The future of psychopharmacology: a critical appraisal of ongoing phase 2/3 trials, and of some current trends aiming to de-risk trial programmes of novel agents

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Despite considerable progress in pharmacotherapy over the past seven decades, many mental disorders remain insufficiently treated. This situation is in part due to the limited knowledge of the pathophysiology of these disorders and the lack of biological markers to stratify and individualize patient selection, but also to a still restricted number of mechanisms of action being targeted in monotherapy or combination/augmentation treatment, as well as to a variety of challenges threatening the successful development and testing of new drugs. In this paper, we first provide an overview of the most promising drugs with innovative mechanisms of action that are undergoing phase 2 or 3 testing for schizophrenia, bipolar disorder, major depressive disorder, anxiety and trauma-related disorders, substance use disorders, and dementia. Promising repurposing of established medications for new psychiatric indications, as well as variations in the modulation of dopamine, noradrenaline and serotonin receptor functioning, are also considered. We then critically discuss the clinical trial parameters that need to be considered in depth when developing and testing new pharmacological agents for the treatment of mental disorders. Hurdles and perils threatening success of new drug development and testing include inadequacy and imprecision of inclusion/exclusion criteria and ratings, sub-optimally suited clinical trial participants, multiple factors contributing to a large/increasing placebo effect, and problems with statistical analyses. This information should be considered in order to de-risk trial programmes of novel agents or known agents for novel psychiatric indications, increasing their chances of success.

Key words: Psychopharmacology, clinical trials, design, methodology, novel mechanisms of action, schizophrenia, bipolar disorder, major depressive disorder, anxiety disorders, trauma-related disorders, substance use disorders, dementia

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The timely as well as effective and safe treatment of mental disorders is a key focus in medicine, due to the early onset of these disorders, and their severity, chronicity and major effects on multiple biopsychosocial aspects of human life[1-4]. Clinicians, patients, family members and the society at large have substantial interest in the availability of new treatment options that have greater, broader or more specific efficacy and similar or enhanced tolerability compared to already available agents, ideally also involving new mechanisms of action that may help personalization of treatment[5-7].

Pharmacological approaches to mental disorders were initially mostly the outcome of observation and serendipitous discoveries, also informed by substances that could alter mental states and lead to addiction. In the 1950s and 1960s, there was a steep increase in the availability of pharmacological agents that were helpful in improving mental health by reducing symptoms of multiple psychiatric disorders. Most of the finer understanding of brain mechanisms involved in mental illness generation was derived from inductive reasoning, i.e., the effect of a medication on the brain was observed, the mechanism of action of the drug was studied in animal and human models, and the insights were used as the basis for hypothesizing biological underpinnings of mental disorders.

In that sense, psychopharmacology is essentially a symptom-based discipline. This approach is further related to the fact that our systems for classifying mental illness consist of patterns of often co-occurring and/or connected symptoms, which are elevated to the status of disorders as long as they lead to distress or dysfunction and are not due to the effects of a substance or a medical condition. This classification is not related to an underlying biology of the identified disorders. Comorbidities are very common and medications often do not work in a substantial number of people with a given diagnosis and/or have pleiotropic and non-specific effects, working for more than one disorder. Recognizing these shortcomings of current nosological systems, alternative approaches are being

proposed[8-10], but are not adopted in the clinical and regulatory classification and drug approval process.

Moreover, the pharmacological nomenclature has remained arcane, being only rarely or incompletely related to the mechanisms of action of medications, as is common in medicine to characterize drug classes. Instead, medications are usually named after their first indication. This has given rise to a terminology that can confuse patients, family members, clinicians and even regulators[11]. For example, the so-called antipsychotics are approved for such diverse indications as schizophrenia, bipolar mania, bipolar depression, major depressive disorder, tic disorder, and irritability associated with autism[12,13]; and have been also found effective for anxiety, insomnia, agitation/aggression, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD)[14]. Similarly, the so-called antidepressants have been approved for major depressive disorder, various types of anxiety disorders, and OCD; and are used clinically also for bipolar depression and insomnia, among other conditions[12,13,15,16].

This diagnostically non-specific, pleiotropic use of medication classes is certainly in part due to the complexity and overlap of the biological mechanisms underlying behavioral, emotional and cognitive manifestations. At the same time, medications often do not impact a single biological system, but have a variety of biological effects, that would need to be dissected further and may be dose-dependent. For example, quetiapine, one of the most prescribed so-called antipsychotics, is more frequently administered in combination with other drugs than in monotherapy for psychosis, and is more often used for mood, anxiety and sleep disorders than for psychotic symptoms. The use of quetiapine for such diverging diagnoses and symptoms is linked to the fact that the main pharmacodynamic effect of this medication varies according to the dose at which it is administered[17]. For example, at low doses (25-50 mg/day), it acts as an antihistaminic, which can help treat anxiety, insomnia and agitation/tension. At medium doses (150-300 mg/day), it turns out to have alpha-2 adrenergic receptor blocking and noradrenaline-reuptake inhibiting activity, making it useful as a treatment for major depressive disorder and bipolar depression. At higher doses (450-600 mg/day and above), its postsynaptic dopamine antagonism becomes relevant, making it useful for the treatment of psychosis and mania.

This disorder-driven approach to psychopharmacology is shared by regulatory bodies. Thus, for example, a medication initially marketed for a given disorder may automatically get a black box warning when it becomes indicated for another disorder, even though the safety risk data motivating that warning apply to a pharmacologically entirely different drug class, and no such risk has been described for that medication. This carry-over effect has occurred, for instance, for all dopamine receptor blockers and partial dopamine agonists with respect to the risk of suicide, when they received regulatory approval by the US Food and Drug Administration (FDA) for major depressive disorder, although the relevant (possibly medication-related) data in adolescents and young adults[18,19] were restricted to traditional "antidepressants" that are monoamine reuptake inhibitors or modulators.

The neuroscience-based nomenclature initiative has been to some extent helpful in trying to refine our pharmacological terminology, bringing to bear the knowledge that we have so far in order to classify medication classes and members of each class[20-23].

At the core of state-of-the-art testing of the risks and benefits of a new molecular entity in psychopharmacology are randomized controlled parallel-group clinical trials. However, multiple hurdles in trial design and conduct may interfere with the development of molecular entities showing promise in phase 1 and 2 trials, when they are tested in increasingly large phase 3 trial programmes. Relatively recent failures concerning medications for schizophrenia have included pomaglumetad for total symptoms[24,25], encenicline for cognitive symptoms[26,27], and bitopertin for negative symptoms[28-30]. Similarly, multiple drug development failures on the translational trajectory from phase 1 and 2 into phase 3 trials have involved drugs targeting dementia[31].

Reasons for these failures may be related to the true inefficacy of a drug, its toxicity profile, insufficiently understood dose-response relationships, unknown patient factors, but also the limited knowledge of the biological mechanisms underpinning mental disorders, which prevents the identification of potentially relevant subgroups. An additional factor involved is the increasing placebo response across multiple mental disorders, whose reasons remain insufficiently understood[32-40].

After many decades with few, if any, discoveries of novel effective targets beyond enhancing serotonin and noradrenaline or blocking postsynaptic dopamine transmission for the treatment of mental disorders, some advances have recently occurred. Medications with more recent regulatory approval have targeted the melatonin[41], orexin[42], GABA-A[43,44], opioid[45,46] and N-methyl-D-aspartate (NMDA)[47,48] receptor systems, the vesicular monoamine transporter-2 (VMAT-2) for tardive dyskinesia[49], and inverse agonism of 5-HT2A receptors[50]. Furthermore, there is currently a renaissance of exploiting mechanisms of action of psychedelics, attempting to isolate their beneficial effects without their short- or longer-term risk of brain harm or addictive potential[51-55]. Nonetheless, there is great concern that many, if not most, of the currently studied drugs with new mechanisms of action may not pass through the "valley of death" of their phase 2 and, especially, phase 3 development.

In this paper, we first provide an overview – based on a systematic search in clinicaltrials.gov and clinicaltrialsregister.eu (EudraCT) – of medications with innovative mechanisms of action that are undergoing phase 2 or 3 testing for the treatment of a main mental disorder in adults, such as schizophrenia, bipolar disorder, major depressive disorder, anxiety and trauma-related disorders, substance use disorders, and dementia, highlighting those agents that are seen as having the most promise (as emerging from documented superiority over placebo, magnitude of the observed effect, and demonstration of requirements for safety and tolerability). We then critically discuss the ongoing developments in clinical trial methodology, design and conduct that need to be considered in depth when developing and testing pharmacological agents for the treatment of men-

tal disorders, in order to de-risk trial programmes of novel agents or known agents for novel psychiatric indications.

