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Incretin-based therapies in psychiatry: A landscape analysis of ongoing randomized trials registered on ClinicalTrials.gov

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ABSTRACT

Background: Incretin-based therapies, including conventional glucagon-like peptide-1 receptor agonists (GLP-1RAs) and GLP-1-containing co-agonists, are being repurposed for psychiatric disorders. The breadth and maturity of the randomized pipeline are easily misread.

Methods: We searched ClinicalTrials.gov on 1 September 2026 for ongoing randomized trials in which a psychiatric disorder or addictive behaviour was central to recruitment and a psychiatric or behavioural outcome was registered as primary or co-primary. The search queried the intervention field for 56 named agents and development codes and all record fields for five mechanism phrases, with an automated audit for agents absent from the term list. Trials with metabolic endpoints in psychiatric populations, neurocognitive trials, and non-randomized studies were catalogued separately.

Results: Thirty-four ongoing randomized trials met the core criteria, with a planned enrolment of 8519 participants; 25 (74%) were recruiting, 21 were phase 2 and six phase 3. Three compounds accounted for the entire pipeline, and 17 trials (50%) tested a GLP-1-containing co-agonist. Targets were alcohol use disorder (14 trials; n = 3686), major depressive disorder (3; n = 2116), opioid use disorder (4; n = 1021), tobacco or nicotine use (5; n = 708), bipolar disorder (1; n = 400), cannabis (3; n = 206), methamphetamine (1; n = 162), cocaine (2; n = 115), and binge-eating disorder (1; n = 105). Twenty-nine trials concerned addiction or tobacco use, and seven trials of a single co-agonist from one sponsor accounted for 62% of planned enrolment. Six further trials in schizophrenia-spectrum disorders registered metabolic rather than psychiatric primary endpoints.

Conclusions: The ClinicalTrials.gov-registered psychiatric pipeline is larger than previously described but remains concentrated in addiction, and almost all development outside addiction belongs to one manufacturer's programme, which is proceeding without a positive randomized result in any psychiatric indication. Half of all trials use co-agonists, so a positive result would not identify the responsible mechanism.

1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have transformed the treatment of type 2 diabetes and obesity, and their potential relevance to psychiatry extends beyond weight reduction. GLP-1 receptors are expressed in brain networks that support appetite, salience, reinforcement, and motivated behavior, and experimental GLP-1 receptor activation modulates responses in reward-related regions in humans (van Bloemendaal et al., 2014, 2015). These observations, together with reports of reduced craving or consummatory behavior during clinical use, have stimulated rapid repurposing across mood, eating, addictive, and severe mental disorders.

Throughout this analysis we use "incretin-based therapy" to cover both conventional GLP-1RAs and unimolecular co-agonists that include a GLP-1 component, such as the GIP/GLP-1 receptor agonists tirzepatide and brenipatide. We include co-agonists because they are the pharmacological engine of current psychiatric development, but we count them separately throughout, because efficacy or toxicity observed with a co-agonist cannot be attributed to GLP-1 receptor activation alone.

The translational signal is most developed in alcohol use disorder (AUD). In a 127-participant randomized trial, weekly exenatide did not reduce heavy drinking days in the overall sample, although alcohol-cue reactivity was attenuated and an obesity-defined subgroup appeared to benefit (Klausen et al., 2022). A subsequent 48-participant laboratory trial found that low-dose semaglutide reduced alcohol self-administration, craving, drinks per drinking day, and the probability of heavy drinking, but did not reduce drinking days or average drinks per calendar day (Hendershot et al., 2025). The 108-participant

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SEMALCO trial then compared once-weekly semaglutide with placebo, with standardized cognitive behavioral therapy in both arms, and showed a 13.7-percentage-point adjusted advantage in the reduction of heavy drinking days after 26 weeks among treatment-seeking adults with AUD and obesity (Klausen et al., 2026). Observational studies have also associated GLP-1RA exposure with lower incidence or recurrence of AUD and other substance-use disorders, but such data cannot establish efficacy (Wang et al., 2024; Cai et al., 2026).

Evidence in other psychiatric domains is more heterogeneous. Pilot smoking-cessation trials have produced discordant results: exenatide added to nicotine replacement increased the estimated probability of abstinence in a small study, whereas dulaglutide added to varenicline did not improve abstinence in a larger trial despite preventing post-cessation weight gain (Yammine et al., 2021; Lengsfeld et al., 2023). A recent 24-participant semaglutide trial did not meet its co-primary laboratory smoking endpoints, although craving and body weight decreased (Hendershot et al., 2026). A pilot liraglutide trial in binge-eating disorder (BED) was underpowered and did not demonstrate superiority for binge episodes, but showed greater weight loss (Allison et al., 2023). In major depressive disorder (MDD), a 72-participant trial of oral semaglutide did not improve its primary executive-function outcome or depressive symptom severity; secondary analyses suggested improvement in global cognition and effort-based decision-making (Badulescu et al., 2026; Gill et al., 2026). The studies cited in this section are illustrative of the range of completed randomized evidence rather than the product of a systematic search; the systematic component of this work concerns ongoing registered trials only.

