Immune-Targeted Therapies for Depression:

Current Evidence for Antidepressant Effects of Monoclonal Antibodies

Mina M. Rizk, MD; Lindsay Bolton, BS; Flurin Cathomas, MD, PhD; Helen He, MD, PhD; Scott J. Russo, PhD; Emma Guttman-Yassky, MD, PhD; J. John Mann, MD; and James Murrough, MD, PhD

Abstract

Importance: Increasing evidence suggests a potential role of immune-modulatory drugs for treatment-resistant depression. This scoping review explores the emerging evidence regarding the antidepressant effects of monoclonal antibodies (mAbs), a relatively newer class of immune therapeutics with favorable safety profile.

Observations: PubMed was searched up to November 2023 for English publications addressing the antidepressant effects of mAbs, including meta-analyses, randomized controlled trials, open-label, single-arm studies, and case series. Several mAbs have shown potential antidepressant effects, but most studies in primary inflammatory disorders included patients with mild depression. Only infliximab and sirukumab were directly examined in individuals with primary depression. mAbs that do not require laboratory monitoring, such as ixekizumab and dupilumab, could hold potential promise if future studies establish their safety profile regarding suicide risk.

Conclusions and Relevance: The use of several mAbs for the treatment of primary inflammatory disorders has been associated with improvement of comorbid depressive symptoms. Given their unique mechanisms of action, mAbs may offer a new hope for depressed patients who do not respond to currently available antidepressants. Further research addressing individuals with more severe depressive symptoms is essential. Direct examination of antidepressant effects of mAbs in people with primary depressive disorders is also crucial to refine their clinical use in the treatment of depression.

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Author affiliations are listed at the end of this article.

Major depressive disorder (MDD) remains a major public health problem affecting about 20.6% of US individuals within their lifetime.[1] The prevalence of MDD has climbed by 12.9% between 2010 and 2018 in the United States[2] and continues to increase.[3] MDD is associated with significant financial burden.[2] Two-thirds of individuals with MDD experience suicidal thoughts and 13.6% attempt suicide.[1] Successful treatment of MDD may help reduce disease burden, minimize suicide risk, and improve functional outcomes.

LIMITATIONS OF CURRENT ANTIDEPRESSANT MEDICATIONS

Current treatment options for MDD have limitations. Presently available antidepressants, such as those targeting monoamine neurotransmitters, take weeks to work fully and do not lead to a significant benefit in about half of the patients who adhere to them. Studies like the Sequenced Treatment Alternatives to Relieve Depression trial,[4] the largest prospective study of antidepressant efficacy, found that even after several months of sequential treatment trials, one-third of patients with MDD remained depressed.[5] More recent evidence indicates that only 43.5% of adults who take antidepressant medications achieve remission after at least 3 months.[6] Depression that does not respond to 2 antidepressants at an adequate dose and duration is classified as treatment-resistant.[7] Treatment-resistant depression (TRD) is associated with elevated risk of all-cause mortality (including suicide), greater utilization of health care resources, lost workdays, and psychiatric comorbidities such as anxiety and stress.[8,9] Identifying drugs with novel antidepressant mechanisms could help provide relief for the significant portion of people whose depression does not respond to current medications.

Immune Dysregulation and MDD

Much evidence indicates that immune dysregulation is associated with depression.[10,11] Immune abnormalities in MDD include elevated levels of proinflammatory cytokines and acute phase proteins in blood and cerebrospinal fluid, a dysregulated adaptive immune response, changes in the proportions of specific immune cell types, primary humoral immunodeficiencies, a

Clinical Points

- Immune dysregulation is associated with depression and may contribute to treatment resistance.
- Monoclonal antibodies are novel immune therapies that have shown promise in the treatment of depression when used for primary inflammatory disorders.
- Future research is needed to determine the efficacy and safety of the use of monoclonal antibodies for patients with primary depression.

tendency toward autoimmunity, and activation of microglia.[12,13] Some of these immune changes have been shown to contribute to treatment resistance.[14–16] Elevated levels of the proinflammatory interleukin (IL)-17A predict nonresponse to antidepressants at 6 weeks in people with MDD.[15] Higher baseline IL-6 is more common in patients with TRD, compared with those whose depression responds to antidepressant medications.[16] Individuals with MDD and elevated inflammatory and metabolic markers are more likely to remain depressed for 2 years despite taking antidepressants.[14]

Drugs that modulate dysregulated immune pathways could thus be particularly beneficial for TRD. In fact, increasing evidence supports the role of immune modulation in the treatment of depression. A meta-analysis of 18 randomized controlled trials (RCTs) on more than 10,000 patients with primary inflammatory disorders shows that the use of immune-modulatory drugs is associated with significant reduction of depressive symptoms in the subgroup of patients with high baseline depression scores, even after controlling for the physical health benefits of these treatments.[17] In addition, previous review articles have commented on some anti-inflammatory and immune-modulating agents as potential treatments for depression.[12,18] A meta-analysis of 14 RCTs on various nonsteroidal anti-inflammatory drugs (NSAIDs) and cytokine inhibitors suggested that these interventions reduced depressive symptoms compared with placebo, in both patients with depression and those with primary inflammatory disorders and comorbid depressive symptoms.[19] However, there was a significant heterogeneity among included studies. Another meta-analysis of 30 RCTs suggested that anti-inflammatory agents, including NSAIDs, omega-3 fatty acids, statins, and minocyclines, reduced depressive symptoms and resulted in higher response and remission rates compared with placebo, an effect that was more pronounced when the anti-inflammatory agents were used as adjunctive treatments to antidepressants, rather than monotherapies.[20]

In recent years, there has been a translational revolution in our understanding of the biomarkers underlying the pathogenesis of immune and inflammatory disorders across skin, gastrointestinal, and other compartments.[21,22] This has led to the development of specific anti-inflammatory agents that target these markers, improving patient outcomes. Prior to these advancements, systemic immunosuppressant drugs were used to treat these disorders, but they often resulted in significant side effects. Monoclonal antibodies (mAbs) are a relatively newer class of drugs that target specific cytokines and have shown remarkable efficacy in treating inflammatory immune disorders with high precision and fewer side effects.[23] As researchers began to explore the link between immune dysregulation and depression, the potential of mAbs to treat depression, particularly TRD, became an area of interest. A meta-analysis of 7 RCTs involving more than 2,000 participants showed a significant antidepressant effect of anticytokine treatments, including etanercept, infliximab, adalimumab, and tocilizumab, compared with placebo.[24] Another analysis of 2 RCTs of adjunctive treatment with anticytokine therapy and 8 nonrandomized and/or nonplacebo studies yielded similar small-to-medium effect estimates favoring those anticytokine therapy for depressive symptoms.[24] In this scoping review, we will focus on the newer emerging evidence of the potential antidepressant effects of mAbs.