OVERVIEW OF MEDICATIONS UNDERGOING PHASE 2 AND 3 CLINICAL TRIALS

Schizophrenia

Agents in development for the treatment of schizophrenia target directly or indirectly, among others, the cannabinoid, cholinergic, dopamine, estrogen, GABA, glutamatergic, histamine, inflammatory, immunological, ion channel, melatonin, noradrenaline, opioid, phosphodiesterase, serotonin, sigma, and trace amine associated receptor (TAAR) systems (see Table 1 and supplementary information). Across 176 identified phase 2 or 3 trials, only 12 molecules that were tested in 42 trials have so far outperformed placebo on primary outcomes in 13 positive trials (see Table 1).

For total symptoms of schizophrenia, a 5-week phase 2 trial (NCT03697252) showed that KarXT (containing a fixed combination of the muscarinic M1/M4 agonist xanomeline plus the non-centrally acting anticholinergic trospium chloride), given twice daily, outperformed placebo (effect size = 0.75), without relevant cardiometabolic or neuromotor adverse effects, but with some modest and mostly time-limited anticholinergic adverse events[56,57]. In August 2022, positive topline results for the primary outcome total Positive and Negative Syndrome Scale (PANSS) score (effect size = 0.61) and secondary outcomes have been released for the first of two similarly designed, placebo-controlled phase 3 studies in patients with acutely exacerbated schizophrenia (NCT04659161). The second phase 3 trial of KarXT in monotherapy vs. placebo (NCT04738123), as well as one 6-week trial in patients with residual positive symptoms testing KarXT in an augmentation design (NCT05145413), are ongoing.

Moreover, in a small, 6-week, phase 1B study (which is therefore not included in Table 1), emraclidine, an M4 positive allosteric modulator, also separated from placebo both in the 20 mg bid and 30 mg qd dose arms (NCT04136873). Results are being followed up in two 6-week phase 2 trials testing 10 mg and 30 mg qd (NCT05227690) as well as 15 mg and 30 mg qd (NCT05227703) vs. placebo.

Ulotaront, a TAAR-1 and 5-HT1A agonist, outperformed placebo in a 4-week, phase 2 trial in patients with schizophrenia aged 40 or younger and with no more than two prior lifetime hospitalizations for exacerbation of schizophrenia, without relevant neuromotor or cardiometabolic adverse effect risk (NCT02969382)[58]. Three additional placebo-controlled trials are ongoing (NCT04825860, NCT04072354, NCT04092686), extending the age until 65 years and being less restrictive about prior number of hospitalizations. Additionally, ralmitaront, a TAAR-1 partial agonist, is undergoing phase 2 testing (NCT04512066, NCT03669640).

Brilaroxazine, a D2, D3, D4, 5-HT1A, 5-HT2A partial agonist, and 5-HT2B, 5-HT6, 5-HT7 antagonist, was superior to placebo in a 4-week phase 2 trial (NCT01490086)[59], and a phase 3 trial has recently started (NCT05184335). Two phase 3 trials (NCT03893825, NCT03503318) have been completed for a novel subcutaneous once monthly and every two months injected long-acting formulation of risperidone, TV-46000, confirming the efficacy of other formulations of this drug in the acute treatment and relapse prevention of schizophrenia.

Raloxifene, an estrogen receptor modulator, improved PANSS total, general and negative symptoms in a phase 3 trial in postmenopausal women with schizophrenia (NCT01573637)[60], but another phase 3 trial showed inferior efficacy compared with placebo (NCT01280305)[61]. Melatonin also improved PANSS total symptoms more than placebo in a phase 2 trial (NCT01593774)[62].

For positive symptoms (co-primary outcome), a phase 2 trial (NCT02006628) showed that adjunctive cannabidiol outperformed placebo after six weeks of treatment[63]. While a significant difference was also reported for Clinical Global Impression - Severity (CGI-S), cannabidiol was not superior to placebo regarding total symptoms (co-primary outcome). Finally, estradiol outperformed placebo on PANSS positive symptoms after eight weeks of treatment in a phase 2 trial (NCT03848234)[64].

For negative symptoms of schizophrenia, the 5-HT2A inverse agonist/antagonist pimavanserin (approved for Parkinson's disease psychosis and under review for dementia-related psychosis) had one positive phase 2 study with regards to the primary outcome, Negative Symptom Assessment-16 (NSA-16) total scale change, but without greater improvement versus placebo in CGI-S and other negative symptom assessment scales (NCT02970305)[65].

Targeting schizophrenia patients with residual psychotic symptoms, a phase 3 trial reported no improvement of total symptoms with adjunctive pimavanserin in the entire sample, but there were favorable results in the approximately 80% European subsample, and significant improvements in negative symptoms and CGI-S in the total sample (NCT02970292).

Roluperidone, a 5-HT2A and sigma-2 receptor antagonist, had one successful phase 2 trial (EU2014-004878-42) for negative symptoms[66], albeit in the context of an unusually low placebo response. The subsequent phase 3 trial (NCT03397134) was suggestive of efficacy, but missed statistical significance versus placebo in the intent-to-treat analysis[67]. A potential complication is that this drug has been tested only in monotherapy, i.e., in patients with schizophrenia who were off traditional dopamine receptor blockers or partial agonists, without documentation that it is effective on total and positive symptoms.

Concerning cognitive dysfunction in schizophrenia, a phase 3 clinical trial programme follows up on a successful phase 2 study with BI 425809 (NCT02832037), a glycine transporter-1 inhibitor, that outperformed placebo at week 12 on MATRICS Consensus Cognitive Battery[68], but not on the Schizophrenia Cognition Rating Scale (SCoRS), which measures functional impact of cognitive improvement, a required co-primary endpoint for regulatory approval of agents targeting cognitive dysfunction in schizophrenia.

Regarding the management of adverse events of already approved antipsychotics in schizophrenia, glycopyrrolate (a muscarinic receptor antagonist) improved sialorrhea more than placebo in a phase 2 trial (EU2012-002299-15)[69].

While a number of trials targeting multiple mechanisms of action are ongoing or

Table 1 Medications for schizophrenia with positive results in phase 2 or 3 randomized controlled trials

Drug	Mechanisms of action	Control	Duration (weeks)	Phase	NCT/EudraCT number	Status	Results
BI 425809	Glycine transporter-1 inhibitor	Placebo	26	3	NCT04860830	R	No results available
BI 425809		Placebo	26	3	NCT04846868	R	No results available
BI 425809		Placebo	26	3	NCT04846881	R	No results available
BI 425809		Placebo	12	2	NCT03859973	R	No results available
BI 425809		Placebo	26	3	EU2020-003726-23	O	No results available
BI 425809		Placebo	12	2	NCT02832037	C	Superior on cognition
Brilaroxazine	Dopamine-5-HT partial agonist, 5-HT antagonist	Placebo, Aripiprazole	4	2	NCT01490086	C	Superior (PANSS)
Brilaroxazine		Placebo	4	3	NCT05184335	R	No results available
Cannabidiol	Multiple (among others, binds to CB1/CB2 receptors, activates 5-HT1A receptors, antagonizes alpha-1 adrenergic and mu opioid receptors, inhibits synaptosomal uptake of noradrenaline, dopamine, serotonin and GABA)	Placebo	26	2	NCT02926859	ANR	No results available
Cannabidiol		Placebo, Olanzapine	4	2	NCT02088060	ANR	No results available
Cannabidiol		Placebo	10	2	NCT02504151	ANR	No results available
Cannabidiol		Placebo	8	3	NCT04411225	R	No results available
Cannabidiol		Risperidone	7	2	NCT04105231	R	No results available
Cannabidiol		Placebo	12	2	NCT04421456	R	No results available
Cannabidiol		Placebo	6	2	NCT02006628	C	Superior on PANSS positive, CGI-S
Estradiol	Estrogen receptor agonist	Placebo	8	3	NCT03848234	C	Superior on PANSS positive
Estradiol		Placebo	16	3	NCT04093518	R	No results available
Glycopyrrolate	Muscarinic receptor antagonist	Placebo	1	3	EU2012-002299-15	C	Superior on sialorrhea
Melatonin	Melatonin receptor agonist	Placebo	24	4	NCT01431092	C	Data available for a subsample of 48 participants
Melatonin		Placebo	8	2	NCT01593774	C	Superior on PANSS total
Pimavanserin	5-HT2A inverse agonist/ antagonist	Placebo	26	3	NCT04531982	R	No results available
Pimavanserin		Placebo	6	3	NCT02970292	C	No effect on PANSS total
Pimavanserin		Placebo	26	2	NCT02970305	C	Superior on NSA-16
Pimavanserin		Placebo	26	3	EU2016-003437-18	C	No results available
Raloxifene	Estrogen receptor modulator	Placebo	24	3	NCT01573637	C	Superior on PANSS total, negative, general
Raloxifene		Placebo	12	3	NCT01280305	C	Inferior on PANSS total
Raloxifene		Placebo	12	4	NCT03418831	C	No results available
Raloxifene		Placebo	12	4	NCT02354001	C	No results available
Raloxifene		Placebo	12	4	NCT01481883	R	No results available
Raloxifene		Placebo	12	3	NCT03043820	R	No results available
Roluperidone	5-HT2A and sigma-2 receptor antagonist	Placebo	12	2	EU2014-004878-42	C	Superior on negative symptoms
Roluperidone		Placebo	12	3	NCT03397134 EU2017-003333-29	C	No difference in intention-to-treat analysis, superior on negative symptoms in modified intention-to-treat analysis
TV-46000 (subcutaneous risperidone)	Dopamine antagonist	Placebo	56	3	NCT03893825	C	Superior in acute and long-term treatment
TV-46000 (subcutaneous risperidone)		Placebo	108	3	NCT03503318	C	Superior on relapse prevention

