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Review

Repurposing Memantine in Psychiatry: From NMDA Receptor Modulation to Symptom-Domain Targeting

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Abstract

Memantine, an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist approved for moderate-to-severe Alzheimer disease, has attracted increasing interest as a potential adjunctive treatment in psychiatry. This narrative, critical review examines the mechanistic rationale for memantine and synthesizes the clinical evidence for its off-label use across psychiatric diagnoses and symptom domains. Memantine's pharmacological profile differs from that of high-affinity dissociative NMDA antagonists because it has low-to-moderate affinity, voltage-dependent binding, rapid off-rate kinetics, and preferential blockade of excessive tonic glutamatergic activity while relatively sparing physiological synaptic transmission. This mechanism provides a rationale for exploring memantine in psychiatric conditions characterized by glutamatergic dysregulation, excitotoxic stress, impaired neuroplasticity, cognitive dysfunction, compulsivity, irritability, and negative symptoms. We searched PubMed/MEDLINE from inception to 24 July 2026. No formal risk-of-bias or certainty-grading instrument was applied. Controlled evidence is most developed for selected negative-symptom and cognitive outcomes in schizophrenia. Obsessive-compulsive disorder (OCD) has the largest augmentation literature among nonpsychotic indications, but recent randomized trials and an updated meta-analysis do not support routine use in unselected patients; a hypothesis-generating signal may remain in rigorously defined treatment-resistant obsessive-compulsive disorder. A single positive controlled trial provides an emerging signal in trichotillomania and skin-picking disorder. Evidence in other psychiatric and neuropsychiatric indications remains limited/mixed, preliminary, or insufficient. Memantine should not be considered a first-line psychiatric treatment or a substitute for established pharmacological, psychotherapeutic, or neuromodulatory interventions. At most, it represents a mechanistically rational, explicitly off-label adjunct for carefully selected symptom domains and research-enriched populations. This review provides clinical positioning rather than prescribing recommendations; any off-label use requires prior optimization of standard care, individualized risk-benefit assessment, and informed consent.

Keywords: memantine; N-methyl-D-aspartate receptor; glutamate; obsessive-compulsive disorder; schizophrenia; drug repurposing

Main Points

1. Memantine's uncompetitive, low-to-moderate-affinity, voltage-dependent NMDA receptor blockade provides a mechanistic rationale for targeting pathological glutamatergic signaling across several psychiatric symptom domains while relatively sparing physiological neurotransmission.

2. The most developed signal concerns adjunctive treatment of selected negative and cognitive symptoms in schizophrenia. Evidence in OCD is limited/mixed overall: routine augmentation in unselected patients is not supported, although treatment-resistant populations warrant definitive study. A single positive trial provides an emerging signal in trichotillomania and skin-picking disorder.

3. Memantine is not a first-line psychiatric treatment. Its most defensible role is investigational, adjunctive, explicitly off-label, and phenotype-guided rather than diagnosis-wide; future trials should be adequately powered, biomarker-informed, and enriched for compulsivity, persistent negative symptoms, executive dysfunction, or other prespecified target domains.

1. Introduction

The pharmacological treatment of psychiatric disorders has traditionally been organized around monoaminergic, dopaminergic, serotonergic, and gamma-aminobutyric acid (GABA)-ergic models. Antidepressants are commonly framed through serotonergic, noradrenergic, and dopaminergic modulation; antipsychotics through dopamine D2 receptor antagonism or partial agonism; anxiolytics through GABAergic modulation; and mood stabilizers through effects on neuronal excitability, intracellular signaling, and neuroprotection. These models remain clinically useful, but they do not fully explain treatment resistance, residual symptoms, cognitive impairment, negative symptoms, compulsivity, craving, irritability, and incomplete functional recovery.

Glutamate is the principal excitatory neurotransmitter in the central nervous system and is central to synaptic plasticity, learning, memory, cortical integration, and corticostriatal function. Abnormal glutamatergic neurotransmission has been implicated in schizophrenia, obsessive-compulsive disorder (OCD), mood disorders, autism spec-

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trum disorder (ASD), addiction, and neurocognitive impairment. Tsai and Coyle emphasized the role of glutamatergic mechanisms in schizophrenia [1], while several authors highlighted glutamatergic abnormalities and glutamate-modulating therapeutic strategies in obsessive-compulsive disorder and related disorders [2,3,4].

Memantine is particularly relevant because it is an N-methyl-D-aspartate (NMDA) receptor antagonist with pharmacological characteristics that differ from high-affinity dissociative NMDA antagonists. Its low-to-moderate affinity, voltage-dependent channel blockade, and relatively rapid unblocking kinetics have been proposed to permit attenuation of excessive pathological NMDA receptor activation while largely preserving physiological synaptic transmission [5,6,7]. This pharmacological profile explains why memantine is generally better tolerated than more disruptive NMDA antagonists and why it has been investigated beyond dementia.

In Alzheimer disease, memantine demonstrated symptomatic benefit in cognition, global outcome, and daily functioning in moderate-to-severe disease, supporting its approval and clinical use in neurodegenerative illness [8]. Its investigation in psychiatry began from the premise that glutamatergic dysregulation is not limited to dementia but may also contribute to psychiatric symptoms such as cognitive impairment, negative symptoms, compulsivity, irritability, and pathological repetitive behaviors. Zdanys and Tampi [9] reviewed early off-label psychiatric uses of memantine, while Lu and Nasrallah [10] later summarized evidence across neuropsychiatric disorders. Overall, the literature suggests that memantine is biologically plausible and sometimes clinically useful, but not uniformly effective across diagnoses. More recent overviews have re-examined N-methyl-D-aspartate receptor modulators and glutamate-based mechanisms of action in psychiatry, underscoring the continued interest in this therapeutic approach [11,12].

The aim of this review is to examine the mechanistic rationale for memantine as an adjunctive psychiatric strategy, summarize the evidence across major diagnostic and symptom domains, and propose a cautious clinical framework for future research and selected off-label use.

This review is distinguished from previous overviews by its explicit organization around transdiagnostic symptom domains—compulsivity and repetitive behavior, negative symptoms, cognitive impairment, irritability, and glutamatergic dysregulation—rather than around diagnostic categories alone. We integrate diagnosis-specific findings within a phenotype-guided framework and classify the evidence using predefined narrative descriptors described in the Methods. Fig. 1 summarizes proposed links among symptom domains, candidate neural circuits, hypothesized mechanisms, and representative disorders; disorder-specific evidence classifications and clinical positioning are presented separately in Table 1 (Ref. [8,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69]). This separation avoids assigning a single evidence level to heterogeneous conditions that may share a symptom domain.