Psychiatric interest also encompasses cardiometabolic treatment in severe mental illness. Randomized studies of liraglutide, exenatide, and semaglutide show that these agents can improve glycemia or weight in antipsychotic-treated schizophrenia-spectrum disorders (Ishøy et al., 2017; Larsen et al., 2017; Siskind et al., 2018; Ganeshalingam et al., 2025; Sass et al., 2026). These are clinically important psychiatric applications, but they should not be conflated with evidence that incretin therapies treat psychosis itself: recent semaglutide trials improved metabolic outcomes without improving Positive and Negative Syndrome Scale scores (Ganeshalingam et al., 2025; Sass et al., 2026).

One prior registry analysis has mapped part of this field. Patil et al. identified 33 trials of GLP-1 receptor agonists in substance-use disorders registered on ClinicalTrials.gov, reported marked heterogeneity of interventions and endpoints, and found no trial in cannabis use disorder (Patil et al., 2026); the present search identifies three. The present analysis differs in four respects: it is restricted to ongoing randomized studies rather than records of any status or design; it extends beyond substance use to the full psychiatric range, including mood, psychotic, eating, and neurocognitive disorders; it applies explicit boundaries separating direct psychiatric efficacy from cardiometabolic treatment in psychiatric populations and from neurocognitive development; and it uses a search strategy designed to capture investigational co-agonists that are not identifiable by drug name alone. That last point proved decisive, and is discussed in Section 4.7.

Our objectives were to identify the psychiatric disorders currently targeted by ongoing randomized trials registered on ClinicalTrials.gov, to quantify the maturity and pharmacological composition of that pipeline, to distinguish direct psychiatric efficacy trials from metabolic-psychiatry and neurocognitive studies, and to identify clinically important gaps.

2. Methods

2.1. Design and data source

We conducted a cross-sectional landscape analysis of registered trials using the ClinicalTrials.gov application programming interface, version 2 (ClinicalTrials.gov, 2026). The final search was executed on 1 September 2026 and the registry dataset carried the same version date. ClinicalTrials.gov is sponsor-reported and widely used, but it is not a global registry: studies registered only in the European Union Clinical Trials Information System, the ISRCTN registry, the Australian New Zealand Clinical Trials Registry, or other constituent registries of the World Health Organization International Clinical Trials Registry Platform are not captured. Every statement in this article therefore concerns the ClinicalTrials.gov-registered pipeline, and negative findings should be read as the absence of an eligible ClinicalTrials.gov record rather than the absence of any trial worldwide. Where applicable to a registry-based cross-sectional design, reporting was informed by the PRISMA 2020 statement.

2.2. Search strategy

The search used two complementary passes, and the reason for the second is important. The intervention field of a registry record contains the name of the drug administered, not its mechanism, so a query restricted to that field retrieves an investigational compound only if the compound is named explicitly. Searching by drug name alone therefore cannot be complete for a pharmacological class that is still expanding.

In the first pass we queried the intervention field for 56 named agents and sponsor development codes, spanning conventional GLP-1RAs, oral small-molecule GLP-1 agonists, GIP/GLP-1 co-agonists, GLP-1/glucagon co-agonists, and triple agonists. In the second pass we queried all record fields, including brief summary, detailed description, and eligibility criteria, for five mechanism phrases: “GLP-1 receptor agonist”, “GLP-1 agonist”, “glucagon-like peptide-1″, “GIP/GLP-1″, and “incretin”. Records with the statuses recruiting, not yet recruiting, active not recruiting, or enrolling by invitation were retained. Titles, conditions, keywords, brief summaries, and outcome fields were then screened for mood, psychotic, anxiety, trauma-related, obsessive-compulsive, eating, addictive, suicidal, neurodevelopmental, and neurocognitive terms. Records retrieved by more than one term were deduplicated by National Clinical Trial (NCT) number.

We additionally ran an automated audit of every retrieved intervention name for incretin word stems and sponsor development codes, and reviewed each detected compound that was not already in the search list. The full specification, the screening vocabulary, and the audit output are given in Supplementary Methods S1.

2.3. Eligibility and scope

Core inclusion required all of the following: an interventional study; randomized allocation; administration of a conventional GLP-1RA or a GLP-1-containing co-agonist as a randomized intervention; a psychiatric disorder, addictive behavior, or clinically relevant psychiatric symptom required for or central to recruitment; and a psychiatric or behavioral endpoint registered as primary or co-primary.

We excluded completed, terminated, withdrawn, and unknown-status studies; trials in general diabetes, obesity, or liver-disease populations in which psychiatric measures were ancillary; studies of neurologic disease; and studies in which an incretin was measured as an outcome or biomarker rather than administered as the randomized intervention. This last category is a consequence of the all-field search and accounts for a substantial minority of exclusions.

We catalogued separately, and excluded from all counts: randomized trials with metabolic primary endpoints in psychiatric populations; complex multicomponent trials in which the incretin was not separately randomized; neurocognitive trials in Alzheimer disease, mild cognitive impairment, or dementia; and non-randomized interventional and observational studies with a psychiatric or behavioral target, which are reported in Table 3.

Because the requirement for a registered psychiatric primary endpoint involves judgment at the margin, we prespecified a stricter sensitivity set that excludes trials whose registered primary outcomes are feasibility, recruitment, or adverse-event measures rather than clinical efficacy.