METHODS

We searched PubMed (up to November 2023) for studies published, using the key terms “depression,” “depressive,” “depressive disorder,” and “major depressive disorder,” with specifiers “monoclonal antibodies,” “immune,” “inflammation,” “inflammatory,” “anti-inflammatory,” as well as “suicide,” “mechanism,” and “safe(ty),” and chose the articles we deemed relevant. We also searched the reference lists of articles identified with the use of this search strategy and included papers that we judged to be applicable. We restricted the search to English-language publications. Table 1 shows details about the studies on potential antidepressant effects of mAbs included in this review. Figure 1 shows the mechanisms of action of these mAbs and the reported changes in their cytokine targets in people with depression.

This narrative review aims to provide a comprehensive summary of the association between changes in depressive symptoms and mAbs treatment. To achieve this, we included 2 types of studies: (1) studies focusing on the efficacy of mAbs for primary inflammatory disorders, where depression assessment served as a secondary outcome measure; (2) studies investigating the antidepressant effects of mAbs in patients with a primary diagnosis of depression,

Table 1.

Summary of Studies Reporting Changes in Depression Scores With mAbs Treatment

Study	Study design	Primary disorder	Depression scale	Sample	Baseline score Mean (SD)[a]	Follow-up scores Mean (SD)[a]	Treatment vs placebo	Relationship between depression and physical symptoms	Concurrent medications	Quality of evidence (GRADE score)	Adverse events
Adalimumab											
Loftus et al[25]	Randomized, double-blind	Crohn disease	ZDS	Adalimumab induction only then placebo: n = 170 Adalimumab biweekly maintenance 40 mg: n = 172 Adalimumab weekly maintenance 40 mg: n = 157	Placebo: 55.2 (11.7) Adalimumab biweekly maintenance: 54.8 (11.4) Adalimumab weekly maintenance: 56.7 (11.1)	Wk 4: Placebo: 46.1 (11.9) Biweekly: 44.9 (10.7) Weekly: 47.0 (11.2) Wk 12: Placebo: 47.4 (12.8) Biweekly: 43.4 (11.0) Weekly: 12: 46.1 (11.5) Wk 26: Placebo: 47.4 (12.7) Biweekly: 43.7 (10.9) Weekly: 46.3 (12.1) Wk 56: Placebo: 47.9 (13.1) Biweekly: 43.7 (11.0) Weekly: 45.9 (12.3)	Biweekly vs placebo: $P < .01$ Weekly vs placebo: $P < .05$		Immunosuppressants: placebo: 49% Adalimumab biweekly: 45% Adalimumab weekly: 50% No psychotropic medications reported	Moderate	
Menter et al[26]	Randomized, placebo-controlled, double-blind	Psoriasis	ZDS	Adalimumab: n = 44 Placebo: n = 52	Adalimumab: 42.9 (12.4) Placebo: 45.8 (14.0)	Wk 12: Adalimumab: 36.2 (11.5) Placebo: 44.2 (14.2)	95% CI, 2.5–9.5; $P < .001$	Improvement in psoriasis area and Severity Index score and Dermatology Life Quality Index score correlate with depression score reduction	No anti-inflammatory or psychotropic medications reported	Moderate	
Bimekizumab											
Blauvelt et al[27]	Secondary analysis of 9 randomized, controlled trials	Psoriasis	PHQ-9	Bimekizumab vs placebo (n = 670 vs n = 169) Bimekizumab vs adalimumab (n = 319 vs n = 159) Bimekizumab vs secukinumab (n = 373 vs n = 370) Bimekizumab vs ustekinumab (n = 321 vs n = 163)	Bimekizumab vs placebo: 2.5 vs 2.7 Bimekizumab vs adalimumab: 2.8 vs 3.0 Bimekizumab vs secukinumab: 2.6 vs 2.5 Bimekizumab vs ustekinumab: 2.5 vs 2.6	Wk 16: Bimekizumab vs placebo: 1.2 vs 2.4 Bimekizumab vs adalimumab: 1.3 vs 1.5 Bimekizumab vs secukinumab: 1.1 vs 1.0 Bimekizumab vs ustekinumab: 1.1 vs 1.2	None reported		No anti-inflammatory or psychotropic medications reported	Very low	

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Table 1 (continued).

Study	Study design	Primary disorder	Depression scale	Sample	Baseline score Mean (SD)[a]	Follow-up scores Mean (SD)[a]	Treatment vs placebo	Relationship between depression and physical symptoms	Concurrent medications	Quality of evidence (GRADE score)	Adverse events
Brodalumab											
Papp et al[28]	Randomized, placebo-controlled, double-blind	Plaque psoriasis	HADS depression	Brodalumab biweekly 140 mg: n = 219 Brodalumab biweekly 210 mg: n = 222 Placebo: n = 220	Brodalumab 140 mg: 5.2 (4.1) Brodalumab 210 mg: 5.5 (4.2) Placebo: 5.3 (3.9)	Wk 12: Brodalumab 140 mg: 3.6 (0.3) Brodalumab 210 mg: 3.5 (0.2) Placebo: 5.5 (0.3)	95% CI brodalumab 140 mg vs placebo: 3.1–4.1, $P < .001$ 95% CI brodalumab 140 mg vs placebo: 3.0–3.9, $P < .001$		No anti-inflammatory or psychotropic medications reported	Moderate	Brodalumab 140 mg: Any (n = 126), depression (n = 1), local reaction (n = 3), neutropenia (n = 1), serious infection (n = 2), *Candida* infection (n = 1), nasopharyngitis (n = 20), respiratory tract infection (n = 18), headache (n = 12) Brodalumab 210 mg: Any (n = 131), depression (n = 1), local reaction (n = 1), serious infection (n = 1), *Candida* infections (n = 5), nasopharyngitis (n = 21), respiratory tract infection (n = 18), headache (n = 11) Placebo: Any (n = 112), depression (n = 1), *Candida* infections (n = 3), nasopharyngitis (n = 22), respiratory tract infection (n = 14), headache (n = 7)
Ohata et al[29]	Single-arm, open-label	Plaque psoriasis	PHQ-8	n = 73 (n = 16 with baseline PHQ-8 scores of ≥5)	Median (Q1–Q3): 7.5 (6.5–11.5)	Wk 12: median (Q1–Q3) = 5.0 (1.5–8.5) Wk 48: median (Q1–Q3) = 6.0 (1.0–8.0)	$P = .006$ at wk 12, $P = .01$ at wk 48		No anti-inflammatory or psychotropic medications reported	Very low	Worsened depression/anxiety (n = 2), worsened psoriasis (n = 1), eczema (n = 1), coxalgia (n = 1)
Dupilumab											
Lönndahl et al[30]	Case series	Prurigo nodularis	MADRS	n = 19	Median (IQR): 13 (8–19)	Median (IQR): 6 (4–10) at 1–3 mo	$P = .002$		Methotrexate: 70% Cyclosporine: 30% No psychotropic medications reported	Very low	Dry eyes (n = 4), injection site redness (n = 1), headache (n = 1)

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Table 1 (continued).