2. Methods

This is a narrative, critical review informed by the Scale for the Assessment of Narrative Review Articles (SANRA) [70]. It was designed to synthesize the mechanistic rationale, clinical evidence, and cautious clinical positioning of memantine across psychiatric symptom domains rather than to generate pooled efficacy estimates. We searched PubMed/MEDLINE from inception to 24 July 2026, combining the free-text term “memantine” and, where available, the corresponding MeSH term with diagnostic and symptom-related terms using the Boolean structure: memantine AND (“psychiatry” OR “schizophrenia” OR “negative symptoms” OR “obsessive-compulsive disorder” OR “trichotillomania” OR “skin-picking” OR “bipolar disorder” OR “depression” OR “autism” OR “attention-deficit/hyperactivity disorder (ADHD)” OR “eating disorder” OR “gambling” OR “substance use” OR “anxiety” OR “post-traumatic stress disorder (PTSD)” OR “catatonia” OR “electroconvulsive therapy”). The search was restricted to English-language reports, and reference lists of relevant articles and previous reviews were screened manually for additional sources.

Eligible sources included randomized controlled trials, meta-analyses, systematic reviews, open-label and observational studies, and illustrative case reports or case series addressing memantine in psychiatric or neuropsychiatric conditions; preclinical and mechanistic papers were included only to support the pharmacological rationale. Non-English reports, conference abstracts without extractable data, and publications not addressing memantine were excluded. Records were screened by title and abstract and then assessed at full text. Study selection and data extraction were performed by two authors (M.P. and M.B.R.), who cross-checked their assessments; disagreements were resolved by discussion and, where necessary, adjudication by the senior authors (A.F. and A.C.). This was a single-database narrative process and not a formally independent dual-reviewer systematic screening. For each clinical study, we narratively extracted the disorder and target symptom domain, design, sample size, dose, treatment duration, comparator, principal outcomes, and reported limitations. Because the review was not conducted under a prospectively registered systematic-review protocol, screening counts were not prospectively recorded, and a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)- style flow diagram is not reported. Retrieval was limited to one bibliographic database and English-language reports, and study selection was guided by clinical and mechanistic relevance; the synthesis

Table 1. Summary of the evidence for memantine across psychiatric disorders and symptom domains, using the six predefined narrative evidence classifications and cautious clinical positioning.

Disorder/domain	Representative evidence	Evidence classification	Clinical positioning
Schizophrenia (negative symptoms, cognition)	RCTs [25,26,27,28,29,30,31] and meta-analyses [13,32,42]	Moderate	Investigational adjunct for persistent negative symptoms or selected cognitive deficits; never an antipsychotic substitute.
Obsessive-compulsive disorder	Positive and neutral/negative RCTs [14,15,16,18,19,20]; reviews/meta-analyses [21,22,23,24]	Limited/mixed	Routine use not supported; cautious investigational discussion only in rigorously defined treatment-resistant cases after standard care.
Trichotillomania/ skin-picking disorder	Single placebo-controlled RCT [33]	Emerging	Investigational adjunct to habit-reversal therapy; independent replication required.
Impulse-control disorders (gambling, compulsive buying)	Open-label pilot studies [53,54]	Preliminary	Research setting only; no controlled evidence.
Bipolar disorder	Small RCTs and naturalistic/case evidence [34,35,36,37,69]; broad meta-analysis [42]	Limited/mixed	Experimental only; not a treatment for mania, bipolar depression, or maintenance.
Major depressive disorder/TRD	Negative and small positive RCTs [38,39,40,41]; meta-analysis and review [42,43]	Limited/mixed	Not supported as routine antidepressant augmentation.
Autism spectrum disorder	Observational studies and mixed RCT/review evidence [44,45,46,47,48,49]	Limited/mixed	Investigational, symptom-domain and biomarker-enriched research only.
ADHD	Open-label monotherapy and small pilot adjunctive RCT [50,51]	Preliminary	Investigational; established ADHD treatments remain first-line.
Eating disorders (binge eating)	Single open-label prospective trial [52]	Preliminary	Research setting only.
Substance use disorders	Mechanistic studies and predominantly negative controlled trials [55,56,57,58,59]	Limited/mixed	Not a standard anti-craving or relapse-prevention treatment.
Anxiety disorders/ PTSD	Open-label trial and case-series evidence [17,60,61]	Preliminary	Speculative; not recommended for routine use.
Catatonia	Review and case reports [62,63]	Insufficient	Specialist adjunct only in exceptional refractory cases; must not delay benzodiazepines or ECT.
Behavioral and psychological symptoms of dementia	Approved memantine context in moderate-to-severe Alzheimer disease [8]; detailed BPSD appraisal excluded	Not applicable—outside review scope	Follow dementia-treatment guidance; not evidence for psychiatric repurposing.
ECT-related cognitive complaints	Small placebo/active-comparator RCTs [64,65,66,68] and meta-analysis [67]	Limited/mixed	Research only; routine prophylactic use is not supported.

BPSD, behavioral and psychological symptoms of dementia; ECT, electroconvulsive therapy; RCT, randomized controlled trial; TRD, treatment-resistant depression. The six evidence classifications—moderate, promising, emerging, limited/mixed, preliminary, and insufficient—are defined in the Methods. "Not applicable—outside review scope" is not an evidence category and is used only for BPSD. The table does not constitute a treatment recommendation or dosing guide.