Table 1 Medications for schizophrenia with positive results in phase 2 or 3 randomized controlled trials *(continued)*

Drug	Mechanisms of action	Control	Duration (weeks)	Phase	NCT/EudraCT number	Status	Results
Ulotaront	TAAR-1/5-HT1A agonist	Quetiapine XR	52	3	NCT04115319	R	No results available
Ulotaront		Placebo	4	2	NCT02969382	C	Superior on PANSS total
Ulotaront		Placebo	6	2/3	NCT04825860	R	No results available
Ulotaront		Placebo	5	3	NCT04072354	R	No results available
Ulotaront		Placebo	6	3	NCT04092686	R	No results available
Xanomeline + Trospium Chloride (KarXT)	M1/M4 muscarinic agonist, peripheral muscarinic antagonist	Placebo	5	2	NCT03697252	C	Superior on PANSS total
Xanomeline + Trospium Chloride (KarXT)		Placebo	5	3	NCT04738123	R	No results available
Xanomeline + Trospium Chloride (KarXT)		Placebo	5	3	NCT04659161	C	Superior on PANSS total
Xanomeline + Trospium Chloride (KarXT)		Placebo	6	3	NCT05145413	R	No results available

NCT/EudraCT number – number in clinicaltrials.gov or clinicaltrialsregister.eu, R – recruiting, O – ongoing, C – completed, ANR – active, not recruiting, TAAR-1 – trace amine-associated receptor-1, PANSS – Positive and Negative Syndrome Scale, CGI-S – Clinical Global Impression - Severity, NSA-16 – Negative Symptom Assessment-16. Results without information on statistical significance are classified among "results not available".

have been completed without available results (see supplementary information), the currently most promising targets for schizophrenia appear to be M1/M4 muscarinic receptor agonism, M4 muscarinic positive allosteric agonism, TAAR-1 agonism, and dopamine-serotonin partial agonism/serotonin antagonism. Due to mixed/inconclusive findings, questions remain about 5-HT2A inverse agonism/antagonism for negative and residual psychotic symptoms, and 5-HT2A/sigma-2 antagonism for negative symptoms, as well as about glycine transporter-1 inhibition for improvement of cognitive dysfunction, that is required to also significantly improve functionality to gain regulatory approval.

Bipolar disorder

Agents in development for the treatment of bipolar disorder target directly or indirectly, among others, the cholinergic, dopamine, GABA, glutamatergic, inflammatory, immunological, ion channel, melatonin, neurotrophic, noradrenaline, and serotonin systems (see Table 2 and supplementary information). Across 38 identified trials, only six molecules that were tested in 11 trials outperformed placebo on primary outcomes in six positive trials (see Table 2).

For bipolar depression, N-acetyl cysteine (a glutathione precursor) plus acetylsalicylic acid, added to treatment-as-usual, outperformed placebo regarding response in one phase 2 trial (NCT01797575)[70]. Furthermore, non-racemic amisulpride (SEP-4199) was superior to placebo at 6 weeks on the Montgomery-Asberg Depression Rating Scale (MADRS) in the US, European Union and Japanese cohorts, at doses of 200 or 400 mg/day[71,72]. Adjunctive armodafinil, an R-enantiomer of modafinil, was associated with a significantly greater reduction in the 30-item Inventory of Depressive Symptomatology, Clinician Rated (IDS-C) total score at week 8[73] in one phase 3 trial vs. placebo (NCT01072929), but two other phase 3 trials (NCT01072630 and NCT01305408) did not confirm this superiority[74,75].

D-cycloserine (an NMDA antagonist) plus lurasidone outperformed lurasidone plus placebo after an initial ketamine infusion in reducing depressive symptoms in severely depressed patients with bipolar disorder (NCT02974010)[76]. Moreover, adjunctive infliximab – a tumor necrosis factor-alpha (TNF-α) inhibitor – was superior to placebo regarding depressive symptoms in a phase 2 trial (NCT02363738), yet with no difference regarding treatment response[77-79]. Interestingly, secondary analyses suggested higher efficacy in subjects with childhood maltreatment. Ketamine outperformed placebo in a phase 2 trial targeting suicidal ideation (NCT01944293).

We did not identify any positive randomized controlled trial (RCT) for treatment of acute mania or for the maintenance treatment of bipolar disorder.

While a number of trials targeting multiple mechanisms of action are ongoing or have been completed without available results (see supplementary information), the currently most promising targets for bipolar depression are dopamine antagonism plus 5-HT7 antagonism, non-steroidal anti-inflammatory action plus glutathione precursor activity, NMDA receptor antagonism, and TNF-α inhibition. Notably, neither bipolar mania nor bipolar disorder maintenance are currently relevant targets in drug development, and the most promising agents for bipolar depression are all repurposed from different existing indications.

Major depressive disorder

Agents in development for the treatment of major depressive disorder target directly or indirectly, among others, the cannabinoid, cholinergic, dopamine, estrogen, GABA, glutamatergic, inflammatory, immunological, ion channel, neurotrophic, noradrenaline, opioid, peroxisome proliferator-activated receptor, serotonin, sigma, TAAR, and substance P systems (see Table 3 and supple-

Table 2 Medications for bipolar depression with positive results in phase 2 or 3 randomized controlled trials

Drug	Mechanisms of action	Control	Duration (weeks)	Phase	NCT/EudraCT number	Status	Results
N-acetyl cysteine + Acetylsalicylic acid	Glutathione precursor + NSAID	Placebo	16	2	NCT01797575	C	Superior on response
Amisulpride, non-racemic	Dopamine/5-HT7 antagonist	Placebo	6	2	NCT03543410	C	Superior on depressive symptoms
Armodafinil	Sympathomimetic	Placebo	8	3	NCT01072630	C	No difference
Armodafinil		Placebo	8	3	NCT01072929	C	Superior on depressive symptoms
Armodafinil		Placebo	8	3	NCT01305408	C	No difference
D-cycloserine + Lurasidone	NMDA antagonist + dopamine antagonist	Lurasidone + Placebo	6	2	NCT02974010	C	Superior on depressive symptoms
Infliximab	TNF-α inhibitor	Placebo	12	2	NCT02363738	C	Superior on depressive symptoms
Ketamine	NMDA antagonist	Midazolam	28	3	NCT04939649	R	No results available
Ketamine		Placebo	2	2	NCT05004896	NYR	No results available
Ketamine		Midazolam	2	2	EU2016-002068-14	C	No results available
Ketamine		Midazolam	1 day	2	NCT01944293	C	Superior on suicidal ideation

NCT/EudraCT number – number in clinicaltrials.gov or clinicaltrialsregister.eu, R – recruiting, C – completed, NYR – not yet recruiting, NSAID – non-steroidal anti-inflammatory drug, NMDA – N-methyl-D-aspartate, TNF-α – tumor necrosis factor alpha. Results without information on statistical significance are classified among "results not available".

mentary information). Across 177 identified trials, 19 molecules that were tested in 43 trials outperformed placebo on primary outcomes in 19 positive trials (see Table 3).

Cariprazine, a D3-preferring D3/D2 partial dopamine agonist with antagonist activity at 5-HT2B and 5-HT2A receptors, is currently under FDA review as augmentation in major depressive disorder, following a positive phase 3 trial (NCT03738215) and one partially positive phase 2 trial (at 2-4.5 mg/day, but not at 1-2 mg/day) (NCT01469377)[80], alongside a negative trial (NCT03739203). Lurasidone, a 5-HT2A-D2 antagonist with 5-HT7 antagonism, was superior to placebo in a phase 3 trial of subjects with major depressive disorder and mixed features (NCT01421134)[81].