Study	Study design	Primary disorder	Depression scale	Sample	Baseline score Mean (SD)[a]	Follow-up scores Mean (SD)[a]	Treatment vs placebo	Relationship between depression and physical symptoms	Concurrent medications	Quality of evidence (GRADE score)	Adverse events
Cork et al[31]	Randomized, placebo-controlled, double-blind	Atopic dermatitis	HADS	Dupilumab 300 mg biweekly: n = 457 Dupilumab 300 mg weekly: n = 462 Placebo: n = 460	Dupilumab biweekly: 13.0 (7.4) Dupilumab weekly: 13.7 (8.2) Placebo: 13.2 (8.3)	Wk 2: Dupilumab biweekly: 10.1 (7.17) Dupilumab weekly: 10.7 (7.97) Placebo: 12.4 (8.07) Wk 16: Dupilumab biweekly: 8.3 (7.12) Dupilumab weekly: 8.7 (7.92) Placebo: 12.2 (8.02)	*P*s < .0001		No anti-inflammatory or psychotropic medications reported	Moderate	
Ferrucci et al[32]	Retrospective	Atopic dermatitis	HADS depression	n = 117	Median IQR): 7 (4–10)	Wk 4: Median (IQR): 4 (1–7) Wk 16: median (IQR): 3 (0–6)	*P* < .0001		Current topical corticosteroids or calcineurin inhibitors were allowed No psychotropic medications reported	Very low	Blepharoconjunctivitis (n = 14), facial redness (n = 6), paradoxical psoriasis (n = 1)
Miniotti et al[33]	Observational prospective cohort	Atopic dermatitis	HADS depression	n = 171	6.0 (3.0–9.0)	Wk 16: 3.0 (2.0–6.0) Wk 32: 3.0 (1.0–6.0)	*P* < .001		No psychotropic anti-inflammatory or medications reported	Very low	Injection site reaction (n = 2), herpes (n = 6), blepharitis or conjunctivitis (n = 18), cephalea (n = 5), itchy eye (n = 11)
Koya et al[34]	Single-arm	Asthma with eosinophilic chronic rhinosinusitis	PHQ-9	n = 31	Median (range): 5 (0–14)	PHQ-9 score was reduced (exact change not reported)	*P* = .003	Nasal symptom score reduction and improvement in asthma correlated with depression score reduction	Oral corticosteroids: n = 9 Long-acting β agonist: n = 31 No psychotropic medications reported	Very low	
Guselkumab											
Gordon et al[35]	Randomized, double-blind, placebo- and adalimumab-controlled	Plaque psoriasis	HADS depression	Guselkumab: n = 496 Adalimumab: n = 248 Placebo: n = 248	Guselkumab: 5.3 (4.2) Adalimumab: 5.3 (4.3) Placebo: 5.1 (4.3)	Wk 8: Guselkumab: 4.0 (0.9) Adalimumab: 4.1 (1.3) Placebo: 5.1 (1.4) Wk 16: Guselkumab: 3.7 (0.6) Adalimumab: 4.1 (0.9) Placebo: 5.0 (1.4) Wk 24: Guselkumab: 3.6 (0.4) Adalimumab: 4.2 (0.7)	Wk 8 and 16: Guselkumab vs placebo: *P*s < .001 Adalimumab vs placebo: *P*s < .001 Wk 24: Guselkumab vs Adalimumab: *P* = .06	Improvement in Psoriasis Area and Severity Index correlated with depression score reduction in those with a baseline HADS of ≥8	No anti-inflammatory medications reported Antidepressants: 3.7% across all groups Benzodiazepines: 2.4% across all groups	Moderate	Guselkumab: generalized anxiety disorder (n = 1), suicidal ideation (n = 1) Adalimumab: generalized anxiety disorder (n = 2), suicide attempt (n = 1), other anxiety (n = 1), panic attack (n = 1), depression (n = 2) Placebo: anxiety (n = 1)

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Table 1 (continued).

Study	Study design	Primary disorder	Depression scale	Sample	Baseline score Mean (SD)[a]	Follow-up scores Mean (SD)[a]	Treatment vs placebo	Relationship between depression and physical symptoms	Concurrent medications	Quality of evidence (GRADE score)	Adverse events
Infliximab											
Minderhoud et al[36]	Single-blinded	Crohn disease	CES-D	n = 14 (all received placebo at d 0 then infliximab at Day 14 and 28)	Infliximab: 17.0 (2.9) Placebo: 20.4 (9.4)	Day 14: Infliximab: 14.0 (2.4) Placebo: 17.0 (2.9)	$P \leq .01$		No anti-inflammatory or psychotropic medications reported	Very low	
Ertenli et al[37]	Open-label, single-arm	Ankylosing spondylitis	HADS depression, BDI	n = 16	HADS depression: 7.6 (4.1) BDI: 15.4 (7.1)	Day 2: HADS: 6.6 (3.6) BDI: 10.1 (7.2) Day 14: HADS: 5.0 (3.4) BDI: 6.7 (7.5) Day 42: HADS: 4.6 (3.9) BDI: 7.1 (7.8)	Time effect: HADS: $F = 3.39$, $P = .058$, $df = 1.7$ BDI: $\chi^2 = 20.8$, $df = 3$, $P < .01$	Change in physical symptoms did not correlate with depression scores reduction	No anti-inflammatory or psychotropic medications reported	Very low	
Raison et al[38]	Randomized, placebo-controlled, double-blind	Treatment-resistant depression	HDRS	Infliximab: n = 30 Placebo: n = 30	Infliximab: 24.1 (4.0) Placebo: 23.6 (3.8)		Treatment× time× log hs-CRP interaction: ($t = 2.65$, $df = 302$, $P = .01$) Effect driven by those with hs-CRP of > 5		Anti-inflammatory medications (except Aspirin) were not allowed Current psychotropic medications continued at stable doses	Moderate	Infliximab: headache (n = 20), coughing (n = 5), sore throat (n = 4), insomnia (n = 5), diarrhea (n = 3), upper respiratory infection (n = 4), nasal congestion (n = 4), myalgia (n = 4), panic attacks (n = 2), rash (n = 4), fever (n = 1), sinus congestion (n = 4), yeast infection (n = 3) Placebo: Headaches (n = 18), coughing (n = 5), sore throat (n = 6), insomnia (n = 4), diarrhea (n = 6), upper respiratory infection (n = 2), nasal congestion (n = 2), myalgia (n = 1), panic attacks (n = 3), rash (n = 1), fever (n = 1), increased urinary leukocyte esterase (n = 10), yeast infection (n = 1), increased urinary white blood cells (n = 3)
Lee et al[39]	Randomized, double-blind, placebo-controlled	Bipolar I/II depression	SHAPS	Infliximab: n = 29 Placebo: n = 31	Infliximab: 34.04 (1.73) Placebo: 34.78 (1.45)	Wk 6: Infliximab: 40.68 (1.90) Placebo: 37.18 (2.05) Wk 12: Infliximab: 37.17 (1.55) Placebo: 40.79 (1.69)	Treatment× time interaction effect: $\chi^2 = 7.15$, $df = 2$, $P = .03$	Baseline and changes in soluble TNF receptors concentrations did not correlate with reduction in anhedonia	Anti-inflammatory medications (except Aspirin) were not allowed Current psychotropic medications continued at stable doses	Moderate	Moderate allergic reaction (n = 3)

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Table 1 (continued).