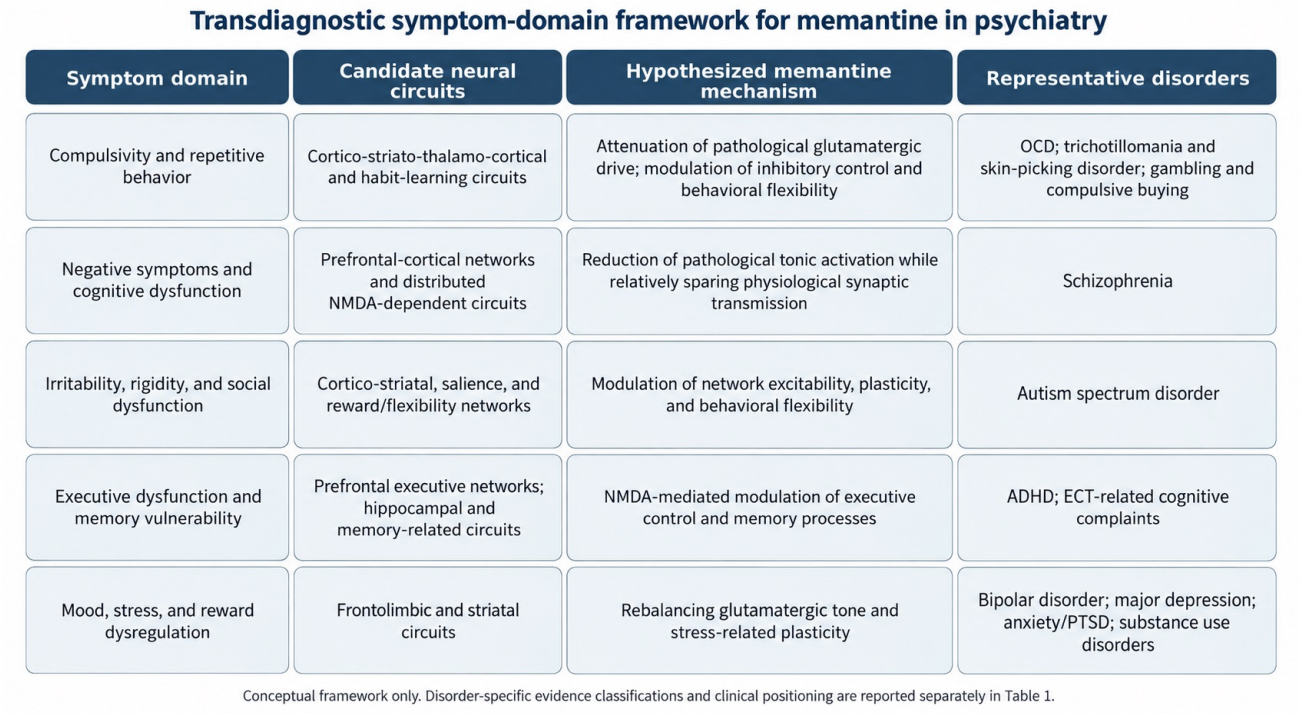


Fig. 1. Conceptual overview linking transdiagnostic symptom domains to candidate neural circuits, hypothesized mechanisms of memantine, and representative disorders. Evidence classifications are deliberately presented separately in Table 1 because strength varies across disorders within the same symptom domain. The figure is conceptual and does not imply an established indication. NMDA, N-methyl-D-aspartate; OCD, obsessive-compulsive disorder; ADHD, attention-deficit/hyperactivity disorder; PTSD, post-traumatic stress disorder.

is therefore interpretive and potentially subject to selection bias. No formal risk-of-bias or certainty instrument, such as the Cochrane Risk of Bias 2 (RoB 2) tool or the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, was applied, and no pooled effect sizes were calculated. The review should therefore not be interpreted as a systematic efficacy assessment.

To improve transparency and consistency of interpretation, the clinical evidence for each disorder was classified using six predefined narrative descriptors based on study design, replication, sample size, consistency, and clinical relevance. "Moderate" denotes several randomized controlled trials and/or meta-analytic data with broadly consistent, domain-specific findings. "Promising" denotes more than one positive randomized controlled trial, but with small samples, heterogeneity, or other limitations requiring replication. "Emerging" denotes a single methodologically sound positive controlled trial not yet independently replicated. "Limited/mixed" denotes few, small, conflicting, or methodologically heterogeneous controlled studies, including a non-significant or highly heterogeneous overall meta-analytic estimate. "Preliminary" denotes predominantly open-label, pilot, subgroup, or other uncontrolled evidence. "Insufficient" denotes anecdotal or very sparse evidence that does not support a clinical inference. These descriptors are heuristic narrative summaries, not validated certainty ratings or prescribing recommendations. Behavioral and psychological symptoms of dementia are included in Table 1 only to delimit memantine's approved dementia context and are marked "not applicable—outside review scope", rather than assigned an evidence category. Fig. 1 is deliberately conceptual and does not display evidence classifications.

3. Pharmacological and Mechanistic Rationale

Memantine's potential utility in psychiatry rests on a pharmacological argument that must be established before the clinical evidence is examined. Three questions structure this rationale and this section: how memantine acts on the NMDA receptor, why glutamatergic dysregulation is relevant across psychiatric symptom domains rather than within any single diagnosis, and the mechanistic routes through which clinical benefit might plausibly arise.

3.1 How Memantine Acts on the NMDA Receptor

Memantine is an uncompetitive antagonist of the NMDA receptor. Unlike competitive antagonists, it binds preferentially when the ion channel is open. Its voltage dependency allows stronger interaction under conditions of excessive receptor activation, and its relatively rapid off-rate may preserve physiological NMDA receptor activity

required for normal synaptic function [6,7]. Parsons and colleagues [5] emphasized that this profile may explain why memantine is clinically tolerated despite acting at a receptor system central to cognition, plasticity, and learning, a point further developed in analyses of clinically tolerated open-channel blockers [71,72]. Memantine should therefore not be conceptualized as a simple glutamate suppressor: rather than abolishing transmission, it attenuates excessive, pathological channel activation while relatively sparing physiological synaptic signaling.

3.2 Glutamatergic Dysregulation Across Psychiatric Symptom Domains

NMDA receptors are central to synaptic plasticity, memory formation, cortical information processing, and excitatory-inhibitory balance, and both excessive and insufficient receptor activity may be pathological. This makes glutamatergic dysregulation a plausible substrate for several psychiatric symptom domains rather than for any single disorder. NMDA receptor hypofunction has been linked to the negative-symptom and cognitive dimensions of psychosis, supported by the observation that NMDA antagonists such as phencyclidine and ketamine reproduce positive, negative, and cognitive features of psychosis [1,73,74,75]. Dysregulation within cortico-striato-thalamo-cortical loops has been implicated in the compulsivity, impaired inhibitory control, and persistent repetitive behavior that cut across obsessive-compulsive and body-focused repetitive symptom domains [2,4]. In mood-related pathology, glutamate abnormalities may interact with neuroplasticity, stress-related excitotoxicity, and treatment resistance.

A related rationale concerns neuroprotection. Excessive glutamatergic activation contributes to excitotoxic injury, and persistent NMDA receptor overactivation may drive neuronal stress in neurodegenerative conditions [7,72]; the clinical benefit of memantine in moderate-to-severe Alzheimer disease shows that NMDA receptor modulation can be meaningful where neuronal dysfunction is prominent [8]. In psychiatry, this neuroprotective concept is more speculative. Excitotoxic stress, impaired plasticity, and abnormal network excitability may contribute to chronic illness burden, cognitive impairment, and residual symptoms, but these processes are difficult to measure clinically and remain insufficiently proven outside neurodegenerative disorders.

3.3 Mechanistic Routes to Potential Clinical Benefit

If memantine is to be useful in psychiatry, the benefit is likely to arise through one or more of three overlapping routes. The first is rebalancing of pathological glutamatergic signaling, attenuating excessive channel activation while sparing physiological transmission. The second is modulation of cortico-striatal and prefrontal circuits that govern inhibitory control, habit formation, and behavioral flexibility, which may influence behavioral symptoms such as irritability, impulsivity, compulsivity, and repetitive behaviors independently of global cognition. The third is a direct effect on cognition, although the evidence here is inconsistent: a meta-analysis of adjunctive pharmacotherapies for cognitive deficits in schizophrenia found limited evidence for broad cognitive benefit [76], whereas adjunctive memantine has been associated with improved neurocognitive performance in schizophrenia in analyses limited by small trial numbers and heterogeneity [13].