The extended release (ER) formulation of levomilnacipran, a serotonin-noradrenaline reuptake inhibitor, outperformed placebo in a phase 3 trial (NCT01377194)[82], although the switch to levomilnacipran ER was not superior to quetiapine plus antidepressants in another phase 3 trial (NCT 02720198). Pimavanserin, a 5-HT2A antagonist/inverse agonist, had a positive phase 2 sequential parallel comparison design study (positive in stage 1+2 and 1, but not in stage 2) as augmentation in major depressive disorder (NCT03018340)[83], followed by a negative standard phase 3 study (NCT03968159) compared to placebo.

With the FDA approval of intranasal esketamine[84] and the widespread off-label use of racemic ketamine, both intravenously and intranasally, for resistant depression[85,86], the field of psychopharmacology has seen a renewed focus on the development of antidepressant therapies that modulate the glutamatergic system.

One such agent is AXS-05, the combination of dextromethorphan with low-dose bupropion, whose pharmacological actions are non-competitive NMDA receptor antagonism, sigma-1 receptor agonism, nicotinic acetylcholine receptor antagonism, and inhibition of serotonin, noradrenaline and dopamine transporters. In two phase 2 trials, AXS-05 was superior to low-dose bupropion[87] (NCT03595579) or to placebo (NCT04019704) on the MADRS at week 6, leading to FDA approval for major depressive disorder in August 2022. For treatment-resistant depression, AXS-05 showed in a one-year study significantly delayed time to relapse (primary outcome) and decreased relapse rate (secondary outcome) (NCT04608396); however, it did not separate from bupropion 150 mg/day in a 12-week study (NCT02741791).

A second anti-glutamatergic agent is esmethadone, an NMDA receptor antagonist with very weak opioid mu agonism, which is being developed as an augmenting agent in treatment-resistant depression, following a positive phase 2 trial (NCT03051256)[88]. The phase 3 programme is ongoing, with three 4-week placebo-controlled studies (NCT04855747, NCT05081167, NCT04688164). A single dose of rapastinel, a NMDA partial agonist, was superior to placebo, when given at 5 or 10 mg, but not 1 mg, in a phase 2 trial (NCT01234558)[89], but three phase 3 trials were negative (NCT02951988, NCT02943564, NCT02943577).

There has also been significant interest in GABAergic modulation for the treatment of depression. Following FDA approval of the intravenous GABA-A receptor positive allosteric modulator brexanolone in postpartum depression[90,91], the orally administered zuranolone, which is also a neuroactive steroid binding to GABA-A receptors, is being developed for both postpartum depression and major depressive disorder. Zuranolone had a positive phase 2 study in severe postpartum depression, despite a large placebo response (NCT02978326)[92]. A second trial for postpartum depression is

Table 3 Medications for major depressive disorder with positive results in phase 2 or 3 randomized controlled trials

Drug	Mechanisms of action	Control	Duration (weeks)	Phase	NCT number	Status	Results
Ayahuasca	5-HT multimodal modulator, TAAR-1 and sigma-1 agonist	Placebo	1	2	NCT02914769	C	Superior on HAM-D
Botulinum toxin type A neurotoxin complex	Acetylcholine release inhibitor	Placebo	12	2	NCT01392963	C	Superior on HAM-D
Buprenorphine + Samidorphan + Antidepressant	Kappa opioid agonist + mu opioid antagonist	Placebo + Antidepressant	4	2	NCT01500200	C	Superior on HAM-D (only 2 + 2 mg/day)
Buprenorphine + Samidorphan + Antidepressant		Placebo + Antidepressant	6	3	NCT02218008	C	Superior on MADRS
Buprenorphine + Samidorphan + Antidepressant		Placebo + Antidepressant	6	3	NCT03188185	C	No difference
Buprenorphine + Samidorphan + Antidepressant		Placebo + Antidepressant	6	3	NCT02158546	C	No difference
Buprenorphine + Samidorphan + Antidepressant		Placebo + Antidepressant	5	3	NCT02158533	C	No difference
Dextromethorphan + Bupropion (AXS-05)	NMDA antagonist, sigma-1 agonist, nicotinic acetylcholine receptor antagonist, 5-HT/noradrenaline/dopamine reuptake inhibitor	Bupropion SR	6	2	NCT04971291	R	No results available
Dextromethorphan + Bupropion (AXS-05)		Bupropion	12	3	NCT02741791	C	No superiority for treatment-resistant depression
Dextromethorphan + Bupropion (AXS-05)		Placebo	52	2	NCT04608396	C	Delayed time to relapse
Cariprazine + Antidepressant	Dopamine D3/D2 partial agonist, serotonin antagonist	Placebo + Antidepressant	8	2	NCT01469377	C	Superior on MADRS at week 8 (only 2-4.5 mg/day)
Cariprazine + Antidepressant		Placebo + Antidepressant	6	3	NCT03738215	C	Superior at week 6
Cariprazine + Antidepressant		Placebo + Antidepressant	6	3	NCT03739203	C	No difference
Esmethadone + Antidepressant	NMDA antagonist	Placebo + Antidepressant	3	2	NCT03051256	C	Superior on MADRS at week 2
Esmethadone + Antidepressant		Placebo + Antidepressant	4	3	NCT04855747	R	No results available
Esmethadone + Antidepressant		Placebo + Antidepressant	4	3	NCT05081167	R	No results available
Esmethadone + Antidepressant		Placebo+ Antidepressant	4	3	NCT04688164	R	No results available
Estradiol + Progesterone	Estrogen receptor agonist, progesterone receptor agonist	Placebo	52	2/3	NCT01308814	C	Superior on CES-D
Ezogabine	Opening of neuronal voltage activated potassium channels	Placebo	5	2	NCT03043560	C	Superior on MADRS
Levomilnacipran ER	5-HT/noradrenaline reuptake inhibitor	Quetiapine + Antidepressant	8	3	NCT02720198	C	No difference
Levomilnacipran ER		Placebo	8	3	NCT01377194	C	Superior on MADRS
Lurasidone	5-HT7, 5-HT2A and dopamine antagonist	Placebo	6	3	NCT01421134	C	Superior on MADRS
Metformin + Fluoxetine	AMP-activated protein kinase	Placebo + Fluoxetine	12	1/2	NCT04088448	C	Superior on HAM-D
Naltrexone + Antidepressant	Opioid receptor antagonist	Placebo + Antidepressant	3	2	NCT01874951	C	Superior on MADRS but not on HAM-D
Nitrous Oxide	Inhalation anesthetic	Placebo	1	2	NCT03283670	C	Superior on HAM-D
Nitrous Oxide		Placebo	1	2	NCT02139540	C	Superior on depressive symptoms at 24 hours
Nitrous Oxide		Placebo	2	2	NCT03932825	C	No results available
Nitrous Oxide		Placebo	4	2	NCT03869736	NA	No results available

Table 3 Medications for major depressive disorder with positive results in phase 2 or 3 randomized controlled trials *(continued)*

Drug	Mechanisms of action	Control	Duration (weeks)	Phase	NCT number	Status	Results
Pimavanserin + Antidepressant	5-HT2A inverse agonist/ antagonist	Placebo + Antidepressant	5	2	NCT03018340	C	Superior on HAM-D (stage 1 and 1+2, not stage 2)
Pimavanserin + Antidepressant		Placebo + Antidepressant	5	3	NCT03968159	C	No difference
Pioglitazone + Citalopram + Chlordiazepoxide	PPARγ agonist	Placebo + Citalopram + Chlordiazepoxide	6	2/3	NCT01109030	C	Superior on response (HAM-D)
Psilocybin	5-HT1A/5-HT2A agonist	Waitlist	8	2	NCT03181529	C	Superior on GRID-HAM-D
Psilocybin		Escitalopram	6	2	NCT03429075	C	No difference
Psilocybin		Placebo	5	2	NCT03715127	O	No results available
Psilocybin		Placebo	8	2	NCT04989972	O	No results available
Psilocybin		Ketamine	26	2	NCT03380442	O	No results available
Psilocybin		Placebo	4	2	NCT04620759	O	No results available
Psilocybin		Niacin	1	2	NCT04630964	O	No results available
Psilocybin		Niacin	7	2	NCT03866174	O	No results available
Psilocybin + Psychological therapy		Placebo + Psychological therapy	3	2	NCT04959253	O	No results available
Psilocybin		Placebo	4	2	NCT05259943	O	No results available
Psilocybin + Psychological therapy		Nicotinamide + Psychological therapy	6	2	NCT04670081	O	No results available
Rapastinel + Antidepressant	NMDA partial agonist	Placebo + Antidepressant	3	3	NCT02932943	C	No difference
Rapastinel		Placebo	1 dose	2	NCT01234558	C	Superior (5-10 mg, not 1 mg)
Rapastinel		Placebo	52	3	NCT02951988	C	No difference
Rapastinel + Antidepressant		Placebo + Antidepressant	6	2	NCT01684163	C	No results available
Rapastinel		Placebo	3	3	NCT02943564	C	No difference
Rapastinel		Placebo	3	3	NCT02943577	C	No difference
Zuranolone (30 mg/day)	GABA-A receptor positive allosteric modulator	Placebo	7	3	NCT02978326	C	Superior for postpartum depression on HAM-D at day 15
Zuranolone		Placebo	2	3	NCT04442503	NYR	No results for postpartum depression available
Zuranolone (30 mg/day)		Placebo	2	2	NCT03000530	C	Superior for major depression on HAM-D at day 15
Zuranolone (20 mg/day and 30 mg/day)		Placebo	2	3	NCT03672175	C	No superiority on HAM-D at day 15
Zuranolone (50 mg/day)		Placebo	2	3	NCT04442490	C	Superior for major depression on HAM-D at day 15
Zuranolone (50 mg/day) + Antidepressant		Placebo + Antidepressant	2	3	NCT04476030	C	Superior for major depression on HAM-D at day 3 (primary endpoint), but not day 15