Study	Study design	Primary disorder	Depression scale	Sample	Baseline score Mean (SD)[a]	Follow-up scores Mean (SD)[a]	Treatment vs placebo	Relationship between depression and physical symptoms	Concurrent medications	Quality of evidence (GRADE score)	Adverse events
McIntyre et al[40]	Randomized, double-blind, placebo-controlled	Bipolar I/II depression	MADRS	Infliximab: n = 29 Placebo: n = 31	Infliximab: 30.6 (7.2) Placebo: 29.5 (7.0)	Wk 2: Infliximab: 23.4 Placebo: 26.2 Wk 6: Infliximab: 20.42 Placebo: 22.65 Wk 8: Infliximab: 20.3 Placebo: 17.23 Wk 12: Infliximab: 19.63 Placebo: 17.77	Treatment × time interaction: $\chi^2 = 10.33$, $P = .04$	Patients with childhood history of physical abuse exhibited greater reductions in depression scores	No anti-inflammatory medications reported Antidepressants: Infliximab: 50% Placebo: 74% Other psychotropic medications: 4–26% across groups	Moderate	Allergic reactions (n = 3), atypical liver function (n = 1), psychosis (n = 1)
Ixekizumab											
Griffiths et al[41]	Randomized, placebo-controlled, double-blind	Plaque psoriasis	QIDS-SR	Patients with a baseline QIDS-SR total score ≥11 Ixekizumab biweekly: n = 107 Ixekizumab monthly: n = 120 Placebo: n = 93	Ixekizumab biweekly: 13.8 (2.6) Ixekizumab monthly: 14.2 (2.6) Placebo: 14.0 (3.1)	Wk 12: Ixekizumab biweekly: 6.7 (2.16) Ixekizumab monthly: 8.1 (2.19) Placebo: 10.6 (2.62)	All Ps < .001	Improvement of Psoriasis Area and Severity Index score and decrease in hsCRP correlated with depression score reduction	No anti-inflammatory or psychotropic medications reported	Moderate	
Omalizumab											
Diluvio et al[42]	Open-label, single-arm	Chronic spontaneous urticaria	HADS depression	n = 15 (n = 7 with a baseline clinical depression score)	9.58	4.0 (at 6 mo)	$P > .05$ (nonsignificant)		No anti-inflammatory or psychotropic medications reported	Very low	
Uzer and Ozbudak[43]	Open-label, single-arm	Asthma	BDI	n = 20	25.35	8.55 (at a mean of 17.6 mo; range: 2–40 mo)	$P < .001$		No anti-inflammatory or psychotropic medications reported	Very low	
Siltuximab and sirukumab											
Sun et al[44]	Secondary analyses of 2 randomized, placebo-controlled trials	(1) Multicentric Castleman disease (2) Rheumatoid arthritis	SF-36	Patients with depressed mood/anhedonia: (1) Siltuximab: n = 6 Placebo: n = 4 (2) Sirukumab: n = 34 Placebo: n = 12	(1) Sirukumab: 25.9 Placebo: 26.6 (2) Siltuximab: 27.3 Placebo: 27.5	(1) Wk 12: Sirukumab: 39.9 Placebo: 33.3 (2) Wk 15: Siltuximab: 39.3 Placebo: 15.7	(1) $P = .077$ (2) $P = .06$	Improvement of primary disease symptoms accounted for depression score reduction in sirukumab, but not siltuximab study.	No anti-inflammatory or psychotropic medications reported	Moderate and low	
Sirukumab											
Salvadore et al[45]	Randomized, placebo-controlled, double-blind	Major depressive disorder with suboptimal response to oral antidepressants and hs-CRP≥3	HDRS	Not reported	Not reported	Not reported	No significant difference between sirukumab and placebo in depression severity, response and remission rates at wk 12	Sirukumab was more effective than placebo in decreasing anhedonia symptoms measured with the SHAPS at wk 12	No anti-inflammatory or psychotropic medications reported	Very low	

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Table 1 (continued).

Study	Study design	Primary disorder	Depression scale	Sample	Baseline score Mean (SD)[a]	Follow-up scores Mean (SD)[a]	Treatment vs placebo	Relationship between depression and physical symptoms	Concurrent medications	Quality of evidence (GRADE score)	Adverse events
Secukinumab											
Talamonti et al[46]	Open-label, single-arm	Psoriasis	HADS depression	Patients with moderate-severe depression (HADS-D score ≥11): n = 17		Wk 16: 81.3% had HADS-D scores of <11 Wk 48: 70.6% had HADS-D scores of <11	Wk 16: $P < .001$ Wk 48: $P = .06$		No anti-inflammatory or psychotropic medications reported	Very low	
Tocilizumab											
Traki et al[47]	Open-label, single-arm	Rheumatoid arthritis	HADS depression	n = 29	9.4 (2.6)	8.4 (3.8)	$P = .22$		Corticosteroids: n = 29 No psychotropic medications reported	Very low	Pulmonary embolism (n = 1), acute hepatitis (n = 1), heart failure (n = 1)
Tiosano et al[48]	Open-label, single-arm	Rheumatoid arthritis	HDRS	n = 99	7.81 (7.09)	Wk 24: 4.95 (5.84)	$P < .001$		Current anti-inflammatory medications (eg, steroids, NSAIDs) continued at stable doses No psychotropic medications reported	Very low	
Knight et al[49]	Observational cohort	Allogeneic hematopoietic stem cell transplantation (HCT) patients	IDAS depression subscale	Single dose tocilizumab + HCT: n = 25 HCT alone: n = 62	Tocilizumab + HCT: 34.8 (8.8) HCT alone: 36.1 (11.7)	Day 28: Tocilizumab + HCT: 42.7 (10.2) HCT alone: 38.2 (12.1)	95% CI, 0.75–10.73; $P = .03$	Results persisted even after control of physical symptoms severity	No anti-inflammatory or psychotropic medications reported	Very low	Worse depression score in tocilizumab group
Ustekinumab											
Langley et al[50]	Randomized, placebo-controlled, double-blind	Psoriasis	HADS depression	Ustekinumab 45 mg: n = 409 Ustekinumab 90 mg: n = 411 Placebo: n = 410	Ustekinumab 45 mg: 4.9 (3.8) Ustekinumab 90 mg: 5.4 (4.2) Placebo: 4.9 (3.7)	Wk 12: Ustekinumab 45 mg: 3.2 (0.7) Ustekinumab 90 mg: 3.3 (0.8) Placebo: 4.7 (0.9)	$Ps < .001$	Improvement of Psoriasis Area and Severity Index score correlated with depression score reduction	No anti-inflammatory medications reported Antidepressants: 11% across all groups Benzodiazepines: 4% across all groups Antipsychotics: 1% across all groups	Moderate	Depression (n = 5), anxiety (n = 2)
Kim et al[51]	Open-label, uncontrolled	Psoriasis	BDI and HDRS	n = 15	BDI: 12.73 (9.26) HDRS: 10.33 (7.18)	BDI: 5.07 (4.74) HDRS: 3.67 (3.56)	BDI: $P = .0002$ HDRS: $P < .0001$	Improvement of Psoriasis Area and Severity Index score did not correlate with depression score reduction	No anti-inflammatory or psychotropic medications reported	Very low	