These mechanisms are best understood as hypotheses rather than established pathways. They are presented here to frame, not to anticipate, the disorder-specific clinical evidence examined in the following section.

4. Disorders With the Most Developed Controlled Evidence

The most developed controlled literature is concentrated in obsessive-compulsive disorder and in the negative and cognitive symptom domains of schizophrenia. “Most developed” refers to the volume of controlled research, not to established efficacy or routine clinical use. These indications are therefore discussed first; body-focused repetitive behaviors, which currently rest on a single positive controlled trial, are considered separately as emerging evidence.

4.1 Obsessive-Compulsive Disorder

Obsessive-compulsive disorder is among the most extensively studied nonpsychotic indications for memantine augmentation. The rationale is based on glutamatergic dysregulation within cortico-striato-thalamo-cortical circuits. Rosenberg and colleagues [2] reported altered caudate glutamatergic concentrations in pediatric OCD, and subsequent reviews summarized converging evidence implicating glutamate abnormalities in OCD neurobiology and treatment [3,4].

The clinical need is substantial. Selective serotonin reuptake inhibitors, clomipramine, and exposure and response prevention are established interventions, yet a clinically important subgroup remains symptomatic. Memantine offers a mechanistically distinct augmentation strategy, but biological plausibility does not establish efficacy. Other glutamate-modulating agents, including riluzole and N-acetylcysteine, have likewise produced mixed findings [77,78,79].

Several early small studies reported positive findings. Ghaleiha and colleagues [14] found benefit when memantine was added to fluvoxamine in moderate-to-severe OCD, Haghighi and colleagues [15] reported improvement in refractory inpatients, and Modarresi and colleagues [16] reported efficacy in serotonin reuptake inhibitor-refractory OCD. A single-blind case-control study and open-label work also suggested benefit [17,80]. These studies, however, were generally small and differed in resistance defi-

nitions, background treatment, design, and outcome assessment.

Later controlled evidence has been less consistent. In a three-arm randomized trial, adjunctive memantine and gabapentin did not provide additional yale-brown obsessive compulsive scale (Y-BOCS) benefit over fluoxetine plus placebo [18]. In the 70-participant Askari trial, Y-BOCS scores improved in both groups without a significant between-group difference; only the number of completed categories on the Wisconsin Card Sorting Test favored memantine [19]. In a 60-participant, 16-week trial of escitalopram augmentation, memantine again did not improve Y-BOCS outcomes versus placebo, although one executive-function subdomain—time management—favored memantine [20].

Earlier meta-analyses reported substantial benefits [21,22], but Andrade highlighted the fragility of unusually large effects derived from small studies, as well as possible publication bias [81]. A 2026 narrative synthesis concluded that the evidence did not support routine use [23]. The updated 2026 systematic review and meta-analysis included six randomized trials (n = 288) and found no statistically significant overall reduction in endpoint Y-BOCS score versus placebo (mean difference –3.74, 95% confidence interval (CI) –9.95 to 2.47; $I^2 = 97.9\%$) [24]. A larger but imprecise subgroup estimate in treatment-resistant populations was based on only two trials and was explicitly hypothesis-generating. Taken together, the evidence is best classified as limited/mixed rather than promising overall.

Routine memantine augmentation in unselected OCD is therefore not supported. In rigorously defined treatment-resistant OCD, cautious off-label discussion may be reasonable only after adequate trials of evidence-based pharmacological and psychotherapeutic treatment, when established augmentation options are ineffective, contraindicated, or unsuitable. Because no validated strategy has been established for identifying which treatment-resistant patients are likely to respond, this represents an individualized, investigational consideration rather than an evidence-based recommendation. Even in this setting, the approach remains investigational and requires explicit informed consent, careful outcome measurement, and recognition that definitive multicenter replication is lacking.

4.2 Schizophrenia: Negative and Cognitive Symptoms

Schizophrenia is one of the psychiatric disorders in which adjunctive memantine has been most extensively studied. The rationale derives from the glutamate hypothesis of schizophrenia, particularly the idea that NMDA receptor dysfunction contributes to negative symptoms, cognitive impairment, and abnormal cortical integration. Tsai and Coyle [1] described glutamatergic mechanisms as central to schizophrenia pathophysiology, and the psychotomimetic effects of NMDA antagonists such as ketamine and phencyclidine have long supported a role for NMDA-related dysfunction in psychosis-spectrum disorders [75]. This creates an apparent pharmacological paradox: if NMDA receptor hypofunction contributes to schizophrenia pathophysiology, the rationale for an NMDA receptor antagonist requires careful qualification. Memantine differs from high-affinity psychotomimetic NMDA antagonists because of its low-to-moderate affinity, voltage dependence, and rapid unblocking kinetics, which may preferentially attenuate pathological tonic activation while relatively sparing physiological synaptic NMDA signaling.

The clinical rationale for memantine is strongest for negative and cognitive symptoms rather than positive symptoms. Antipsychotics generally reduce hallucinations, delusions, and disorganized thought more reliably than they improve avolition, anhedonia, blunted affect, alogia, social withdrawal, and cognitive dysfunction. These latter domains are closely linked to disability and poor functional recovery. A compound targeting glutamatergic dysfunction might therefore have particular relevance as an adjunct to antipsychotic treatment.

The clinical evidence is mixed. Lieberman and colleagues [25] conducted a randomized placebo-controlled study of memantine adjunctive to antipsychotic treatment in patients with schizophrenia and residual psychopathology. This trial did not provide convincing evidence of broad clinical benefit and remains an important negative study. It cautions against the assumption that NMDA receptor modulation alone is sufficient to improve schizophrenia outcomes.

Other studies have been more encouraging. Rezaei and colleagues [26] reported that memantine added to risperidone improved negative symptoms in stable schizophrenia, a finding echoed by Mazinani and colleagues [27], who reported improvement in negative and cognitive symptoms with the same combination. Veerman and colleagues [28] examined memantine augmentation in clozapine-refractory schizophrenia and reported benefits for memory and negative symptoms in a crossover design, while Hassanpour and colleagues [29] reported cognitive benefits including effects on verbal and working memory. De Lucena and colleagues [30], in a trial of memantine added to clozapine in treatment-refractory schizophrenia, reported improvement in both negative and positive symptoms. Not all trials were positive: a pilot study by Lee and colleagues [31] did not detect cognitive benefit.

