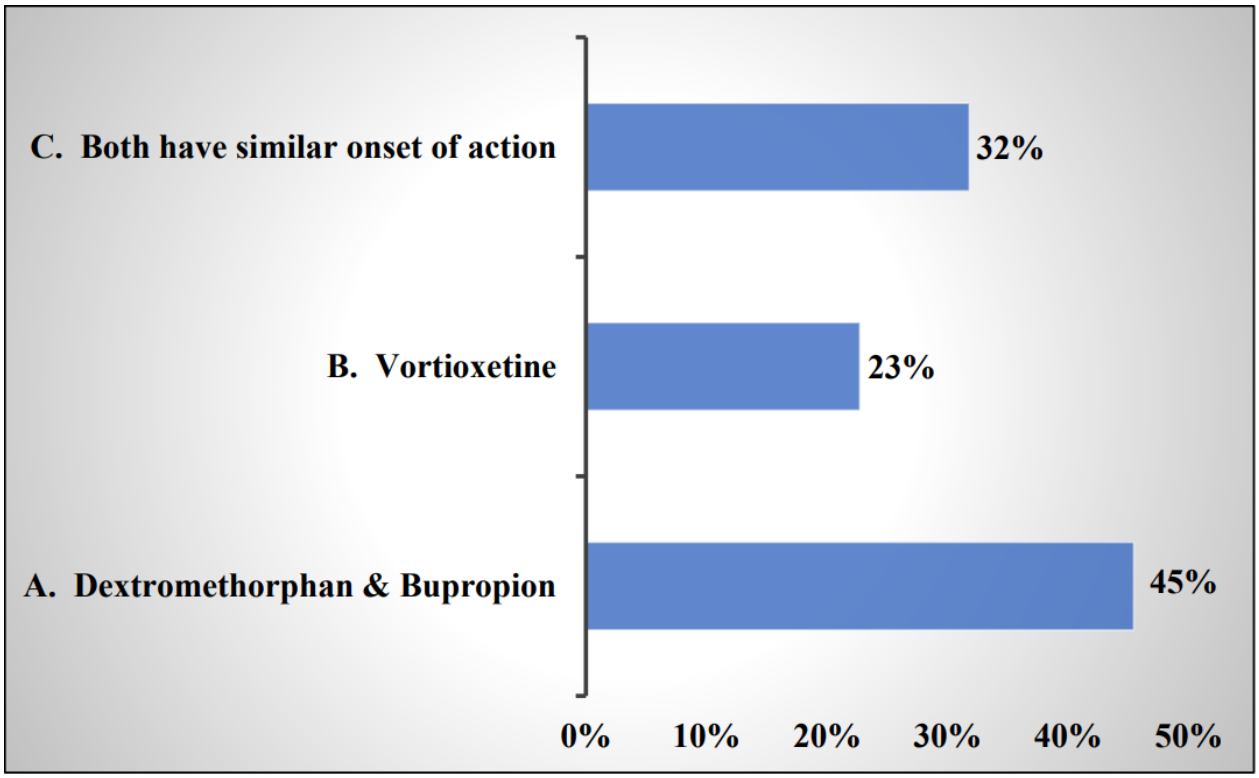
- 43% of clinicians report that Dextromethorphan & Bupropion has a better patient adherence rate compared to other medications.
- 23% believe Vortioxetine is more likely to be adhered to by patients, while 34% feel that both medications have similar adherence rates.
- This suggests that Dextromethorphan & Bupropion may be preferred by patients for better compliance in treatment.

15. In your clinical practice, which medication do you consider to have a faster onset of action in alleviating depressive symptoms?

A. Dextromethorphan & Bupropion

B. Vortioxetine

C. Both have similar onset of action



- 45% of healthcare professionals believe that the combination of Dextromethorphan & Bupropion has a faster onset of action in alleviating depressive symptoms.
- Meanwhile, 23% feel that Vortioxetine provides a quicker relief.
- The remaining 32% believe that both medications have similar onset times.
- This suggests variability in clinicians' experiences with how quickly these treatments start showing effectiveness in their patients.

Summary

This study provides critical insights into clinicians' perspectives and practices regarding the treatment of depression, focusing on the use of Dextromethorphan and Bupropion in comparison to other antidepressants. The findings highlight preferences, safety, efficacy, and prescribing trends for managing depressive symptoms.

- **Prevalence of Depression in Practice:** Most clinicians encounter depression in a significant portion of their patients, with 55% reporting its prevalence in 26-50% of their caseload and 41% seeing it in 51-75% of patients.

- **Factors Influencing Antidepressant Selection:** Efficacy is the top priority for 45% of clinicians, followed by side effect profiles (27%) and patient preference (23%). Cost is less influential, cited by only 5% of clinicians.

- **Prescribing Practices:** Dextromethorphan & Bupropion is prescribed more frequently by 52% of clinicians, with Vortioxetine chosen by 14%, while 34% use alternative treatments.

- **Perceived Efficacy:** 36% of clinicians consider Dextromethorphan & Bupropion more effective than Vortioxetine, while 18% favor Vortioxetine. The majority (46%) believe both have similar efficacy.