[a]Except in the cases of medians, standard errors, and other different measurements.

Abbreviations: BDI = Beck Depression Inventory, CES-D = Center for Epidemiological Studies Depression Scale, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, HADS = Hospital Anxiety and Depression Scale, HDRS = Hamilton Depression Rating Scale, hs-CRP = high-sensitivity C-reactive protein, IQR = interquartile range, IDAS = Inventory of Depression and Anxiety Symptoms, mAbs = monoclonal antibodies, MADRS = Montgomery-Asberg Depression Rating Scale, NSAIDs = nonsteroidal anti-inflammatory drugs, PHQ-8 = Patient Health Questionnaire-8, PHQ-9 = Patient Health Questionnaire-9, QIDS-SR = 16-Item Quick Inventory of Depressive Symptomology Self-Report, SF-36 = 36-Item Short Form Health Survey questionnaire, SHAPS = Snaith-Hamilton Pleasure Scale, ZDS = Zung Self-rating Depression Scale.

including MDD, major depressive episodes of bipolar disorder, or TRD.

We included studies with various designs such as RCTs, observational studies, and uncontrolled studies. While we acknowledge the limitations of including uncontrolled studies, it was necessary to consider them due to the absence of RCTs for some mAbs included in our review. The Grading of Recommendations Assessment, Development, and Evaluation approach was utilized to assess the quality of publications included in this review. RCTs were initially rated as "high quality" and then downgraded by 1 level for serious concerns (or by 2 levels for very serious concerns) about risk of bias, inconsistency, indirectness, imprecision, or publication bias. Similarly, observational nonrandomized studies were rated as "low quality" and then downgraded based on the same factors/concerns. Two coauthors independently assessed the quality of the articles. Given the relative scarcity of publications on the topic of this review, we included all levels of evidence.

TARGETS, MECHANISMS, AND ANTIDEPRESSANT EFFECTS OF MONOCLONAL ANTIBODIES

Tumor Necrosis Factor-α Inhibitors

Tumor necrosis factor-α (TNF-α) is a multifunctional cytokine that induces proinflammatory responses.[52,53] TNF-α is associated with an impaired ability to recover from a state of learned helplessness in animals, likely through disruption of the blood-brain barrier (BBB).[54] Elevated TNF-α levels are also reported in depressed patients[55] and correlate with more severe suicidal ideation.[56]

Adalimumab. Adalimumab is a TNF-α inhibitor approved for the treatment of moderate-to-severe plaque psoriasis and psoriatic arthritis,[57] moderate-to-severe hidradenitis suppurativa,[58] rheumatoid arthritis, ankylosing spondylitis, Crohn disease, and ulcerative colitis.[59]

Two RCTs examined changes in depressive symptoms in association with adalimumab treatment for patients with inflammatory disorders. Loftus et al[25] noted that patients with moderate-to-severe Crohn's disease experienced greater improvement of their comorbid depressive symptoms with adalimumab treatment, compared with placebo. Menter et al[26] reported that, in patients with moderate-to-severe psoriasis, depressive symptoms significantly decreased in the adalimumab-treated group, compared with placebo. It is worth noting, however, that improvement in depressive symptoms correlated with a reduction in the physical symptoms of psoriasis.[26] Also of note, the baseline scores for both the treatment and placebo groups fell in the normal to minimal depression range. In contrast, a case series on the impact of adalimumab in complex regional pain syndrome reported no significant improvements in comorbid depression.[60]

Infliximab. Infliximab is another TNF-α inhibitor mAb approved for the treatment of moderate-to-severe Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and severe plaque psoriasis.[53]

A mouse study of inflammation and depression with chronic, mild stress found that infliximab prevented TNF-α increases and depressive symptoms brought on by the stress.[61] Further, depressed patients treated with infliximab experienced improvement in depressive symptoms related to reduction in TNF-α receptor levels.[62]

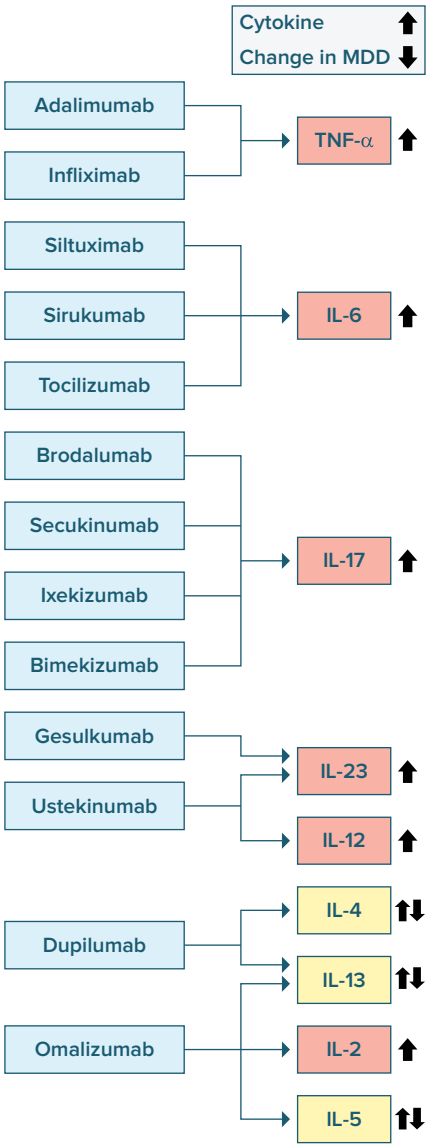
In a single-blinded study of patients with Crohn's disease, placebo was administered to all patients at baseline, followed by 2 infliximab doses 2 weeks apart.[36] Improvement was observed in depressive symptoms 2 and 4 weeks following the start of infliximab, but not with placebo. Further, Ertenli et al[37] reported improvements in mild depression scores among patients with ankylosing spondylitis treated with infliximab.