Meta-analytic evidence supports a cautious interpretation. Zheng and colleagues [13] analyzed randomized double-blind placebo-controlled trials and found that adjunctive memantine was associated with improvement in negative symptoms and neurocognitive performance, but not total, positive, or general psychopathology. A more recent meta-analysis of randomized controlled trials likewise reported benefit for primary negative symptoms in schizophrenia, while emphasizing persisting heterogeneity and the need for larger trials [32]. Accordingly, the “Moderate” classification assigned to schizophrenia in Table 1

reflects this replicated, meta-analytically supported signal in the negative-symptom and cognitive domains rather than uniformity across individual trials; the heterogeneity described above concerns total, positive, and general psychopathology outcomes and the magnitude of the domain-specific effect, not the existence of the domain-specific benefit itself.

The heterogeneity of the schizophrenia literature may reflect differences in illness stage, baseline negative symptoms, antipsychotic background, clozapine exposure, dose, trial duration, and cognitive outcome measures. Memantine may be more useful in patients with persistent negative and cognitive symptoms than in those with acute psychosis or broad residual psychopathology. This should be read as a mechanistically motivated clinical hypothesis rather than a validated selection strategy: no predictive biomarker or patient-selection algorithm has been prospectively validated, and stratified trials are required to confirm which patients are most likely to benefit. Memantine may also require an adequate duration of treatment to influence cognitive or functional outcomes.

Clinically, memantine should not be considered an antipsychotic and should never replace antipsychotic treatment. Its most plausible role is adjunctive and domain-specific: persistent negative symptoms, cognitive impairment, and functional deficits in stable patients after optimization of standard treatment. Future trials should use modern negative-symptom scales, measurement and treatment research to improve cognition in schizophrenia (MATRICS)-style cognitive batteries, functional outcomes, longer duration, and biological stratification based on glutamatergic, inflammatory, or neurophysiological markers.

5. Disorders With Emerging, Mixed, or Preliminary Evidence

In the following disorders, the rationale is plausible, and some positive signals exist, but controlled evidence is inconsistent, limited to small or subgroup analyses, or partly negative. Memantine remains experimental and, at most, a candidate for symptom-domain-targeted study. Trichotillomania and skin-picking disorder are included here because a single well-conducted controlled trial provides an emerging, not established, signal.

5.1 Trichotillomania and Skin-Picking Disorder

Trichotillomania and skin-picking disorder are body-focused repetitive behaviors characterized by recurrent urges, repetitive motor patterns, impaired inhibitory control, and variable reward or tension-reduction components. Although classified among obsessive-compulsive and related disorders, they differ from classic OCD because they are often less dominated by intrusive obsessional fear and more driven by urge-based repetitive behavior, habit loops, sensory reinforcement, and impaired response inhibition.

This symptom architecture makes glutamatergic modulation particularly relevant. Cortico-striatal circuits involved in habit formation, motor inhibition, reward processing, and behavioral flexibility are likely involved in these behaviors. Support for glutamatergic modulation also comes from studies of N-acetylcysteine, which reduced hair-pulling in adults [82] although not in a pediatric trichotillomania trial [83].

Grant and colleagues [33] conducted an eight-week double-blind, placebo-controlled trial in adults with trichotillomania or skin-picking disorder. Memantine reduced symptom severity and was generally well tolerated. This is an encouraging controlled result, but it derives from one study and has not yet been independently replicated.

The evidence is therefore classified as emerging. Memantine should remain investigational and, if studied or used off-label, should complement rather than replace evidence-based behavioral treatment such as habit-reversal training. Replication should evaluate durability, functional outcomes, combination with behavioral therapy, and whether automatic versus focused pulling or picking and comorbid ADHD, OCD, anxiety, or tic symptoms predict response.

5.2 Bipolar Disorder and Mania

Bipolar disorder is characterized by recurrent episodes of mania, hypomania, and depression, with interepisodic cognitive and functional impairment in many patients. Glutamatergic abnormalities have been implicated in mood dysregulation, excitability, neuroplasticity, and possible neuroprogressive changes. This provides a theoretical rationale for NMDA receptor modulation, although the clinical evidence for memantine remains limited.

Interest in memantine for bipolar disorder has several possible dimensions. First, glutamatergic dysregulation may contribute to manic excitability, impulsivity, and increased goal-directed activity. Second, chronic bipolar illness is associated in some patients with cognitive impairment and functional decline, domains in which a neuroprotective or cognitive-enhancing agent might be relevant. Third, bipolar disorder frequently co-occurs with obsessive-compulsive symptoms, substance use disorders, and irritability, all of which may involve glutamatergic mechanisms.

Sahraian and colleagues [34] studied memantine as an adjuvant treatment for obsessive-compulsive symptoms during the manic phase of bipolar disorder. Anand and colleagues [35] examined memantine augmentation of lamotrigine in bipolar depression and observed an early but not durable advantage. Naturalistic and case-series data have also suggested an antimanic and sustained mood-stabilizing effect of memantine in treatment-resistant bipolar disorder, including its use as a possible lithium substitute when lithium must be discontinued [36,37]. Overall, however, this evidence remains too limited and methodologically

weak to support routine clinical use. In bipolar depression, memantine has not emerged as an established treatment.

At present, memantine should not be described as a standard treatment for mania, bipolar depression, or maintenance therapy. Established treatments such as lithium, valproate, carbamazepine, lamotrigine, quetiapine, lurasidone, cariprazine, olanzapine-fluoxetine, and other evidence-based mood-stabilizing strategies remain central [84,85]. Memantine may be of research interest in bipolar patients with prominent compulsive symptoms, cognitive impairment, treatment resistance, or intolerance to other augmentation strategies, but its use should be framed as experimental and carefully monitored.

5.3 Major Depressive Disorder and Treatment-Resistant Depression

Zarate and colleagues [38] conducted a randomized placebo-controlled study of memantine in major depression and did not find significant antidepressant benefit, and a larger augmentation trial by Smith and colleagues [39] likewise found no significant advantage of memantine over placebo. These negative trials are important because they show that NMDA receptor antagonism alone is not sufficient to produce an antidepressant effect.

A few small trials have nonetheless reported positive signals: memantine combined with sertraline improved symptoms in moderate-to-severe depression [40], and memantine added to citalopram benefited elderly depressed patients [41]. However, these findings come from small samples and require replication, and a meta-analysis across major mental disorders found no significant overall benefit in major depression [42]. More recent reviews of glutamatergic modulators for major depression continue to position memantine as an investigational option rather than an established antidepressant strategy [43].

The clinical implication is clear. Memantine should not be positioned at the same evidentiary level as lithium augmentation, selected atypical antipsychotic augmentation, thyroid hormone augmentation, ketamine or esketamine, electroconvulsive therapy, repetitive transcranial magnetic stimulation, or other guideline-supported strategies. It may be discussed as an investigational glutamatergic adjunct, particularly in patients with cognitive impairment or comorbid compulsive symptoms, but this remains a research-oriented rather than standard clinical approach.