NCT number – number in clinicaltrials.gov, R – recruiting, C – completed, O – ongoing, NYR – not yet recruiting, NA – not available, NMDA – N-methyl-D-aspartate, PPARγ – peroxisome proliferator-activated receptor gamma, TAAR-1 – trace amine-associated receptor-1, HAM-D – Hamilton Depression Rating Scale, MADRS – Montgomery-Åsberg Depression Rating Scale, CES-D – Center for Epidemiological Studies-Depression Scale. Results without information on statistical significance are classified among "results not available".

awaiting results (NCT04442503).

In patients with major depressive disorder, one study of zuranolone at 30 mg/day (NCT0300530) met the primary endpoint on the Hamilton Depression Rating Scale (HAM-D) on day 15[93]. Another monotherapy study of the drug at 50 mg/day (NCT04 442490) also met the primary endpoint of superiority vs. placebo on the HAM-D at day 15. However, high placebo response accounted for a negative study at day 15 for zuranolone 20 mg/day and 30 mg/day, despite superiority over placebo on the HAM-D in the 30 mg/day arm at days 3, 8 and 12 (NCT03672175). In a phase 3 trial (NCT04476030), zuranolone 50 mg/day co-initiated with a standard antidepressant was superior to placebo on HAM-D total score at day 3 (primary endpoint), and throughout the 2-week treatment period (key secondary endpoint), but not at day 15, confirming an effect in speeding up of efficacy.

Other mechanisms of action are also being pursued. For example, pioglitazone, an agonist of the peroxisome proliferator-activated receptor gamma, plus citalopram plus chlordiazepoxide was superior to placebo in a phase 2/3 study (NCT01109030) regarding treatment response based on HAM-D scores[94]. Naltrexone, an opioid receptor antagonist, plus antidepressants was superior to placebo plus antidepressants in a phase 2 trial in preventing relapse or symptom recurrence on the MADRS, but not the HAM-D (NCT01874951)[95].

The combination of buprenorphine, a kappa opioid agonist, with the opioid mu antagonist samidorphan as adjunctive treatment in major depressive disorder was superior to placebo in two trials (phase 2: NCT01500200; phase 3: NCT02218008)[96], but not in three other phase 3 trials (NCT0 3188185, NCT02158546, NCT02158533) [96,97], without significant separation of buprenorphine alone from placebo in a meta-analysis[98].

Ezogabine, which induces the opening of neuronal voltage activated potassium channels, was superior to placebo on the MADRS in a phase 2 trial (NCT03043560)[99]. Botulinum toxin type A neurotoxin complex, an acetylcholine release inhibitor, was superior to placebo in a phase 2 trial (NCT0139 2963)[100]. The anaesthetic nitrous oxide was superior to placebo at 24 hours in a phase 2 study (NCT02139540), and at 2 hours, 24 hours, and 1 week in another phase 2 trial (NCT03283670)[101].

Psychedelics are also being investigated increasingly, with positive findings in phase 2 trials of Ayahuasca (5-HT2A partial agonism, affinity for multiple other 5-HT receptors, TAAR-1 agonism, sigma-1 agonism) (NCT02914769)[102] and psilocybin (5-HT2A agonism) (NCT03181529)[103]. Psilocybin was also found to be not inferior to escitalopram in a phase 2 trial (NCT03429075)[104].

The combination of metformin (glucose-lowering, insulin-sensitizing) and fluoxetine (selective serotonin reuptake inhibitor) was superior to placebo plus fluoxetine on the HAM-D in a phase 1/2 trial (NCT04088448) [105]. Finally, transdermal estradiol plus intermittent micronized progesterone (NCT01308 814) was more efficacious than placebo in preventing the development of clinically significant depressive symptoms among initially euthymic peri-menopausal and early post-menopausal women in a phase 2/3 study[106].

While a number of trials targeting multiple mechanisms of action are ongoing or have been completed without available results (see supplementary information), the currently most promising targets for major depressive disorder appear to be D3/D2 partial agonism with 5-HT2A/B antagonism, D2/5-HT2A/5-HT7 antagonism, 5-HT2A antagonism/inverse agonism, NMDA receptor antagonism and partial agonism, sigma-1 receptor agonism, nicotinic acetylcholine receptor antagonism, GABA-A receptor positive allosteric modulation, peroxisome proliferator-activated receptor gamma agonism, opening of neuronal voltage activated potassium channels, acetylcholine release inhibition, and 5-HT2A agonism.

Anxiety and trauma-related disorders

Agents in development for the treatment of anxiety and trauma-related disorders target directly or indirectly, among others, the cannabinoid, cholinergic, dopamine, GABA, glucocorticoid, glutamatergic, melatonin, noradrenaline, oxytocin, serotonin, and substance P systems (see Table 4 and supplementary information). Across 98 identified trials, only nine molecules that were tested in 31 trials outperformed placebo on primary outcomes in 18 trials (see Table 4).

In PTSD, intranasal oxytocin was more effective than placebo on amygdala connectivity in a phase 2 trial (EU2012-001288-58), and 3,4-methylenedioxy-methamphetamine (MDMA)-assisted psychotherapy (via release of serotonin and noradrenaline) was superior to placebo on characteristic symptoms in four phase 2 trials (NCT00090064, NCT01211405, NCT01793610, NCT00353 938) and one phase 3 trial (NCT03537 014)[107-114], although in one trial (NCT017936 10) the superiority was not observed in intent-to-treat analysis.

In panic disorder, d-cycloserine (NMDA co-agonist) as augmentation of exposure therapy outperformed placebo on neurocognitive processing in a phase 2 trial (NCT 01680107)[115]. In social anxiety disorder, one phase 2 trial showed that d-cycloserine as augmentation of cognitive behavioral therapy (CBT) outperformed placebo (NCT 02066792)[116-119], although two other studies were negative (NCT00633984, NCT00128 401)[120-122].

In generalized anxiety disorder, ABIO 08/01 (a selective inhibitor of GABA- and glutamate-gated chloride channels) outperformed placebo on CGI in a phase 3 trial (EU2006-003643-23). Agomelatine (melatonin receptor agonist) was superior to placebo on relapse rate in one phase 3 trial (EU2006-005674-47), and on anxiety symptoms in two phase 3 trials (EU2004-002577-23, EU2009-013789-17). Pregabalin (voltage-gated calcium channel modulator) was more efficacious than placebo on anxiety symptoms in two phase 3 trials (EU2006-006339-31, EU2004-001500-13). Quetiapine extended-release (histamine antagonist, alpha-2 antagonist, noradrenaline reuptake inhibitor) was superior to placebo in two phase 3 trials on anxiety symptoms (EU2005-005054-46) and relapse rate (EU2005-005055-18). Finally, SR58611A (selective beta-3 adrenoceptor agonist) reduced anxiety symptoms more than placebo in a phase 3 trial (NCT00266747), and vortioxetine (multimodal serotonergic modulator) prevented relapse in one phase 3 trial (EU2008-001673-15).