Infliximab has also been tested directly in patients with primary mood disorders, but the findings have been inconclusive. Raison et al[38] found that, compared with placebo, infliximab did not reduce depressive symptoms in patients with TRD whose depression was moderate-to-severe, but it did improve depression in those with evidence of inflammation [ie, high-sensitivity C-reactive protein (hs-CRP) of greater than 5 mg/L]. Patients treated with infliximab in this study tended to have more improvement in their symptoms of psychomotor retardation, psychic anxiety, anhedonia, depressed mood, and suicidal ideation. Further, in a 12-week RCT on the effectiveness of adjunctive infliximab for the treatment of bipolar depression, McIntyre et al[40] reported no difference in depressive symptoms between infliximab and placebo groups. However, a subgroup of patients with a history of childhood trauma showed a reduction in depressive symptoms and higher response rates with infliximab, compared with placebo. In a secondary analysis of data from the same study, Lee et al[39] observed an improvement in anhedonia among those treated with infliximab compared with placebo at week 6, but not week 12.

To explain variability in the antidepressant effects of infliximab, Mehta et al[63] examined if certain transcriptional genetic changes were related to such effects. They found that genomic indices related to glucose and lipid metabolism predicted treatment response to infliximab in patients with TRD. Another study suggested that patients with TRD and high levels of inflammation along with high levels of lipids and cholesterols were more responsive to infliximab's antidepressant properties.[64] It is worth noting however that a meta-analysis of both studies failed to find that

Figure 1.

Mechanisms of mAbs With Potential Antidepressant Effects[a]



[a]Arrows indicate direction of change of expression of cytokine targets in MDD.
Abbreviations: mAbs = monoclonal antibodies, MDD = major depressive disorder

infliximab reduced depressive symptoms when used as an adjuvant treatment for those with TRD.[65]

IL-6 Inhibitors

IL-6 is a multifunctional proinflammatory cytokine that plays a central role in host defense. IL-6 has been most consistently elevated in patients with MDD[66,67] and has been linked to depression severity,[68] treatment resistance,[69,70] and suicidal behavior.[71] IL-6 is also linked to the development of a susceptible behavioral phenotype in mice following chronic stress.[70] Further, mice treated with a systemic IL-6 mAb are resilient to social stress.[70]

Siltuximab and Sirukumab. Siltuximab and sirukumab are anti-IL-6 mAbs.[72,73] Siltuximab is approved to treat multicentric Castleman disease.[74] Sirukumab has been considered as a treatment for rheumatoid arthritis but has not yet been approved by the Food and Drug Administration (FDA).[75]

In their secondary analyses of data from 2 controlled trials, Sun et al[44] reported reduction in depressive symptoms with sirukumab and siltuximab treatment for multicentric Castleman disease and rheumatoid arthritis, respectively, compared with placebo. Improvement in physical symptoms of the primary disease accounted for depressive symptoms reduction in the group treated with sirukumab, but not siltuximab. In addition, sirukumab was tested as an adjunctive treatment in patients with TRD and plasma CRP levels ≥3 mg/L.[45] Although depression severity at week 12 did not differ significantly between sirukumab and placebo, anhedonia rating improved with sirukumab, compared with placebo.[45] Moreover, patients with baseline CRP values ≥8 mg/L had greater reduction of depressive symptoms with sirukumab versus placebo.[45]

Tocilizumab. Tocilizumab is an IL-6 inhibitor approved to treat moderate-to-severe rheumatoid arthritis,[76] giant cell arteritis,[77] systemic sclerosis-associated interstitial lung disease,[78] polyarticular juvenile idiopathic arthritis,[79] systemic juvenile idiopathic arthritis,[80] cytokine release syndrome,[81] and COVID-19.[82]

Research on the impact of tocilizumab on symptoms of depression has been mixed. Although an open-label study on patients with rheumatoid arthritis reported improvement in depression scores following treatment with tocilizumab,[47] another study in similar population found no change in depression with tocilizumab.[48] Furthermore, worsening depressive symptoms have been noted with single tocilizumab treatment for individuals undergoing hematopoietic cell transplantation.[49]

T Helper-17 Blockers

T helper (Th)-17 cells, and the cytokines they produce, play an integral role in host defense as well as the pathogenesis of several autoimmune and inflammatory disorders.[83] IL-17A influences disorders such as psoriasis and Crohn's disease, among others.[84] IL-17A is one of the proinflammatory cytokines that may disrupt the BBB[85] and thus is hypothesized to promote depression by allowing circulating proinflammatory factors to gain access to mood-relevant brain circuits. IL-17A may also contribute to treatment resistance in MDD, as it has been found to predict nonresponse to antidepressants.[15] IL-17F has overlapping functionality with IL-17A.[86] IL-17E is a barrier cytokine that alarms the immune cells, among other functions.[87]

Brodalumab. Brodalumab blocks IL-17 receptor and inhibits IL-17A, IL-17F, IL-17A/F, and IL-17E.[88] Brodalumab is an FDA-approved mAb for moderate-to-severe plaque psoriasis.[89]

In their RCT on moderate-to-severe plaque psoriasis, Papp et al[90] noted an improvement in depressive symptoms with brodalumab, compared with placebo, although the baseline scores for the treatment and placebo groups fell in the normal range. Further, Ohata et al[29] noted that depressive symptoms decreased with brodalumab treatment, but only in those with baseline Patient Health Questionnaire-8 scores of 5 or more (ie, at least mildly depressed). Of note, 2 patients in this study had worsening depressive and anxiety symptoms after the administration of brodalumab. Along similar lines, Rivera-Oyola et al[91] reported that although brodalumab treatment was associated with improvements in depressive symptoms in 2 cases of patients with psoriasis and comorbid depression, another patient, who had a history of bipolar I disorder, later developed mania, psychosis, and suicidal ideation during treatment.

Ixekizumab. Ixekizumab is an IL-17A antagonist approved to treat psoriatic arthritis, moderate-to-severe plaque psoriasis,[92] and ankylosing spondylitis.[93]

An analysis of 3 phase III RCTs of ixekizumab treatment for psoriasis noted a significant improvement in depressive symptoms.[41] Patients in these studies had moderate depression scores at baseline, and a greater percentage of those treated with ixekizumab met criteria for response and remission criteria at week 12, compared with the placebo. An RCT is being currently conducted to examine the antidepressant effects of ixekuzimab in adults with TRD (NCT04979910).