2.4. Screening, data extraction, and synthesis

Records were screened by both authors, and disagreements were

resolved by discussion. For each eligible record we extracted registry status and verification date, phase, planned enrollment, intervention, allocation, masking, primary outcome, primary completion date, sponsor, and country. Disorders were grouped by intended clinical target. Counts and planned sample sizes were summarized descriptively; no inferential analyses were performed. Because only public registry records were analyzed, ethics approval and informed consent were not required.

3. Results

3.1. Overall pipeline

The search retrieved 2677 records, of which 1165 remained after deduplication. Screening excluded 1,004, and 161 records were assessed against the full criteria (Supplementary Fig. S1). Thirty-four ongoing randomized trials met the core criteria (Table 1), with a total planned enrollment of 8519 participants. Twenty-five studies (74%) were recruiting, seven were not yet recruiting, one was active but not recruiting, and one was enrolling by invitation.

Twenty-one trials were registered as phase 2, six as phase 3, three as phase 1, two as phase 4, and two did not report a conventional phase. Two of the phase 4 studies concern agents that hold no psychiatric marketing authorization, which is consistent with the registry convention that phase 4 may denote a marketed drug studied in a new population; the designation therefore does not by itself indicate confirmatory psychiatric development.

Three compounds account for the entire pipeline: semaglutide in 15 trials, tirzepatide in 10, and brenipatide in seven; the intervention was recorded generically in the remaining two records. No trial of a GLP-1/glucagon co-agonist met the core criteria at this search date. Seventeen of the 34 trials (50%) evaluated a GLP-1-containing co-agonist rather than a selective GLP-1RA. Exenatide, liraglutide, and dulaglutide, the three agents with completed randomized psychiatric trials, have no ongoing eligible study.

Twenty-nine of the 34 trials concern a substance-use disorder or tobacco use. AUD accounted for 14 studies and 3686 planned participants; MDD for three and 2116; opioid use disorder (OUD) for four and 1021; tobacco or nicotine use for five and 708; bipolar disorder for one and 400; cannabis use disorder for three and 206; methamphetamine use disorder for one and 162; cocaine use disorder for two and 115; and BED for one and 105.

The distribution of sponsors is as concentrated as the distribution of diagnoses. All seven brenipatide trials belong to a single manufacturer, and they account for 5287 planned participants, or 62% of the entire pipeline by enrollment.

In the stricter sensitivity set, which excludes the three trials whose registered primary outcomes are feasibility, recruitment, or adverse-event measures (NCT07059377, NCT07204249, NCT07249554), 31 trials and 8212 planned participants remain, and none of the disorder-level findings change.

3.2. Major depressive disorder

Three ongoing trials target MDD. Two are phase 3 studies of brenipatide, each planning to randomize 1000 adults to drug or placebo, with time to relapse as the registered primary outcome (NCT07412756,

Table 1
Ongoing randomized trials with a direct psychiatric or addictive-behaviour target (ClinicalTrials.gov, 1 September 2026).

Target area	NCT number	Agent (class)	n	Phase/status	Primary focus
AUD	NCT07219953	Brenipatide (GIP/GLP-1)	1100	3/R	Change in drinking patterns
AUD	NCT07219966	Brenipatide (GIP/GLP-1)	1100	3/R	Change in drinking patterns
AUD	NCT07218354	Semaglutide (GLP-1RA)	622	3/R	WHO drinking-risk reduction
AUD + HIV	NCT07221214	Semaglutide (GLP-1RA)	200	2/R	Drinks per week
AUD	NCT07559500	Tirzepatide (GIP/GLP-1)	176	1/R	Dopamine and cue reactivity
AUD + SCZ	NCT06939088	Tirzepatide (GIP/GLP-1)	108	2/R	Heavy drinking days
AUD	NCT07772960	Semaglutide (GLP-1RA)	90	1/NYR	Alcohol use days
AUD	NCT06546384	Semaglutide (GLP-1RA)	64	NR/NYR	PEth-confirmed abstinence
AUD	NCT06015893	Semaglutide (GLP-1RA)	63	2/ANR	Alcohol drinking
AUD	NCT07292519	Tirzepatide (GIP/GLP-1)	46	2/NYR	Heavy drinking days
AUD	NCT07249554[b]	GLP-1RA, unspecified	45	2/NYR	Participant-reported AEs
AUD	NCT06994338	Tirzepatide (GIP/GLP-1)	42	2/R	Heavy drinking days
AUD	NCT06727331	Tirzepatide (GIP/GLP-1)	20	2/R	Cue-induced alcohol craving
AUD	NCT07223983	Semaglutide (GLP-1RA)	10	1/R	Weight; drinks per day
MDD	NCT07412756	Brenipatide (GIP/GLP-1)	1000	3/R	Time to relapse
MDD	NCT07775300	Brenipatide (GIP/GLP-1)	1000	3/NYR	Time to relapse
MDD	NCT07136714	Semaglutide (GLP-1RA)	116	4/R	Depressive symptoms
Bipolar	NCT07286175	Brenipatide (GIP/GLP-1)	400	2/R	Time to relapse
BED	NCT06847399	Tirzepatide (GIP/GLP-1)	105	2/R	Weight loss; binge episodes
Tobacco/nicotine	NCT07602699	Tirzepatide (GIP/GLP-1)	300	2/R	7-day point-prev. abstinence
Tobacco/nicotine	NCT07223840	Brenipatide (GIP/GLP-1)	222	2/R	CO-confirmed abstinence
Tobacco/nicotine	NCT07059377[b]	Semaglutide (GLP-1RA)	100	3/R	Trial feasibility
Tobacco/nicotine	NCT06924697	GLP-1RA, unspecified	46	NR/EBI	Nicotine-dependence score
Tobacco/nicotine	NCT06986993	Semaglutide (GLP-1RA)	40	4/R	Cigarettes per day
OUD	NCT07420283	Brenipatide (GIP/GLP-1)	465	2/R	Weeks of opioid abstinence
OUD	NCT06651177	Tirzepatide (GIP/GLP-1)	310	2/R	Buprenorphine retention
OUD	NCT06548490	Semaglutide (GLP-1RA)	200	2/R	Illicit-opioid abstinence
OUD	NCT06639464	Semaglutide (GLP-1RA)	46	2/R	Opioid craving and relapse
Cannabis	NCT07468552	Tirzepatide (GIP/GLP-1)	100	2/NYR	Dose; abstinent days
Cannabis	NCT07523633	Semaglutide (GLP-1RA)	100	2/R	Cannabis consumption
Cannabis	NCT07265752	Tirzepatide (GIP/GLP-1)	6	2/NYR	Cue-induced craving
Cocaine	NCT07227948	Semaglutide (GLP-1RA)	75	2/R	Cue response, craving, UDS
Cocaine	NCT06691243	Semaglutide (GLP-1RA)	40	2/R	Safety and tolerability
Methamphetamine	NCT07204249[b]	Semaglutide (GLP-1RA)	162	2/R	Feasibility; use reduction