Table 4 Medications for anxiety and trauma-related disorders with positive results in phase 2 or 3 randomized controlled trials

Drug	Mechanisms of action	Control	Duration	Phase	NCT/EudraCT number	Status	Results
Post-traumatic stress disorder (PTSD)							
Intranasal oxytocin	Oxytocin receptor agonist	Placebo	12	2	NCT04523922	R	Results not available
Intranasal oxytocin		Placebo	10	2	NCT04228289	R	Results not available
Intranasal oxytocin		Placebo	6	2	EU2012-003072-39	R	Results not available
Intranasal oxytocin		Placebo	1 dose	2	EU2012-001288-58	C	Superior effect on amygdala connectivity
MDMA	5-HT, dopamine, noradrenaline releaser	Placebo	8	2	NCT00090064	C	Superior on PTSD symptoms and response
MDMA		Placebo	4	2	NCT01211405	C	Superior on PTSD symptoms
MDMA		Placebo	4	2	NCT01793610	C	Superior on PTSD symptoms per-protocol, not significant in intention-to-treat
MDMA		Placebo	3	2	NCT00353938	C	Superior on PTSD symptoms
MDMA		Placebo	18	3	NCT03537014	C	Superior on PTSD symptoms
MDMA		Placebo	18	3	NCT04077437	R	Results not available
Panic disorder							
D-cycloserine	NMDA receptor agonist	Placebo	1 dose	2	NCT 01680107	C	Superior effect on both threat bias and amygdala response
D-cycloserine		Placebo	NA	2	EU2010-021198-35	C	Results not available
D-cycloserine		Placebo	56	2	EU2011-001398-19	C	Results not available
Social anxiety disorder							
D-cycloserine	NMDA receptor agonist	Placebo	12	3	NCT02066792	C	Superior on anxiety symptoms
D-cycloserine		Placebo	13	3	NCT00633984	C	No difference
D-cycloserine		Placebo	12	2	NCT00515879	C	Results not available
D-cycloserine		Placebo	12	2	NCT00128401	C	No difference
Generalized anxiety disorder							
ABIO 08/01	Inhibition of GABA- and glutamate-gated chloride channels	Placebo	8	3	EU2006-003643-23	C	Superior on CGI
Agomelatine	Melatonin receptor agonist	Placebo	26	3	EU2006-005674-47	C	Superior on relapse rate
Agomelatine		Placebo	12	3	EU2004-002577-23	C	Superior on anxiety symptoms
Agomelatine		Citalopram	12	2	EU2012-003699-37	C	Not inferior on anxiety symptoms
Agomelatine		Placebo	12	3	EU2009-013789-17	C	Superior on anxiety symptoms
Pregabalin	Voltage-gated calcium channel inhibitor	Placebo	8	3	EU2006-006339-31	C	Superior on anxiety symptoms
Pregabalin		Placebo	8	3	EU2004-001500-13	C	Superior to placebo on anxiety symptoms
Quetiapine fumarate	Histamine, dopamine, 5-HT, noradrenaline multimodal agent	Placebo	8	3	EU2005-005054-46	C	Superior on anxiety symptoms
Quetiapine fumarate		Placebo	52	3	EU2005-005055-18	C	Superior on relapse rate
SR58611A	Noradrenergic agonist	Placebo	10	3	NCT00252343	C	Results not available
SR58611A		Placebo	8	3	NCT00266747 EU2005-003181-41	C	Superior on anxiety symptoms
Vortioxetine	5-HT multimodal agent	Placebo	24	3	EU2008-001673-15	C	Superior on relapse rate

NCT/EudraCT number – number in clinicaltrials.gov or clinicaltrialsregister.eu, R – recruiting, C – completed, NA – not available, MDMA – 3,4-methylenedioxy-methamphetamine, NMDA – N-methyl-D-aspartate, CGI – Clinical Global Impression. Results without information on statistical significance are classified among "results not available".

Notably, no promising treatment was identified for OCD.

While a number of trials targeting multiple mechanisms of action are ongoing or have been completed without available results (see supplementary information), the currently most promising targets for anxiety and trauma-related disorders appear to be serotonin release (MDMA) for PTSD, and glutamate agonism for panic and social anxiety disorder. For generalized anxiety disorder, several candidate mechanisms have been identified, including GABA- and glutamate-gated chloride channel inhibition, melatonin receptor agonism, voltage-gated calcium channel modulation, histamine antagonism, alpha-2 antagonism, noradrenaline reuptake inhibition, selective beta-3 adrenoceptor agonism, and multimodal serotoninergic modulation. This promise reflects the capacity of at least some of these mechanisms to impact extinction-related processes.

Substance use disorders

Agents in development for the treatment of substance use disorders target directly or indirectly, among others, the cannabinoid, cholinergic, dopamine, GABA, glucocorticoid, glutamatergic, histaminergic, inflammatory, insulin, ion channel, melatonin, neurokinin, noradrenaline, opioid, orexin, oxytocin, phosphodiesterase, peroxisome proliferator-activated receptor, serotonin, and vasopressin systems (see Table 5 and supplementary information). Across 185 identified trials, ten molecules that were tested in 17 trials outperformed the control condition on primary outcomes in 12 positive trials (see Table 5).

Many agents outperforming placebo in phase 2/3 clinical trials are repurposed medications already approved for another indication. For alcohol use disorder, these include baclofen (GABA agonist), with one positive phase 3 trial (NCT01711125)[123] on time to lapse and relapse and percentage of abstinent participants; gabapentin (voltage-gated calcium channel modulator) in one phase 2 trial (NCT02349477)[124] on "proportion with heavy drinking"; ibudilast (phosphodiesterase 4 inhibitor and toll-like receptor-4 antagonist, used in the treatment of asthma) in one phase 2 trial (NCT 03489850)[125] again on "proportion with heavy drinking"; and ketamine (NMDA antagonist) in one phase 2 trial (NCT0264931) [126] regarding days of abstinence.

For methamphetamine use disorder, agents with positive placebo-controlled phase 2 trials include mirtazapine (alpha-2-adrenergic, histamine-1, 5-HT2A/C and 5-HT3 antagonist) (NCT01888835)[127], and the combination of naltrexone (opioid antagonist) and extended-release bupropion (noradrenaline-dopamine reuptake inhibitor, nicotinic receptor antagonist, non-selective serotonin reuptake inhibitor and sigma-1 receptor agonist) (NCT03078075)[128], both on the number of substance-positive urine samples.

In amphetamine use disorder, sustained-release methylphenidate (noradrenaline and dopamine reuptake inhibitor) reduced the number of substance-positive urine samples vs. placebo among dependent individuals with comorbid attention-deficit/hyperactivity disorder in a phase 2 trial.

For cocaine use disorder, drugs outperforming controls include AFQ056 (metabotropic glutamate receptor antagonist) on the proportion of cocaine use days in a phase 2 trial (NCT03242928); ketamine (NMDA antagonist) on motivation to quit cocaine and on cue-induced craving in a phase 2 trial (NCT01790490)[129]; and zonisamide (voltage-sensitive sodium channel blocker and allosteric GABA receptor agonist) on Visual Analog Questionnaire in a phase 1/2 trial (NCT01137890),

For nicotine use disorder, the combination of zonisamide plus varenicline was superior on self-reported smoking and nicotine withdrawal, but not on biochemically verified smoking, in a phase 1/2 trial (NCT01685996)[130]. For opioid use disorder, positive findings are available for cortisol on craving in users with low, but not medium or high, daily heroin intake in a phase 2 trial (NCT01718964)[131].

While a number of trials targeting multiple mechanisms of action are ongoing or have been completed without available results (see supplementary information), the currently most promising targets for substance use disorders appear to be calcium channel modulation, GABA agonism, phosphodiesterase 4 inhibition, toll-like receptor 4 antagonism and glutamate antagonism for alcohol use disorder; opioid antagonism, multimodal adrenergic and serotonergic modulation, and noradrenaline/dopamine reuptake inhibition for amphetamine/methamphetamine use disorder; glutamate antagonism and sodium channel blockade for cocaine use disorder; sodium channel blockade for nicotine use disorder; and glucocorticoid receptor agonism for opioid use disorder. However, positive results have mainly involved medications already marketed for other disorders, while novel mechanisms of action have yielded much less positive results, despite strong ongoing efforts.

Dementia

Agents in development for the treatment of dementia-spectrum disorders target directly or indirectly, among others, the cholinergic, dopamine, GABA, glucocorticoid, glutamatergic, histaminergic, immunological, inflammatory, insulin, ion channel, neuroprotection, phosphodiesterase, peroxisome proliferator-activated receptor, serotonin, and sigma systems; and additionally include vaccines against beta-amyloid or tau protein, mesenchymal stem cells, and antibodies (see Table 6 and supplementary information). Across 265 identified trials, only 14 molecules that were tested in 27 trials outperformed placebo on primary outcomes in 15 trials (see Table 6).

Among trials targeting cognition or disease-modifying markers, positive phase 2 trials included those investigating acitretin (retinoid X receptor agonist) (NCT01078168), insulin glulisine (insulin signaling inhibitor) (NCT01436045), neflamapimod (MAP kinase inhibitor) (NCT04001517), ORM-12741 (selective antagonist of alpha-2C adrenoceptors) (NCT01324518)[132], sargramostim (granulocyte-macrophage colony-stimulating factor) (NCT01409915)[133], and rasagiline (monoamine oxidase-B inhibitor) (NCT02359552)[134].