Secukinumab. Secukinumab has a similar mechanism of action to ixekizumab, specifically targeting IL-17A, thereby blocking its binding with IL-17 receptor.[94] Secukinumab is approved for the treatment of moderate-to-severe hidradenitis suppurativa and plaque psoriasis.[95]

In their secondary analysis of a multicenter open-label, single-arm study on secukinumab for patients with moderate-to-severe psoriasis, Talamonti et al[46] reported that more than 80% of patients who had moderate-to-severe depression at baseline experienced improvement in their depression at week 16 and week 48.

Bimekizumab. Bimekizumab is a monoclonal immunoglobulin G1 (IgG1) antibody that selectively inhibits IL-17A and IL-17F and has resulted in better outcomes in moderate-to-severe psoriasis, compared with IL-17A-only antagonists.[96]

A secondary analysis of 9 randomized, placebo-, and active comparator-controlled trials showed that following 16 weeks of treatment with bimekizumab, mean Patient Health Questionnaire-9 scores were numerically lower than placebo and similar to active comparators (including adalimumab, secukinumab, and ustekinumab).[27]

IL-23 Inhibitors

IL-23 is proinflammatory cytokine that belongs to the IL-12 family of cytokines and plays a crucial role in the maintenance and expansion of Th-17 pathway.[97] IL-23 gene expression is elevated in people with recurrent depressive disorders.[98]

Guselkumab. Guselkumab is an IL-23 inhibitor[99] approved for the treatment of moderate-to-severe plaque psoriasis[100] and psoriatic arthritis.[101]

Gordon et al[35] conducted a 24-week, phase 3, randomized, double-blind, placebo- and adalimumab-controlled study to determine the changes in depression and anxiety with guselkumab treatment for more than 900 patients with moderate-to-severe psoriasis. They reported that the number of patients in the guselkumab group with clinical depression decreased significantly at week 16 and week 24, compared with placebo and adalimumab, respectively. However, reduction of depression scores correlated with improvement of psoriasis symptom severity.

Ustekinumab. Ustekinumab is a mAb approved for the treatment of moderate-to-severe plaque psoriasis and psoriatic arthritis,[102] as well as moderate-to-severe Crohn's disease and ulcerative colitis.[103] It inhibits the p40 subunit of IL-23 and IL-12,[104,105] which have been found to be elevated in people with depression.[106]

In an RCT of ustekinumab for moderate-to-severe psoriasis, Langley et al[50] noted improvement in depression scores, compared with placebo. However, baseline scores were below the cutoff for clinical depression. Additionally, in their open-label, uncontrolled ustekinumab trial, Kim et al[51] noted that patients with moderate-to-severe psoriasis and pretreatment mild depressive symptoms experienced a reduction in depression.

Th-2 Blockers

IL-4 and IL-13 are key cytokines of Th-2 inflammatory response with distinct as well as overlapping effects. Specifically, IL-4 drives immunoglobulin class switching to IgG1 and immunoglobulin E (IgE) and induces Th-2 cell differentiation, while IL-13 is involved in B-cell differentiation and eosinophil chemotaxis. Both IL-4 and IL-13 also play a role in inducing alternative macrophages activation and are thus relevant to the pathogenesis of allergic disorders.[107]

Abnormalities of IL-4 and IL-13 have been linked to depression in animal and human studies, but the exact mechanism and direction of these abnormalities are largely unknown. IL-4 may influence depressive-like behaviors in animals, but there is some debate about this claim. In an interferon-α mouse model, there seems to be an association between depressive symptoms and decreased IL-4 responses of microglia.[108] However, Moon et al[109] observed more anxiety behaviors in IL-4

knockout mice than in wild-type mice in the elevated zero maze but did not find a significant association with depressive symptoms. Park et al[110] noted that the action of IL-4 seemed to prevent increases in prostaglandin E_2 and corticosterone levels caused by IL-1β. It also seemed to inhibit tryptophan hydroxylase mRNA and activate the serotonin transporter in hippocampus, thus decreasing the level of IL-1β–induced serotonin. Further, in response to antidepressants given to treatment-naïve depressed patients, plasma IL-4 decreased while IL-13 increased.[111] Elevated levels of IL-13 are associated with MDD[112] and higher likelihood of suicide attempt history[113] and are noted in men who have died by suicide.[114] Elevated IL-4 levels are reported in females who have died by suicide.[114]

Dupilumab. Dupilumab is an FDA-approved mAb for the treatment of moderate-to-severe atopic dermatitis and moderate-to-severe asthma,[115] chronic rhinosinusitis with nasal polyposis,[116] eosinophilic esophagitis,[117] and prurigo nodularis.[118] By binding to type I and II IL-4-α receptors, dupilumab inhibits the responses of cytokines IL-4 and IL-13[119] and downregulates the Th-2 immune response.

In their case series on patients with prurigo nodularis, Lönndahl et al[30] reported that in addition to decrease in pruritus scores, patients with mild depression scores at baseline experienced improvements in depressive symptoms with dupilumab treatment. In a phase 3 RCT on patients with moderate-to-severe atopic dermatitis and moderate depression, Cork et al[31] noted an improvement in depressive symptoms by week 2 through week 16 with dupilumab treatment, compared with placebo. Two uncontrolled studies on patients with atopic dermatitis noted a decrease in depression scores[32,33]—although baseline scores were below the cutoff for mild depression in both studies. Finally, in an uncontrolled study on patients with asthma with eosinophilic chronic rhinosinusitis and comorbid mild depression scores, a significant reduction in depressive symptoms was noted, more prominently in patients who had a nasal symptom score reduction in 50% or greater.[34] It is notable, however, that in addition to dupilumab, the patients in this study were also given corticosteroids and long-acting β-agonists.

Omalizumab. Omalizumab is a mAb that is approved to treat moderate-to-severe asthma[120] and chronic spontaneous urticaria.[121] It is also used as an add-on treatment for nasal polyps.[122] Omalizumab binds to IgE,[123] hence its role in allergic disorders.[124] It also reduces the number of lymphocytes producing IL-2 and IL-13[125] and decreases the levels of IL-5[126]; all are components of Th-2 pathway. Research suggests that allergen-specific IgE-positive people tend to have worse depression scores.[127]

In their study of omalizumab treatment for chronic spontaneous urticaria, Diluvio et al[42] reported that 71% of participants who had mild depressive symptoms at baseline experienced improvement of their depression at 6 months. Further, in an uncontrolled study of omalizumab treatment for asthma, Uzer and Ozbudak[43] noted an improvement of comorbid depression in 9 of 12 patients who had moderate-to-severe depression before treatment initiation.