Note. "Ongoing" reflects registry status and does not guarantee active site-level recruitment. GLP-1RA denotes a conventional GLP-1 receptor agonist; GIP/GLP-1 denotes a co-agonist. Registered phase labels are sponsor-assigned and phase 4 may denote a marketed drug studied in a new population.
Abbreviations: n, planned enrolment; ANR, active not recruiting; AUD, alcohol use disorder; BED, binge-eating disorder; EBI, enrolling by invitation; MDD, major depressive disorder; NR, phase not reported; NYR, not yet recruiting; OUD, opioid use disorder; PEth, phosphatidylethanol; R, recruiting; SCZ, schizophrenia; UDS, urine drug screen; WHO, World Health Organization.
[b]Registered primary outcomes are feasibility, recruitment, or adverse-event measures rather than clinical efficacy; these three trials are excluded from the sensitivity set in Section 3.1.

NCT07775300). The third, SEMAMOOD (NCT07136714), plans to randomize 116 adults with MDD and overweight or obesity to 26 weeks of semaglutide 2.4 mg or placebo, adjunctive to usual treatment, with change in depressive symptoms as the primary endpoint.

The completed randomized evidence in MDD remains limited to a single 72-participant trial of oral semaglutide, in which the prespecified executive-function composite, depressive symptom severity, and suicidal ideation were all unchanged, and gains in global cognition and effort-based motivation emerged only in secondary analyses (Badulescu et al., 2026; Gill et al., 2026). Two phase 3 programs are therefore proceeding in advance of any positive randomized result in the indication.

3.3. Bipolar disorder

One ongoing trial targets bipolar disorder. RENEW-Bipolar-1 (NCT07286175) plans to randomize 400 adults with bipolar I or bipolar II disorder to brenipatide or placebo, each added to standard of care, with time to relapse as the primary outcome. It is registered as phase 2 and is recruiting across 86 sites.

No completed randomized trial has tested an incretin therapy for mood stabilization or relapse prevention in bipolar disorder. This program therefore begins at a stage of evidence comparable to the MDD program, and both rest on mechanistic and observational reasoning rather than on prior randomized signal.

3.4. Binge-eating disorder

One ongoing four-arm phase 2 trial (NCT06847399; n = 105) compares tirzepatide with placebo and with lisdexamfetamine, with guided self-help cognitive behavioral therapy incorporated into the design. Co-primary outcomes address both percent weight loss and change in binge-eating episodes.

This represents BED development with a GIP/GLP-1 co-agonist rather than a conventional GLP-1RA. The only published placebo-controlled GLP-1RA pilot enrolled 27 adults and showed no significant between-group reduction in objective binge episodes or remission with liraglutide, and its interpretation was further limited by a medication-dispensing error (Allison et al., 2023). No ongoing randomized trial targeted bulimia nervosa, anorexia nervosa, avoidant/restrictive food intake disorder, or the core psychopathology of restrictive eating disorders.

3.5. Alcohol use disorder

AUD remains the most developed and most diversified target, and now contains the two largest trials in the pipeline. RENEW-ALC-1 (NCT07219966) and RENEW-ALC-2 (NCT07219953) are phase 3, multicenter, double-blind studies of brenipatide against placebo, each planning 1100 participants over approximately 56 weeks; the first restricts enrollment to moderate-to-severe AUD, the second does not. The 622-participant CRAVE trial (NCT07218354) randomizes United States veterans with moderate-to-severe AUD to semaglutide or placebo for 28 weeks, with a two-level reduction in World Health Organization drinking-risk level as the primary outcome.