- **Safety Considerations:** 43% of clinicians find Dextromethorphan & Bupropion safer, 11% prefer Vortioxetine, and 46% feel both medications are equally safe.

- **Treatment-Resistant Depression:** For treatment-resistant cases, 43% of clinicians prefer Dextromethorphan & Bupropion, 18% opt for Vortioxetine, and 39% consider both equally suitable.

- **Side Effect Profiles:** Vortioxetine is most associated with nausea (48%), followed by sedation (34%). Dextromethorphan & Bupropion is linked to sedation (45%) and nausea (41%).

- **Onset of Action:** 66% believe Dextromethorphan & Bupropion offers a faster onset of action than Escitalopram, making it a preferred choice for quick symptom relief.

- **Patient Adherence:** 43% of clinicians report better adherence with Dextromethorphan & Bupropion, highlighting its tolerability and effectiveness.

Discussion

Based on the survey data, The survey results underscore the growing acceptance of Dextromethorphan & Bupropion as an effective treatment for depression, particularly for its rapid onset of action and favorable side effect profile. Clinicians value the combination for treatment-resistant depression, as its dual mechanism of action addresses unmet needs. The lower incidence of sexual and weight-related side effects enhances adherence, especially for patients who have struggled with traditional antidepressants.

Furthermore, the combination's advantages extend to pediatric and comorbid populations, where safety is paramount. The ability to improve productivity and cognitive function further solidifies its role in comprehensive depression management. While Vortioxetine and other options remain viable, Dextromethorphan & Bupropion's distinct benefits make it a valuable addition to clinicians' therapeutic arsenal.

Clinical Recommendations

- **Treatment Selection:** Prioritize Dextromethorphan & Bupropion for treatment-resistant depression and patients requiring faster symptom relief.
- **Dosage and Monitoring:** Follow recommended dosing regimens, starting low and adjusting based on patient response, while monitoring for sedation and nausea.
- **Patient Communication:** Educate patients on the benefits and side effects to improve adherence and shared decision-making.

Consultant Opinion

Experts express a largely positive view of the combination of Dextromethorphan and Bupropion for treating Major Depressive Disorder (MDD), emphasizing its unique mechanism of action, which involves NMDA receptor modulation and inhibition of dopamine and norepinephrine reuptake. This dual-action approach makes it particularly promising for patients with treatment-resistant depression, where conventional antidepressants often fall short. Consultants highlight the combination's rapid onset of action, providing faster symptom relief for acute depressive episodes, and its favorable side-effect profile, which minimizes issues like sexual dysfunction, weight gain, and sedation, thus improving patient adherence and satisfaction.

The combination is also noted for its applicability in specific patient populations, such as those with treatment-resistant MDD or pediatric patients, where safety and tolerability are critical. While acknowledging its benefits, experts stress the importance of ongoing research to better understand long-term safety and efficacy, ensuring its sustainable use. They advocate for close patient monitoring to identify and manage potential side effects and encourage feedback to refine treatment strategies. Overall, the Dextromethorphan and Bupropion combination is seen as a valuable alternative in MDD management, with the potential to address unmet needs and enhance clinical outcomes.

Market Opportunities

- **Unmet Needs:** There remains a significant gap in effective treatments for patients who do not respond adequately to traditional antidepressants like SSRIs and SNRIs. The Dextromethorphan and Bupropion combination addresses this gap by offering an alternative with a unique mechanism of action and broader efficacy.

- **Adoption Trends:** The combination's prescribing rates, with 52% of clinicians using it frequently, indicate growing confidence in its safety and efficacy. This trend presents an opportunity to further strengthen its adoption as a reliable treatment option in clinical practice.

- **Education and Awareness:** Increasing awareness through educational initiatives can enhance clinicians' understanding of the combination's unique benefits, such as its faster onset of action and favorable side-effect profile. These efforts can improve confidence in prescribing and expand its usage.

- **Positioning:** The Dextromethorphan and Bupropion combination can be marketed as a superior alternative to traditional antidepressants. Its dual-action mechanism, faster symptom relief, and tolerability make it suitable for a wide range of patients, including those with treatment-resistant depression and comorbid conditions.

Market Positioning

- **Clinician Engagement:** Targeted campaigns and Continuing Medical Education (CME) activities can focus on educating clinicians about the Dextromethorphan and Bupropion combination's rapid action and favorable safety profile. These initiatives aim to improve understanding and confidence, encouraging clinicians to consider this combination as a preferred option in their treatment plans.

- **Patient-Focused Strategies:** By showcasing patient success stories, testimonials, and the benefits of improved quality of life with minimal side effects, marketing efforts can appeal directly to patients. This strategy emphasizes adherence benefits, motivating patients to discuss this option with their clinicians and stay committed to the treatment.

- **Access and Affordability:** Collaborations with healthcare systems and insurers can ensure the medication is accessible and affordable. Such partnerships reduce financial barriers for patients, increasing its availability and adoption while maintaining a competitive position in the market.

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