ADVERSE EFFECTS AND SAFETY PROFILES

The most common reported adverse effects with mAbs are injection site reactions, infusion reactions (with intravenous mAbs), headaches, nausea, and increased risk of infections (eg, conjunctivitis and upper or lower respiratory tract infections). Rare serious side effects include increased risk of malignancy (with guselkumab,[128] infliximab,[129–131] and ixekizumab),[132] tuberculosis (with infliximab),[129–131] and cardiovascular events (with fremanezumab[133,134] and ixekizumab)[132] as well as hepatic, pulmonary, and pancreatic reactions (with tocilizumab).[135] Dupilumab has one of the best safety profiles among all mAbs. It has been approved by the FDA for use in children as young as 6 months old. Unlike most other immune-modulating drugs, dupilumab has not been shown to suppress the immune system's ability to fight infections, as shown in a meta-analysis of 8 RCTs.[136] In contrast, sirukumab has been denied approval by the FDA due to concerns of increased all-cause mortality due to markedly increased risk of serious infections.[137,138]

Review of mAbs clinical trials and package inserts shows that suicidal ideation and behavior were reported during the course of treatment with a number of mAbs although a causal link has not been found in these instances.[139–141] Two patients with psoriasis receiving adalimumab reportedly died by suicide.[142] Higher rates of suicidal ideation were reported in bimekizumab-treated patients than in placebo-treated patients in the psoriasis clinical trials. One patient receiving open-label bimekizumab without prior psychiatric history completed suicide. Brodalumab treatment was associated with 6 cases of suicide across all psoriasis clinical trials.[143] This led the FDA to issue a black box warning about worsening of suicidal ideation and behavior during treatment with brodalumab. It is worth noting, however, that brodalumab users with a history of suicidality or depression had an increased incidence of suicidal ideation and behavior as compared to users without such a history. Further, in a 2022 4-year pharmacovigilance report, brodalumab was not associated with any increase in suicide risk.[144] One suicide attempt and 1 death by suicide have been reported in dupilumab treatment studies,[140,141] as well as with guselkumab.[145] An adolescent female developed depression and attempted suicide during infliximab treatment for Crohn disease.[146] One patient developed suicidal ideation during ixekizumab treatment.[132] Undercounts of suicidal ideation and

behavior remain a possibility given that most mAbs clinical studies relied on patient's reporting of suicidality rather than using suicide-specific assessment scales.

CONCLUSIONS AND FUTURE DIRECTIONS

Improvement in depressive symptoms has been reported in association with several mAbs used for the treatment of a wide variety of primary inflammatory skin, joint, and gastrointestinal disorders. Given their specific mechanisms of action, mAbs may offer a new option for the treatment of depression in many patients who do not respond to currently available antidepressants. Ixekizumab and dupilumab (only mAbs that do not require any monitoring)[147,148] seem to be the 2 mAbs that offer the best benefit-risk balance, but further research is needed to refine their use in depression clinical practice. It should be noted that it remains unclear whether improvements in depressive symptoms are due to direct effects of the drugs or secondary to improvements in physical symptoms associated with the primary inflammatory disorders and related positive impact on quality of life. This question would be only addressed by studies examining the antidepressant effects of mAbs in patients with primary depressive disorders and no inflammatory conditions. Few studies such as Raison et al[38] and those analyzed in Bavaresco et al[65] mentioned above have examined this question, but otherwise, research is lacking. Additionally, the effect of concurrent use of psychotropic medications on the changes of depressive symptoms across the duration of mAbs studies should be considered. Participants in the infliximab RCTs in MDD and bipolar depression were allowed to continue using their psychotropic medications provided that doses remained stable during the infliximab trials. A small percentage of patients in the guselkumab and ustekinumab trials were using a wide variety of psychotropic medications. Other studies did not report information about concurrent use of psychiatric medications.

With the exception of a few studies, patients included in most studies examining the changes in depression scores with mAb treatment had mild depression. The lower the depression score, the more likely it is that the symptoms reported are related to the primary inflammatory disorder (eg, vegetative symptoms). Thus, any reported improvements in depression scores could be attributed to improvements in the physical health condition. Conversely, higher depression severity score may mean it is more likely that patients were in fact depressed. Future studies need to examine the effect of mAbs in patients with more severe depressive symptoms as well as those with TRD. These studies could also determine whether the benefits of mAbs outweigh their side effects and/or favor their use for depression over other treatment options. Most of the mAbs showed better safety profiles compared to conventional immune-modulating drugs. For example, dupilumab has been approved for children as young with atopic dermatitis as 6 months and does not require any monitoring.[149,150] It remains unclear whether reported suicidal ideation and behavior with several mAbs are causally related to the drug administration or to the primary disease. Again, these questions could only be answered with RCTs that directly examine the antidepressant effects of mAbs in patients with primary depressive disorders.

While our review primarily focuses on summarizing the existing evidence on changes in depressive symptoms associated with mAb treatment, we recognize the importance of considering the underlying mechanisms of action and potential limitations of this therapeutic approach. The mechanism by which cytokine antagonists may exert their antidepressant effects remains largely unknown, and it is crucial to critically evaluate whether targeting a single cytokine can effectively counteract the multifaceted alterations in inflammatory markers observed in MDD. Future research should aim to elucidate the specific mechanisms underlying the antidepressant effects of mAbs and explore potential synergistic or compensatory mechanisms involved in MDD pathophysiology.

In light of the potential benefits of mAbs in treating depression, it is crucial to consider their practical application in clinical settings. Currently, it is not recommended that psychiatrists consider prescribing these immune therapies for patients who have not responded to traditional treatments because there is not enough evidence to support such use. Much research is needed on the efficacy and safety of mAbs as monotherapy or adjunctive medication to currently available antidepressants. The placement of these immune therapies within treatment hierarchies and guidelines would depend on a variety of factors, including the severity of the patient's symptoms, their overall health status, and their response to other treatments. It is also important to consider the cost of these medications, which can be quite high and will only be covered by insurance for individuals with mood disorders when the FDA approves them for this indication.

Finally, the study of the antidepressant properties of mAbs prompts discussion of the need for immune screening methods in clinical practice. Recent advances in immunology research could help identify the similarities in immune profiles between MDD and primary inflammatory disorders, an important step toward helping select the mAbs that could produce the most positive impact on depressive symptoms. Future studies could also be directed toward developing methods to refine the measurement of dysregulated immune pathways in depression and link those findings to the mechanism of antidepressant action of mAbs.

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Author Affiliations: Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York (Rizk, Russo, Murrough); Molecular Imaging and Neuropathology Division, New York State Psychiatric Institute, New York (Rizk, Bolton, Mann); Nash Family Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York (Cathomas, Russo, Murrough); Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York (Cathomas, Russo, Murrough); Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, New York (He, Guttman-Yassky); Department of Psychiatry, Columbia University Irving Medical Center, New York, New York (Mann); Department of Radiology, Columbia University Irving Medical Center, New York, New York (Mann).

Corresponding Author: Mina M. Rizk, MD, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, 1 Gustave Levy Place, Box #1230, New York, NY 10029 (mina.rizk@mountsinai.org).

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