The remaining eleven AUD trials are smaller phase 1 and phase 2 studies testing semaglutide monotherapy and combinations, tirzepatide alone and with cognitive behavioral therapy, tirzepatide in dual-diagnosis schizophrenia and AUD, and a mechanistic tirzepatide positron-emission tomography study. Primary targets range from heavy drinking days and drinking-risk reduction to phosphatidylethanol-verified abstinence, cue-induced craving, and dopaminergic response.

3.6. Tobacco and nicotine use

Five ongoing trials address tobacco or nicotine use. The largest are a 300-participant placebo-controlled tirzepatide trial in treatment-seeking smokers with overweight or obesity, in which all participants receive nicotine patches and the primary endpoint is seven-day point-prevalence abstinence (NCT07602699), and a 222-participant phase 2 brenipatide study with carbon-monoxide-confirmed abstinence as its primary endpoint (NCT07223840). Smaller trials test semaglutide effects on cigarettes per day and craving, semaglutide as an adjunct to nicotine replacement in diabetes, and a GLP-1RA versus a dipeptidyl-peptidase-4 inhibitor.

This design heterogeneity mirrors the discordant published evidence summarized above (Yammine et al., 2021; Lengsfeld et al., 2023; Hendershot et al., 2026), in which craving, abstinence, and post-cessation weight gain have responded differently to the same drug class. Next-generation trials must therefore distinguish three separable clinical claims: smoking cessation, craving reduction, and prevention of post-cessation weight gain.

3.7. Opioid, cocaine, cannabis, and methamphetamine use disorders

Four ongoing OUD trials plan to enroll 1021 participants. The largest is a 465-participant phase 2 study of brenipatide added to buprenorphine, with the percentage of weeks of opioid abstinence, confirmed by both self-report and urine toxicology, as the primary endpoint (NCT07420283). The others test semaglutide or tirzepatide as adjuncts to established medications for OUD, with outcomes spanning cue-induced craving, illicit-opioid abstinence, relapse, and six-month retention in buprenorphine treatment (Freet et al., 2024, 2025). No completed adequately powered randomized trial yet demonstrates reduced opioid use, overdose, or mortality.

Two semaglutide phase 2 trials in cocaine use disorder (combined n = 115) emphasize safety, tolerability, cue reactivity, craving, and urine toxicology. Three cannabis trials (combined n = 206) test semaglutide or tirzepatide and range from a six-participant mechanistic study to two planned 100-participant efficacy studies. One 162-participant semaglutide study in methamphetamine dependence (NCT07204249) registers feasibility measures alongside change in methamphetamine use, and is one of the three studies excluded from the sensitivity set.

3.8. Schizophrenia-spectrum disorders

Six ongoing randomized trials administer an incretin therapy to people with schizophrenia-spectrum disorders. In every one, the registered primary endpoint is metabolic rather than psychiatric, and all six are therefore catalogued in Table 2 rather than counted in the core analysis.

The largest are a 600-participant phase 3 semaglutide trial whose primary outcome is change in a ten-year cardiovascular risk score (NCT07770282) and a 450-participant phase 2 trial of brenipatide whose primary outcome is percent change from baseline in body weight (NCT07410507). The remaining studies target glycated hemoglobin or weight (NCT04892199, NCT05333003), or address alcohol-associated liver disease in a population that also carries an AUD diagnosis (NCT07046819).

The brenipatide record is the most informative of these. The same compound and the same sponsor register time to relapse as the primary outcome in bipolar disorder and in MDD, and body weight in schizophrenia. The choice of endpoint therefore tracks the indication rather than the drug, and reflects a developmental judgment that incretin therapy addresses cardiometabolic morbidity in psychosis rather than psychotic symptoms themselves. That judgment is consistent with the completed randomized evidence, in which liraglutide and semaglutide improved glucose tolerance, glycated hemoglobin, and weight without changing psychosis symptoms or mental quality of life, and exenatide findings were mixed (Ishøy et al., 2017; Larsen et al., 2017; Siskind et al., 2018; Ganeshalingam et al., 2025; Sass et al., 2026).

No ongoing randomized trial registered on ClinicalTrials.gov directly targeted positive, negative, or cognitive symptoms of schizophrenia, generalized or social anxiety disorder, panic disorder, post-traumatic stress disorder, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, autism spectrum disorder, or suicidal behavior (Table 2). Trichotillomania is addressed only by a single non-randomized open-label study (Table 3).

Table 2
Scope boundaries and negative-space findings.

Scope category	Trial record(s)	Interpretation
Metabolic psychiatry	NCT07770282, NCT07410507, NCT04892199, NCT05333003, NCT07046819, NCT06754163	Six randomized trials giving an incretin therapy to a psychiatric population (five schizophrenia-spectrum, one alcohol use disorder) in which the registered primary endpoint is cardiovascular risk, body weight, glycated haemoglobin, or hepatic steatosis rather than a psychiatric outcome. Combined planned n = 1563.
Complex intervention	NCT07586150	Semaglutide is one module within a personalized package and is not separately randomized, so a drug-specific effect cannot be estimated. Planned n = 140.
Neurocognitive boundary	NCT06072963, NCT07135245, NCT07200622, NCT07651319, NCT07083154	Five randomized studies in Alzheimer disease, mild cognitive impairment, or early dementia (combined planned n = 770); excluded from the core psychiatric count.
No direct ongoing RCT	No eligible ClinicalTrials.gov record	Core positive, negative, or cognitive symptoms of schizophrenia; generalized or social anxiety disorder; panic disorder; post-traumatic stress disorder; obsessive-compulsive disorder; suicidal behaviour; attention-deficit/hyperactivity disorder; autism spectrum disorder. Trichotillomania is addressed only by a non-randomized study (Table 3).