5.4 Autism Spectrum Disorder

Autism spectrum disorder has been another area of memantine investigation, mainly because glutamatergic abnormalities, excitatory-inhibitory imbalance, irritability, repetitive behaviors, cognitive rigidity, and social impairment may be relevant in some individuals. Memantine has been examined not as a treatment for autism itself, but as a possible symptom-domain intervention.

Early uncontrolled and observational work suggested possible benefit in language, social interaction, irritability, or global behavior. Erickson and colleagues [44] reported retrospective data on memantine in children and adolescents with pervasive developmental disorders, and Chez and colleagues [45] described adjunctive memantine in children with autism spectrum disorders, reporting initial clinical response and tolerability. These studies were hypothesis-generating rather than definitive.

Randomized evidence has been mixed. Ghaleiha and colleagues [46] studied memantine adjunctive to risperidone in children with autistic disorder and reported improvement in irritability. Aman and colleagues [47] conducted randomized placebo-controlled and open-label extension studies of memantine extended-release in children with autism, focusing on safety, tolerability, and efficacy; the results were not sufficiently strong to establish memantine as a standard treatment. Brignell and colleagues [48], in a Cochrane review, concluded that the evidence base remains limited and insufficient for confident clinical recommendations.

More recent work has moved toward social impairment and biomarker-informed approaches. Joshi and colleagues [49] reported a randomized clinical trial of memantine for social impairment in youths with autism spectrum disorder. The study involved 42 participants and found a higher improvement rate in social behaviors with memantine than placebo, with response apparently enriched among participants with elevated pregenual anterior cingulate glutamate. This suggests renewed interest in memantine as a targeted, biomarker-guided intervention rather than a broad treatment for autism.

Clinically, memantine should not be described as a treatment for autism itself. It may be considered, at most, as an investigational symptom-domain adjunct for selected patients with social impairment, irritability, cognitive rigidity, or repetitive behaviors. Routine clinical use requires more evidence, especially regarding long-term developmental safety, optimal dosing, predictors of response, and interaction with behavioral interventions.

5.5 Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder has been examined as a potential target for memantine because glutamatergic and NMDA receptor signaling contributes to prefrontal executive control, working memory, and the regulation of dopaminergic tone, functions that are impaired in ADHD. The rationale is not that memantine would replace catecholaminergic stimulants, but that NMDA receptor modulation might complement them by targeting the executive dysfunction that is often incompletely addressed by stimulant monotherapy.

The clinical evidence is limited to small studies. Surman and colleagues [50] conducted a 12-week open-label prospective trial of memantine monotherapy (titrated from

5 to 20 mg/day) in 34 adults with ADHD and reported improvement in ADHD symptoms and neuropsychological performance with good tolerability, although the absence of a control group and the open design markedly limit interpretation. Biederman and colleagues [51] subsequently performed a 12-week pilot double-blind, placebo-controlled randomized trial of memantine added to osmotic-release oral system methylphenidate in adults with ADHD and executive-function deficits (12 receiving memantine, 14 placebo); they observed trend-level improvements on the inhibition and self-monitoring subscales of the Behavior Rating Inventory of Executive Function–Adult version and a higher proportion of responders on a composite executive-function measure (50% versus 20%), without a robust effect on the primary outcome. Both studies were small and of short duration, and neither has been independently replicated.

Overall, the evidence is preliminary; stimulants remain first-line, and memantine is not an established ADHD treatment, but it may warrant study as an adjunct targeting executive dysfunction. Any such use would be strictly off-label and investigational.

5.6 Eating Disorders and Binge Eating

Binge eating disorder and related conditions involve compulsive, reward-driven overeating and impaired inhibitory control, providing a glutamatergic rationale analogous to that for body-focused and impulse-control disorders. In an open-label, prospective trial, memantine reduced the frequency of binge days and episodes and overall illness severity, although without significant change in body weight [52]. Evidence is limited to small uncontrolled studies, and memantine cannot currently be recommended for eating disorders outside research settings; controlled trials are needed.

5.7 Impulse-Control Disorders: Gambling and Compulsive Buying

Glutamatergic modulation has also been explored in impulse-control and related disorders characterized by impaired inhibitory control and urge-driven reward seeking. In a pilot open-label study, memantine reduced gambling severity and improved cognitive flexibility in pathological gambling [53], and a separate open-label study suggested benefit in compulsive buying [54]. These findings are preliminary and uncontrolled. Controlled trials are lacking, and the evidence does not support routine clinical use.

6. Disorders With Sparse, Predominantly Negative, or Specialist-Only Evidence

The remaining areas are characterized by sparse evidence, predominantly negative controlled findings, or specialist-only case-based experience. They are included to complete the clinical map and to define where memantine should not currently be positioned as routine psychiatric treatment.

6.1 Substance Use Disorders

The rationale for memantine in substance use disorders derives from the role of glutamate and NMDA receptors in reward learning, tolerance, withdrawal, cue reactivity, and relapse. Chronic substance exposure changes glutamatergic signaling in prefrontal-limbic and cortico-striatal circuits, and NMDA receptor modulation could theoretically reduce craving, withdrawal-related neuroadaptation, or relapse vulnerability.

Despite this rationale, the clinical evidence is inconsistent. In alcohol use disorder, NMDA receptor activity is relevant to tolerance and withdrawal physiology. Petrakis and colleagues [55] examined altered response to NMDA receptor antagonism in recovering ethanol-dependent patients; Krupitsky and colleagues [56] found that memantine reduced cue-induced alcohol craving but also produced dose-related alcohol-like subjective effects.

Randomized controlled trials of memantine as a relapse-prevention or anti-craving agent have, however, been largely negative. Memantine added to naltrexone did not improve outcomes in opioid dependence in trials using either oral or extended-release naltrexone [57,58], and a placebo-controlled trial found no broad benefit in cocaine dependence [59]. These negative results temper enthusiasm despite the mechanistic rationale.

Clinically, memantine should not be presented as a standard treatment for addiction. Evidence-supported pharmacological treatments such as naltrexone, acamprosate, buprenorphine, methadone, varenicline, bupropion, and nicotine replacement, where appropriate, remain primary. Memantine may be considered a research candidate in subgroups with cognitive impairment, excitatory dysregulation, or comorbid compulsive symptoms, but the present evidence does not support routine use. Future studies should distinguish craving reduction, abstinence initiation, relapse prevention, cognitive control, and withdrawal modulation as separate outcomes.

6.2 Anxiety Disorders, PTSD, and Stress-Related Disorders

The evidence for memantine in anxiety disorders and post-traumatic stress disorder remains limited. The mechanistic rationale is not implausible: glutamate signaling is involved in fear learning, extinction, memory reconsolidation, and stress-related neuroplasticity. NMDA receptor modulation could theoretically influence pathological fear memories or hyperarousal, but the direction of effect may depend on timing, dose, and the relationship to psychotherapy or exposure-based learning.