Among trials aiming to improve behavioral and psychiatric symptoms in people with dementia, brexpiprazole, a dopamine partial agonist (NCT01862640, phase 3)[135]; dextromethorphan/quinidine, a sigma-1 agonist/NMDA antagonist/multimodal agent

Table 5 Medications for substance use disorders with positive results in phase 2 or 3 randomized controlled trials

Drug	Mechanisms of action	Control	Duration (weeks)	Phase	NCT/EudraCT number	Status	Results
Alcohol use disorder							
Baclofen	GABA agonist	Diazepam	1	3	NCT03293017	R	Results not available
Baclofen		Placebo	12	3	NCT01711125	C	Superior on time to lapse and relapse and percentage abstinent
Gabapentin	Voltage-gated calcium channel modulator	Placebo	24	2	NCT02349477	C	Superior on proportion with heavy drinking
Gabapentin		Placebo	9	2	NCT03205423	ANR	Results not available
Gabapentin XR		Placebo	25	2	NCT02252536	C	Results not available
Ibudilast	Phosphodiesterase 4 inhibitor and toll-like receptor-4 antagonist	Placebo	2	2	NCT03489850	C	Superior on proportion with heavy drinking
Ibudilast		Placebo	12	2	NCT03594435	R	Results not available
Ketamine	NMDA antagonist	Placebo	24	2	NCT02649231	C	Superior on days abstinent
Amphetamine/methamphetamine use disorder							
Mirtazapine	Alpha-2 adrenergic, histamine-1, 5-HT2A/C and 5-HT3 antagonist	Placebo	24	2	NCT01888835	C	Superior on substance-positive urine samples
Mirtazapine		Placebo	18	3	NCT02541526	NA	Results not available
Naltrexone + Bupropion ER	Opioid receptor antagonist + noradrenaline/dopamine reuptake inhibitor	Placebo	12	3	NCT03078075	C	Superior on substance-positive urine samples
Sustained-Release Methylphenidate	Noradrenaline/dopamine reuptake inhibitor	Placebo	24	2	EU2006-002249-35	C	Superior on substance-positive urine samples
Cocaine use disorder							
AFQ056	Metabotropic glutamate receptor antagonist	Placebo	14	2	NCT03242928	C	Superior (proportion of cocaine use days)
Ketamine	NMDA antagonist	Lorazepam	1 day	2	NCT01790490	C	Superior on motivation to quit cocaine and on cue-induced craving
Zonisamide	Voltage-gated sodium channel blockade, allosteric GABA receptor agonism	Placebo	5	1/2	NCT01137890	C	Superior on Visual Analog Questionnaire
Nicotine use disorder							
Zonisamide + Varenicline	Voltage-gated sodium channel blockade, allosteric GABA receptor agonism	Placebo	10	1/2	NCT01685996	C	Superior on self-reported smoking, nicotine withdrawal, but not on biochemically verified smoking
Opioid use disorder							
Cortisol	Glucocorticoid receptor agonist	Placebo	1	2	NCT01718964	C	Superior on craving in users with low daily heroin intake

NCT/EudraCT number – number in clinicaltrials.gov or clinicaltrialsregister.eu, R – recruiting, C – completed, ANR – active, not recruiting, NA – not available, NMDA – N-methyl-D-aspartate. Results without information on statistical significance are classified among "results not available".

(NCT01584440, phase 2)[136]; and the CB1/2 partial agonist nabilone (NCT02351882, phase 2/3)[137] each improved agitation. Additionally, AVP-786 (deuterated form of dextromethorphan/quinidine) improved agitation in one phase 3 trial (NCT02442765), but not in another one (NCT02442778)[138]. Furthermore, two orexin receptor 1 and 2 antagonists – lemborexant (NCT03001557, phase 2)[139] and suvorexant (NCT02750306, phase 3)[140] – improved restlessness and sleep, respectively.

AXS-05, the combination of dextromethorphan with low-dose bupropion – whose pharmacological actions are non-competitive NMDA receptor antagonism, sigma-1 receptor agonism, nicotinic acetylcholine receptor antagonism, and inhibition of serotonin, noradrenaline and dopamine transporters – was found superior to placebo on agitation in a phase 2/3 trial (NCT03226522)[141], with another trial ongoing (NCT04797715).

Pimavanserin, a 5-HT2A receptor antagonist/inverse agonist, with lesser activity as a 5-HT2C antagonist/inverse agonist, outperformed placebo for relapse of de-

Table 6 Medications for dementia with positive results in phase 2 or 3 randomized controlled trials

Drug	Mechanisms of action	Control	Duration (weeks)	Phase	NCT number	Status	Results
Acitretin	Retinoid X receptor agonist	Placebo	4	2	NCT01078168	C	Superior on cerebrospinal fluid soluble alpha-cleaved amyloid precursor protein concentration
Insulin glulisine	Insulin receptor agonist	Saline	0.14	2	NCT01436045	C	Superior on cognitive performance
Neflamapimod	MAP kinase inhibitor	Low dose	12	2	NCT02423122	C	Results not available
Neflamapimod		Low dose	12	2	NCT02423200	C	Results not available
Neflamapimod		Placebo	24	2	NCT03402659	C	Results not available
Neflamapimod		Placebo	13	2	NCT03435861	R	Results not available
Neflamapimod		Placebo	16	2	NCT04001517	C	Superior on neuropsychological symptoms
ORM-12741	Alpha-2C adrenoceptor antagonist	Placebo	12	2	NCT01324518	C	Superior on cognition
ORM-12741		Placebo	12	2	NCT02471196	C	Results not available
Rasagiline	MAO-B inhibitor	Placebo	24	2	NCT02359552	C	Superior on FDG-PET measures and quality of life
Sargramostim	Granulocyte-macrophage colony-stimulating factor	Placebo	20	2	NCT01409915	C	Superior on MMSE
Sargramostim		Saline	30	2	NCT04902703	NYR	Results not available
AVP-786	NMDA antagonist, sigma-1 receptor agonist	Placebo	12	3	NCT02442778	C	Not superior on agitation
AVP-786		Placebo	12	3	NCT02442765	C	Superior on agitation
AVP-786		Placebo	12	3	NCT03393520	O	Results not available
Dextromethorphan + Bupropion (AXS-05)	NMDA antagonist, sigma-1 agonist, nicotinic acetylcholine receptor antagonist, serotonin/ noradrenaline/dopamine reuptake inhibitor	Buproprion + Placebo	5	2/3	NCT03226522	C	Superior for agitation
Dextromethorphan + Bupropion (AXS-05)		Placebo	26	3	NCT04797715	O	No results available
Brexpiprazole	Dopamine partial agonist	Placebo	12	3	NCT01922258	C	No difference
Brexpiprazole		Placebo	12	3	NCT01862640	C	Superior in improving agitation
Dextromethorphan/ quinidine	NMDA antagonist, sigma-1 receptor agonist	Placebo	6	3	NCT03854019	R	Results not available
Dextromethorphan/ quinidine		Placebo	10	2	NCT01584440	C	Superior on aggression and agitation
Lemborexant	Orexin receptor antagonist	Placebo	4	2	NCT03001557	C	Superior on restlessness
Nabilone	Cannabinoid receptor partial agonist	Placebo	14	2/3	NCT02351882	C	Superior on agitation
Nabilone		Placebo	8	3	NCT04516057	R	Results not available
Pimavanserin	5-HT inverse agonist/ antagonist	Placebo	6	2	NCT02035553	C	Superior on psychotic symptoms
Pimavanserin		Placebo	26	3	NCT04797715	C	Superior on relapse of psychosis
Suvorexant	Orexin receptor antagonist	Placebo	4	3	NCT02750306	C	Superior on total sleep time

NCT number – number in clinicaltrials.gov, R – recruiting, C – completed, O – ongoing, NYR – not yet recruiting, NMDA – N-methyl-D-aspartate, MAO – monoamine oxidase, FDG-PET – 18F-fluorodeoxyglucose-positron emission tomography, MMSE – Mini Mental State Examination. Results without information on statistical significance are classified among "results not available".

mentia-related psychosis in one phase 2 (NCT02035553)[142,143] and one phase 3 trial (NCT03325556)[144].

While a number of trials targeting multiple mechanisms of action are ongoing or have been completed without available results (see supplementary information), the currently most promising targets for dementia appear to be retinoid X receptor antagonism, insulin signaling inhibition, MAP kinase inhibition, selective antagonism of alpha-2C adrenoceptors, and granulocyte-macrophage colony-stimulation. Dopamine partial agonism, sigma-1 agonism/NMDA antagonism, and CB1/2 partial agonism appear to be promising mechanisms to improve agitation, and orexin receptor inhibition to improve restlessness and sleep. For dementia-related psychosis, 5-HT2A inverse agonism/antagonism has shown promising results.