Note. These records were identified by the same search but fall outside the core count defined in Section 2.3. RCT, randomized controlled trial.

3.9. The neurocognitive boundary

Five ongoing randomized studies (combined planned n = 770) test semaglutide or a GLP-1/glucagon co-agonist, alone or in combination, in Alzheimer disease, mild cognitive impairment, or early dementia. We did not count these as psychiatric indications because their diagnoses, outcome measures, and clinical development pathway are primarily neurologic. The distinction became more important after the 3808-participant evoke and evoke + phase 3 trials found that oral semaglutide did not slow early Alzheimer disease progression and were discontinued for negative clinical outcomes (Cummings et al., 2026).

3.10. Non-randomized and observational studies

Thirteen ongoing studies with a psychiatric or behavioral target did not meet the randomization criterion (Table 3; combined planned n = 524). Most are single-arm open-label studies in stimulant, cannabis, or alcohol use, together with a mechanistic neuroimaging study, two studies of obesity in psychiatric populations, and observational cohorts reporting eating-disorder or craving outcomes. One is a 10-participant open-label semaglutide study in trichotillomania, the only ongoing study anywhere in the obsessive-compulsive spectrum. These designs cannot support efficacy claims and are especially vulnerable in conditions with high placebo response, but they indicate where clinical interest is moving ahead of randomized evidence.

4. Discussion

4.1. What the pipeline does and does not show

Ongoing randomized development registered on ClinicalTrials.gov spans nine target areas: AUD, tobacco or nicotine use, opioid, cocaine, cannabis, and methamphetamine use, MDD, bipolar disorder, and BED. We describe these as target areas rather than diagnoses because tobacco and nicotine trials do not uniformly require a diagnosis of tobacco use disorder.

Two features of this pipeline matter more than its breadth. The first is that it remains overwhelmingly a pipeline about addictive behavior: 29 of 34 trials, and more than half of all planned participants, concern substance use or tobacco. The second is that essentially all development outside addiction belongs to one compound from one sponsor. The three phase 3 mood trials and the bipolar trial are all brenipatide studies, and the seven brenipatide trials account for 62% of the pipeline by planned enrollment. Removing that single program would return the picture to what it was a year ago: exploratory phase 2 work concentrated in alcohol, with one small depression trial and one binge-eating trial. Breadth here is not the aggregate judgment of a field; it is one company's bet.

The contrast between development activity and demonstrated efficacy remains stark. A 2026 meta-analysis of five randomized trials (n = 764) found no statistically significant pooled benefit for days without alcohol consumption, cigarettes per day, or nicotine-dependence scores, and characterized a possible signal in participants with comorbid AUD and obesity as hypothesis-generating (Sarma et al., 2026). That caveat matters here, because several ongoing trials restrict enrollment to participants with elevated body mass index. Two phase 3 mood programs and two phase 3 AUD programs are proceeding without a positive confirmatory randomized result in any psychiatric indication.

The analysis also shows a pharmacological transition that the class label conceals. Half of the ongoing trials test agents that activate GLP-1 receptors but are not selective GLP-1RAs: tirzepatide and brenipatide both add GIP receptor agonism. A positive result with either cannot

Table 3
Ongoing non-randomized interventional and observational studies with a psychiatric or behavioural target.

Category/target	NCT number	Agent (class)	Design	n	Phase/status	Primary focus
Methamphetamine	NCT06745128	Tirzepatide (GIP/GLP-1)	Single-arm, open label	45	2/ANR	Self-reported methamphetamine use
Methamphetamine	NCT07509112	Semaglutide (GLP-1RA)	Single-arm, open label	40	2/NYR	Efficacy (exploratory)
Stimulant use	NCT07693608	Tirzepatide (GIP/GLP-1)	Single-arm, open label	45	2/NYR	Self-reported stimulant use
Cannabis	NCT07671248	Tirzepatide (GIP/GLP-1)	Single-arm, open label	15	3/NYR	Tolerability and feasibility
AUD + HIV	NCT07040592	Semaglutide (GLP-1RA)	Single-arm, open label	30	2/R	Feasibility, adherence, safety
Trichotillomania	NCT07282769	Semaglutide (GLP-1RA)	Single-arm, open label	10	2/NYR	NIMH Trichotillomania Severity Scale
Reward mechanism	NCT07387796	Tirzepatide (GIP/GLP-1)	Single-arm, within subject	40	NR/R	Food cue-evoked BOLD response
Metabolic — bipolar	NCT07213466	Semaglutide (GLP-1RA)[a]	Non-randomized, parallel	100	4/R	Distribution of obesity phenotypes
BED (observational)	NCT07042672	GLP-1RA, unspecified	Prospective cohort	80	—/R	EDE-Q global score
Craving (observational)	NCT06467604	GLP-1RA, unspecified	Prospective cohort	7	—/ANR	Food craving score
Other non-randomized	Three further records	Semaglutide or tirzepatide	Single-arm or cohort	112	—	See Supplementary Material