Unlike D-cycloserine, an NMDA receptor partial agonist studied as an enhancer of exposure learning [86,87], memantine has not established a clear role in exposure-

based psychotherapy augmentation. Small open-label studies of memantine augmentation in anxiety have reported mixed results, with possible benefit in generalized anxiety in some case series [60] but not in a controlled comparison where benefit appeared in OCD rather than generalized anxiety [17]. In PTSD, a small open-label pilot trial suggested improvement in memory and some symptom clusters, but the sample was very small and uncontrolled [61].

At present, memantine should not replace trauma-focused psychotherapy, selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) when indicated, sleep-focused interventions, or integrated approaches for comorbid substance use. Its possible role in PTSD with cognitive impairment, traumatic brain injury, severe hyperarousal, or treatment resistance remains speculative, and evidence is insufficient to support routine use in primary anxiety disorders or PTSD.

6.3 Catatonia

Catatonia is a distinctive area because NMDA receptor antagonists, including amantadine and memantine, have been described in case reports and small series. The rationale involves glutamate-gamma-aminobutyric acid (GABA) imbalance, motor circuit dysfunction, and severe psychomotor dysregulation. Carroll and colleagues [62] reviewed adjunctive glutamate antagonist therapy in catatonic syndromes and described a possible role for agents such as amantadine and memantine in selected cases, and individual reports have described memantine response in catatonia [63].

However, the evidence remains far below that for benzodiazepines and electroconvulsive therapy. Catatonia is a potentially severe syndrome requiring prompt recognition and treatment; delayed treatment can lead to medical complications, including dehydration, malnutrition, thromboembolism, autonomic instability, and malignant catatonia. Therefore, memantine should never delay standard treatment. The appropriate clinical position is that memantine may be considered only as a specialist adjunct in selected refractory cases, particularly when benzodiazepines and electroconvulsive therapy are insufficient, contraindicated, or only partially effective.

6.4 Behavioral and Psychological Symptoms of Dementia

Behavioral and psychological symptoms of dementia (BPSD)—including agitation, irritability, aggression, and psychosis—are referred to in the clinical-positioning section because memantine is approved for moderate-to-severe Alzheimer disease and is used in old-age psychiatry [8]. However, BPSD arises in the context of a neurodegenerative disorder rather than as a primary psychiatric syndrome, and a detailed appraisal of memantine for BPSD is governed by dementia-treatment guidelines and lies outside the scope of this review of psychiatric repurposing. We therefore mention BPSD only to delimit it: its use in this setting falls within the approved, guideline-governed treatment of moderate-to-severe Alzheimer disease and does not constitute evidence of memantine-specific efficacy for behavioral and psychological symptoms per se. The dedicated BPSD evidence is itself mixed; it should therefore not be read as support for broader psychiatric repurposing, and it is listed in Table 1 for completeness with this caveat.

6.5 Electroconvulsive Therapy-Related Cognitive Complaints

Electroconvulsive therapy (ECT) is highly effective for severe mood disorders and catatonia, but acute and sometimes persistent cognitive adverse effects—particularly anterograde and retrograde memory disturbance—remain clinically important. NMDA-receptor modulation has therefore been studied as a strategy to attenuate ECT-related cognitive change. The evidence is more substantial than a purely mechanistic rationale, but it remains small, heterogeneous, and methodologically limited.

Two small placebo-controlled trials published in 2015 reported relative preservation of global cognition or digit-span performance with memantine during an ECT course. Abbasinazari and colleagues [64] randomized 40 patients with major depressive disorder to memantine 5 mg/day or placebo, while Alizadeh and colleagues [65] randomized 38 patients to memantine titrated to 20 mg/day or placebo. A subsequent 40-participant randomized active-comparator trial found a more favorable Mini-Mental State Examination trajectory with memantine 5 mg/day than with melatonin 3 mg/day across six ECT sessions [66]. Interpretation is limited by small samples, heterogeneous dosing and comparators, brief exposure, and reliance on coarse global measures rather than sensitive assessments of autobiographical and retrograde memory.

A 2022 systematic review and meta-analysis found a signal favoring memantine, but rated the evidence as low quality because of heterogeneity in ECT technique, populations, and cognitive measurement [67]. In a 2025 three-arm randomized trial, rivastigmine improved cognitive recovery, whereas memantine showed a positive but non-significant adjusted effect relative to placebo [68]. The ECT evidence is therefore classified as limited/mixed, not insufficient. It does not support routine prophylactic use; adequately powered trials with standardized ECT parameters, prespecified memory outcomes, longer follow-up, and clinically meaningful functional measures are required.

7. Safety, Tolerability, and Practical Considerations

Memantine is generally well tolerated, but it is not free of adverse effects. Common adverse events include dizziness, headache, constipation, somnolence, confusion, hypertension, nausea, and fatigue. In psychiatric populations, additional concerns include agitation, insomnia, irritability,

anxiety, and possible worsening of behavioral activation in vulnerable patients.

Psychiatric studies often use doses similar to those used in Alzheimer disease, commonly titrated toward 20 mg/day. Modaresi and colleagues [21] noted that many OCD augmentation studies used 20 mg/day for at least eight weeks, while Grant and colleagues [33] used 10 to 20 mg/day in trichotillomania and skin-picking disorder.

Memantine has a relatively limited cytochrome P450 interaction burden, but pharmacokinetic and medical considerations remain important. Because it is predominantly eliminated by the kidney, dose recommendations vary according to renal function, formulation, and jurisdiction; clinicians should consult the applicable local product information rather than extrapolate a single universal threshold. Conditions or medicines that raise urinary pH may reduce renal clearance and increase exposure. Caution is also appropriate in patients with seizure disorders, severe agitation, insomnia or behavioral activation, unstable medical illness, or complex polypharmacy. The doses described in this review are study characteristics and should not be interpreted as prescribing instructions.

Additional caution applies in specific populations. In older adults, comorbidity, polypharmacy, and reduced renal clearance increase the potential for adverse effects, and slow titration is advisable. In children and adolescents, psychiatric use of memantine is investigational, long-term developmental safety data are lacking, and it should be considered only within research or specialist settings. Across all psychiatric indications discussed in this review, memantine use is off-label; patients or their carers should be informed that the evidence varies substantially by condition and that memantine is not an approved psychiatric treatment, and appropriate informed consent should be obtained and documented. The doses and durations reported in this review are those used in the cited studies and are provided for descriptive purposes only; they do not constitute prescribing guidance.

8. Clinical Positioning

Memantine is not a first-line psychiatric treatment. It is not a substitute for antipsychotics in schizophrenia, serotonergic treatment and exposure-based therapy in OCD, mood stabilizers in bipolar disorder, evidence-based antidepressant augmentation in depression, or behavioral therapy in body-focused repetitive behaviors.