Note. Thirteen studies met every core criterion except randomization and are excluded from all counts in the main analysis; combined planned enrolment is 524 participants. Single-arm designs cannot support efficacy claims. As in the randomized pipeline, only semaglutide and tirzepatide are under investigation where the agent is specified.
Abbreviations: n, planned enrolment; ANR, active not recruiting; AUD, alcohol use disorder; BED, binge-eating disorder; BOLD, blood-oxygen-level-dependent; EDE-Q, Eating Disorder Examination Questionnaire; NIMH, National Institute of Mental Health; NR, phase not reported; NYR, not yet recruiting; R, recruiting.
[a] Semaglutide is one of several options assigned by obesity phenotype; the other arms are phentermine-topiramate and naltrexone-bupropion.

determine whether GLP-1 receptor activation, GIP receptor activation, greater weight loss, or their interaction produced the effect.

4.2. Central reward effects versus metabolic and aversive pathways

Human neuroimaging studies demonstrate that GLP-1 receptor activation can modulate appetite- and reward-related brain responses (van Bloemendaal et al., 2014, 2015), and several psychiatric trials incorporate cue reactivity, effort-based decision-making, or dopamine imaging. Reduced alcohol, nicotine, or food consumption may nonetheless also result from nausea, delayed gastric emptying, reduced appetite, altered alcohol pharmacokinetics, conditioned aversion, or the psychosocial consequences of weight loss. These are plausible mediators that may differ by drug, dose, and clinical population, and there is now direct evidence that weight change carries part of the effect. In a retrospective cohort of 11,258 outpatient adults who currently drink, initiation of a GLP-1RA ($n = 256$) was associated with a greater reduction in weekly alcohol intake than in controls (-1.0 drinks per week; 95% CI -1.6 to -0.4; $p = 0.002$), but the association became non-significant after adjustment for weight change ($p = 0.10$), and the authors concluded that the reduction in alcohol use was related to the reduction in weight (Basri et al., 2026). The exposed group was small and the design observational, so this is not decisive; but it is the clearest available demonstration that a trial which does not measure and model weight trajectory cannot interpret its own alcohol outcome.

Future trials should prospectively measure nausea, vomiting, satiety, food intake, weight trajectory, glycemia, expectancy, and functional unblinding, and should prespecify mediation analyses rather than performing them after efficacy signals emerge. Recruitment across body mass index strata is critical: repeated restriction to participants with overweight or obesity may identify a clinically useful subgroup, but it cannot establish efficacy in the full psychiatric population. Active-placebo strategies are difficult because gastrointestinal and weight effects are conspicuous, but blinded outcome assessment and credible measurement of expectancy are feasible.

4.3. Endpoint and design heterogeneity

The ongoing trials use outcomes ranging from cue-induced craving and laboratory self-administration to urine toxicology, point-prevalence abstinence, treatment retention, heavy drinking days, phosphatidylethanol-confirmed abstinence, and time to relapse. Early mechanistic endpoints are appropriate for phase 1-2 studies, but they do not all support the same indication. A drug that reduces craving without improving abstinence or hazardous use may still be valuable as an adjunct, yet it should not be described as an established treatment for the disorder.

The arrival of relapse-prevention designs in mood disorders changes what the pipeline can establish. Time to relapse is a recognized regulatory endpoint, but it addresses maintenance rather than acute efficacy, and it requires a stabilized population. Read against the absence of a positive acute-phase randomized trial in either MDD or bipolar disorder, these programs will need to demonstrate that a maintenance benefit is not an artifact of differential withdrawal, weight-related unblinding, or metabolic improvement in a population selected for cardiometabolic risk.

Behavioral co-interventions vary: some AUD trials add cognitive behavioral therapy, smoking trials add nicotine replacement or varenicline, and OUD trials maintain buprenorphine or methadone. These choices improve clinical relevance but change the estimand from monotherapy efficacy to adjunctive benefit. Durability is a further gap. Weight regain after discontinuation is well recognized, and reward-related behavior may similarly rebound when incretin treatment stops; longer follow-up should assess relapse, maintenance of abstinence, weight regain, and whether continued treatment is required.

4.4. Safety and psychiatric implementation

Gastrointestinal adverse events are common and can affect adherence, hydration, nutrition, and blinding. Psychiatric populations may have interacting vulnerabilities, including disordered eating, limited medical monitoring, and concurrent drugs that slow gastrointestinal motility; clozapine-treated patients warrant particular attention because severe constipation and gastrointestinal hypomotility are already clinically important. Nutritional compromise and loss of lean mass deserve explicit assessment, particularly in eating-disorder populations and in trials of long duration. Because many candidate psychiatric indications involve populations with substantial obesity and cardiovascular comorbidity, the broader cardiovascular profile of these agents is also relevant, including recently synthesized randomized evidence on atrial fibrillation risk (Karakasis et al., 2026) and on the magnitude and body-composition profile of incretin-associated weight loss (Karakasis et al., 2025).

The European Medicines Agency concluded in 2024 that the available evidence did not support a causal association between GLP-1RAs and suicidal or self-injurious thoughts or actions (European Medicines Agency, 2024). In January 2026, the United States Food and Drug Administration requested removal of suicidal ideation and behavior warnings from obesity-product labels after a meta-analysis of 91 placebo-controlled trials and a large Sentinel analysis found no increased risk (US Food and Drug Administration, 2026). A meta-analysis of 80 placebo-controlled trials similarly found no increased psychiatric adverse-event signal (Pierret et al., 2025). These findings are reassuring but do not remove the need for psychiatric monitoring: many metabolic trials excluded severe or unstable mental illness and were underpowered for rare events.

4.5. Regulatory and clinical implications

As of 1 September 2026, no GLP-1RA or GLP-1-containing co-agonist held a psychiatric indication authorized by the United States Food and Drug Administration or the European Medicines Agency. The distinction between registered trials and approved indications should be explicit in clinical communication. Off-label prescribing may expose patients to cost, shortages, adverse effects, and discontinuation without evidence that the psychiatric target will improve.

The most advanced pathway is AUD, where two positive semaglutide randomized trials coexist with an earlier overall-negative exenatide trial and three phase 3 programs are now under way. Mood disorders have the largest planned enrollment but the weakest completed evidence. Tobacco cessation and OUD have sizable next-generation trials but mixed or preliminary prior evidence. For cannabis, cocaine, methamphetamine, and BED, development remains proof-generating. In schizophrenia, the evidence and the registered endpoints both support a cardiometabolic role in selected patients rather than treatment of psychosis.

4.6. Research priorities

Five priorities emerge. First, phase 3 trials should use clinically meaningful outcomes, standard-care comparators, adequate representation across body mass index, sex, age, and illness severity, and follow-up beyond discontinuation. Second, mediation and mechanistic measures should distinguish central reward modulation from weight loss, gastrointestinal effects, and expectancy. Third, head-to-head comparisons should test whether selective GLP-1RAs and co-agonists differ in psychiatric efficacy and tolerability. Fourth, trials should harmonize core outcome sets within each disorder to permit meta-analysis. Fifth, the concentration of non-addiction development in a single sponsor's program is itself a risk: if that program fails, the field will retain almost no randomized infrastructure in mood disorders, and independent replication should not wait on its result.

4.7. Limitations

The most consequential limitation concerns search completeness, and our own experience illustrates it. An earlier version of this analysis searched the intervention field for ten named agents and two generic phrases. That strategy missed brenipatide entirely, because a query against the intervention field matches drug names rather than mechanisms, and brenipatide is registered under its own name and development code. The omission concerned seven trials and more than 5000 planned participants, including every ongoing trial in bipolar disorder and both phase 3 mood programs. Any registry analysis of an expanding pharmacological class that relies on named agents alone is exposed to this failure mode, and the all-field mechanism search and automated agent audit described in Section 2.2 are the minimum safeguards we would now recommend. We cannot exclude the possibility that a compound registered under a name we did not anticipate, in a record that uses no mechanism phrase, remains unretrieved.

ClinicalTrials.gov is not a global registry, and the dataset is heavily weighted toward United States sites; studies registered only elsewhere are absent. “Ongoing” denotes registry status rather than verified site-level recruitment, and one trial included in an earlier version of this analysis was no longer retrievable as ongoing at the time of the final search. Planned enrollment may differ from achieved enrollment. Our psychiatric boundary required judgment, particularly for tobacco use, metabolic outcomes in psychiatric populations, and neurocognitive disorders; the sensitivity set in Section 3.1 addresses the most discretionary of these decisions. Including GLP-1-containing co-agonists increases clinical relevance but also pharmacological heterogeneity. Finally, this was a registry landscape analysis rather than a systematic review of completed efficacy data, and it does not assess risk of bias in the trials described.

5. Conclusions

The ongoing randomized pipeline registered on ClinicalTrials.gov spans nine psychiatric target areas and 8519 planned participants, but its shape is easily misread. Twenty-nine of 34 trials concern addictive behavior, and almost all development outside addiction consists of a single manufacturer's program in mood disorders, which accounts for 62% of planned enrollment and is proceeding without a positive randomized result in any psychiatric indication. Half of all trials use co-agonists rather than selective GLP-1 receptor agonists, so a positive result would not by itself identify the responsible mechanism. Incretin-based treatments may ultimately contribute to psychiatry through two distinct routes: direct modulation of addictive or motivated behavior, and treatment of the severe cardiometabolic burden associated with mental illness. The registered endpoints of the largest current program separate those routes explicitly, and clinical communication should do the same. Until adequately powered trials demonstrate durable clinical benefit, these agents remain investigational for psychiatric indications.

CRediT authorship contribution statement

Andrea Fagiolini: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **Alessandro Cuomo:** Writing – review & editing, Writing – original draft, Validation, Methodology, Conceptualization.

Data availability

All data analyzed are publicly available from ClinicalTrials.gov. The search date, eligibility criteria, full search specification, record flow, and National Clinical Trial identifiers are reported in the manuscript, in Tables 1 and in Supplementary Methods S1, Fig. S1, and Table S1. The raw registry output and the extraction dataset are available from the corresponding author on request.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used generative AI tools to assist with English-language editing, formatting, and the construction and auditing of the registry search scripts. After using these tools, the authors reviewed and edited the content as needed, verified all extracted data against the primary registry records, and take full responsibility for the content of the publication.

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Appendix A. Supplementary data

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