The literature most plausibly positions memantine as an investigational, adjunctive, symptom-domain strategy rather than a diagnosis-wide treatment. In schizophrenia, the comparatively stronger signal concerns persistent negative symptoms and selected cognitive outcomes, without substituting for antipsychotic treatment. In OCD, evidence is limited/mixed and routine augmentation is not supported; only rigorously defined treatment-resistant populations justify further definitive study or exceptionally cautious off-label discussion. In trichotillomania and skin-picking disorder, one positive controlled trial provides an emerging signal requiring independent replication. Evidence in autism spectrum disorder, ADHD, eating disorders, impulse-control disorders, mood disorders, anxiety/PTSD, substance use disorders, catatonia, and ECT-related cognitive complaints remains limited/mixed, preliminary, or insufficient. BPSD belongs to the approved dementia-care context and is not evidence for psychiatric repurposing. Table 1 summarizes the evidence and clinical positioning across disorders.

The best future use of memantine in psychiatry is unlikely to be diagnosis-wide. Rather, it should be phenotype-guided: compulsivity, repetitive behavior, negative symptoms, cognitive impairment, glutamatergic biomarker abnormalities, or treatment resistance may be more useful selection criteria than diagnostic and statistical manual of mental disorders (DSM) diagnosis alone.

This clinical positioning summarizes the relative development and direction of the literature; it is not a set of prescribing recommendations. Any off-label use should follow local regulation and applicable product information, occur only after optimization of established treatments, and include individualized risk-benefit assessment, measurement-based follow-up, and documented informed consent.

9. Future Directions

Several limitations of the current evidence should frame these future directions. Across psychiatric indications, the literature is uneven in both quantity and methodological strength, with many findings derived from small studies, heterogeneous clinical populations, adjunctive designs with differing background treatments, and variable outcome measures. Positive signals are often domain-specific and, in several conditions, remain dependent on single studies or lack independent replication, whereas negative or neutral findings are also present. Follow-up is generally insufficient to establish the durability of potential benefits, and few studies have prospectively tested clinical or biological predictors of response. These limitations restrict generalizability and preclude firm conclusions regarding which patients, symptom domains, or treatment contexts are most likely to benefit from memantine.

Future memantine research in psychiatry should move toward precision medicine. Broad diagnostic trials are unlikely to identify the patients most likely to benefit. Candidate response predictors include baseline glutamate or glutamine measures on magnetic resonance spectroscopy, cognitive profile, degree of compulsivity, negative-symptom burden, executive dysfunction, illness stage, treatment resistance, comorbid neurodevelopmental features, and medication background.

Trial design should become more specific and methodologically rigorous. In schizophrenia, studies should en-

rich for persistent primary negative symptoms, use modern negative-symptom instruments and MATRICS-based cognitive batteries, and include functional outcomes over longer follow-up. In OCD, definitive trials should use prospectively operationalized treatment resistance, standardized background therapy, concealed allocation, blinded assessment, functional outcomes, and sufficient power to test the hypothesis-generating refractory subgroup. In trichotillomania and skin-picking disorder, independent replication should examine combination with habit-reversal therapy. In autism spectrum disorder and ADHD, biomarker-enriched, domain-specific designs are preferable to broad syndromic trials. In ECT-related cognition, future studies should standardize ECT parameters and prioritize autobiographical, retrograde, and anterograde memory measures rather than global screening tests. Across indications, preregistered, phenotype-stratified randomized trials with transparent reporting and longer follow-up are the priority.

Memantine also raises a broader conceptual issue. Psychiatric drug development has often treated diagnoses as unitary targets. Memantine suggests a different model: targeting transdiagnostic neurobiological dimensions, such as glutamatergic dysregulation, compulsivity, cognitive dysfunction, and pathological network excitability.

10. Conclusions

Memantine is a biologically plausible but clinically unestablished psychiatric adjunct. Its uncompetitive NMDA-receptor antagonism supports investigation across symptom domains involving pathological glutamatergic signaling, compulsivity, repetitive behavior, negative symptoms, cognitive dysfunction, and network excitability. The most developed and comparatively consistent signal concerns selected negative and cognitive outcomes in schizophrenia. OCD has a substantial augmentation literature, but the overall evidence is limited/mixed, and an updated meta-analysis does not support routine use in unselected patients; a treatment-resistant subgroup signal remains hypothesis-generating. Trichotillomania and skin-picking disorder have an emerging signal from one positive controlled trial. Evidence across other psychiatric indications remains limited/mixed, preliminary, or insufficient, while ECT-related cognition has small controlled and meta-analytic signals that remain too heterogeneous for routine use.

Memantine should therefore be framed neither as a general psychiatric treatment nor as a substitute for established care. Its value at present is primarily conceptual and investigational: it illustrates how drug repurposing may target transdiagnostic phenotypes rather than diagnoses alone. Any exceptional off-label use requires transparent discussion of uncertainty, adherence to local product information, prior optimization of standard treatment, individualized risk-benefit assessment, and measurement-based monitoring.

Abbreviations

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BPSD, behavioral and psychological symptoms of dementia; DSM, diagnostic and statistical manual of mental disorders; ECT, electroconvulsive therapy; GABA, gamma-aminobutyric acid; MATRICS, measurement and treatment research to improve cognition in schizophrenia; NMDA, N-methyl-D-aspartate; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; RCT, randomized controlled trial; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; TRD, treatment-resistant depression; Y-BOCS, yale-brown obsessive compulsive scale; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RoB 2, Cochrane Risk of Bias 2.

Author Contributions

MP: conceptualization, methodology, investigation, resources, writing – original draft, writing – review & editing. AF: conceptualization, supervision, validation, writing – review & editing. MBR: conceptualization, methodology, investigation, writing – review & editing. AC: conceptualization, supervision, validation, writing – review & editing. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

Andrea Fagiolini has received research grants and has been a consultant and a speaker for Allergan, Angelini, Apsend, Generici DOC, Lundbeck, Italfar-maco, Janssen, Otsuka, Pfizer, Recordati, Roche, Sanofi Aventis, and Sunovion; Alessandro Cuomo has been a consultant and a speaker for Angelini, GlaxoSmithKline, Lundbeck, Janssen, Otsuka, Pfizer, and Recordati. The other authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used artificial intelligence-based language tools (ChatGPT, using GPT-5.6, and Claude Fable 5.1) solely to support linguistic refinement, editorial organization, and improvement of clarity and readability (for example, spelling and grammar checking). After using these tools, the authors reviewed and edited the content as needed, and all references and factual statements were independently checked by the authors. The conceptualization, scientific content, interpretation of the literature, critical appraisal, and final intellectual responsibility for the manuscript remain entirely with the authors, who take full responsibility for the content of the publication.

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