However, it is difficult to predict the most promising pharmacological targets for the treatment of the core features of dementia,

and in particular of Alzheimer's disease. Although a substantial proportion of ongoing trials test anti-amyloid and, more recently, anti-tau treatments, all phase 2 and 3 trials in this area have not shown statistical significance on their primary outcomes, except for one phase 3 trial, albeit only in sub-analyses, leading to the controversial approval of aducanumab[145]. Therefore, there is scant available evidence to suggest that the ongoing trials of anti-amyloid and anti-tau treatments will be successful. Anti-inflammatory, metabolic, neuroprotective and cholinergic targets are all viable, but have not been substantially researched.

TRENDS AIMED TO DE-RISK TRIAL PROGRAMMES OF NOVEL AGENTS

The previous overview of the currently active phase 2 and 3 clinical trials of new pharmacotherapies for the main mental disorders indicates that a large number of chemical entities and potentially useful mechanisms of action are undergoing testing. This large activity and investment are motivated and justified by the frequency and impact of the targeted mental health conditions.

However, many, if not most, of these programmes will not yield an approved medication that can be used in clinical care. Why is this so? What must we learn and consider and what can be done to minimize the failure rate? What follows is a critical discussion of the basic tenants, challenges, opportunities and potential solutions with regards to clinical trial methodology, conduct and interpretation. This analysis should help inform future psychopharmacological research with the aim to de-risk trial programmes of novel agents or of known agents for novel psychiatric indications, increasing their chances of success.

Validity and power of clinical trials

Over the past 70 years, psychopharmacology trials have evolved considerably[146]. The RCT has become the cornerstone of clinical research aimed at obtaining regulatory approval for pharmacological agents. It is meant to provide consumers (clinicians, policy makers, patients, families, other researchers) with an accurate assessment of the efficacy/effectiveness and safety of a treatment in a population of patients at risk for or with a disorder.

Since a misleading answer may cause harm, the prime consideration in RCTs is *validity*, i.e., minimizing the probability of a misleading endorsement of an ineffective or unsafe treatment. The usual criterion is that a treatment endorsement must be true "beyond reasonable doubt", with less than a 5% chance of being wrong. However, consumers also have a major stake in rapid identification of safe and effective treatments, as do researchers who conduct RCTs and their funders. Thus, *power* is also important, i.e., the probability of endorsement if the treatment is indeed effective and safe enough in that population to warrant clinical use.

The foundation on which every RCT is based is *a priori* exploration. This process includes a review of the research literature concerning the disorder or target symptom of interest, those liable to that disorder, treatments already available and their effectiveness and safety. It includes relevant results of studies on animals, pre-post or case-control studies on patients, and *post-hoc* exploration of previously performed relevant RCTs. Finally, pilot studies may be performed to assess the feasibility or viability of the strategies considered for the proposed RCT. Important information gleaned from pilot studies include target engagement (if a biological effect is hypothesized via specific mechanisms), patient selection and possibly patient enrichment for the studied mechanism or increase in treatment effect, optimal trial duration, treatment doses, need for dose titration, selection of assessments with maximum precision and sensitivity to change, and potentially required stratification of factors that may affect treatment efficacy or safety and that need to be balanced between treatment groups. The strongest the rationale for the RCT, the more de-risked the trial will be.

This sequential process is necessary for three reasons. First, it allows the formulation of the *a priori* hypothesis, i.e., the statement of what it is exactly hoped the RCT will prove (recorded in RCT registration), that, if true, would lead to regulatory drug approval and advance clinical decision-making. Second, it is unethical to randomize patients unless the RCT researchers are in "clinical equipoise", i.e., there must be a rationale and empirical justification for thinking that the hypothesis may be true and important, but also reasonable doubt as to whether it is true or not. Ethical issues stem primarily from a concern about putting the burden of participation on patients in an RCT with little hope of advancing clinical knowledge, either because the hypothesis is unlikely to be true or because it has already been shown to be true without reasonable doubt. Another reason for the clinical equipoise is methodological in nature. There are scores of decisions that researchers must make in the conduct of an RCT. If they already "know" the "right" answer, they are likely (consciously or unconsciously) to bias decisions in the direction of their "right" answer, increasing the risk of an invalid RCT. Third, the best choice for every one of those scores of decisions depends on what is known from *a priori* exploration. The more the information from careful exploration guides the RCT design, the greater the validity and power of that RCT.

Adaptive trial designs

Several aspects of the trial design can affect the chances of finding significant differences between active and control arm. Traditional non-adaptive trial designs that do not account for evidence generated by the initial stages of the trial, and apply a one-design-fits-all-trial-stages approach, miss the low hanging fruit of adapting randomization and analytic plans based on accruing data generated by the trial itself[147]. By contrast, trials should be "adaptive by design" rather than being characterized by *post-hoc* protocol deviations[147,148]. Early learning stage trials (e.g., minimally effective or toxicity dose) are typically necessary before confirmatory trials, that are instead needed for drug approval from regulatory agencies. The earlier trials need stronger control for type II error (false negatives), and less so for type I errors (false positive), which are instead crucial in phase 2 and 3 trials.

One aspect that can be adapted in terms of design is drug dose. Typically, drug dose is set *a priori*, and tested in different arms, with many patients exposed to drug doses that are not effective, and not necessarily safe. Being able to identify the optimal dose of a medication as soon as possible in an RCT is important, because it could minimize exposure to medication doses that are not effective and potentially not safe, reduce RCT duration, and decrease costs. The continual reassessment method is a Bayesian approach leveraging dose-response curves to identify the maximum tolerated dose (MTD), allowing to promptly set dose around MDT during early stages of trial. MTD design is frequently used in oncology and neurology (in particular in studies on stroke), but it can be adapted to needs of any field[149,150]. The need of identifying MTD, as opposed to *a priori* estimating it, has the additional benefit of avoiding expensive and frequently underpowered trials with multiple arms with different doses. However, there are additional challenges when dose-response-based adaptive designs are implemented in efficacy and approval-aiming trials, given that frequently a dose range, rather than a single dose, more appropriately meets real-world patients' needs.

A second aspect that can be adapted is randomization. While randomization accounts for allocation bias with large sample size, it does not warrant balance in arm assignment across different levels of variables that are potentially influencing safety or efficacy. Hence, potential unbalanced distribution of moderators/mediators of the outcome of interest can affect the whole trial success. To overcome this limitation, covariate adaptive randomization can be applied, which randomizes allocation within matched levels of putative prognostic factors[151,152]. Additional randomization adaptive designs exist, including response adaptive randomization design, or Bayesian adaptive randomization, which however are more prone to type I error[152,153].

One further potentially adaptive trial key element is the sample size[154]. Sample size needs to be as large as possible to warrant enough statistical power to avoid type II error, and has to account for attrition rates, but also has to consider associated costs and duration, which linearly increase with the number of people to be recruited. While there is a type I error risk when using treatment-arm information to recalculate sample size, a masked (or unmasked) internal pilot method that only uses first-stage nuisance parameters can be used in phase 2 and 3 trials.

A fourth trial aspect that can be adapted by design is narrowing population characteristics, to identify subgroups of patients likely benefitting from a treatment. While including selected participants based on specific and not necessarily frequent characteristics goes in the opposite direction of inclusivity and representativeness of trial population, this so-called "enrichment" design has great value in late learning stages, consistent with the concept of precision medicine. The main downfall of enrichment design is that it yields poorly generalizable findings, and there are also concerns about their replicability in real-world confirmatory pragmatic trials, with the risk of type I error[155]. Trials already tend to select partially representative samples[156], on whom then a "super selection" would be operated. Hence, enrichment trial designs tend to be restricted to pharmacogenetic studies[157].

However, enriched sample selection can also be useful for proof of concept and fast-fail trials whereby data are used to make a decision as to whether and how or in whom to continue the drug development process of a given molecule. Successful applications of this approach have included the testing of the TAAR-1 agonist ulotaront in patients ≤40 years old and with no more than two hospitalizations for an exacerbation of schizophrenia, i.e. patients with less dopamine system alterations due to prior treatment and/or the underlying illness (see the previous overview of clinical trials on schizophrenia).

It is unclear, however, to what degree effect size and sample size calculations need to be adjusted when expanding the population to be more inclusive and less enriched. *Post-hoc* analyses of a phase 2 placebo-controlled trial in Alzheimer's dementia-related psychosis (see the previous overview of clinical trials on dementia) found that response to pimavanserin was enhanced in patients with greater baseline psychosis scores[143]. On the other hand, for Parkinson's disease-related psychosis, response to pimavanserin was greater in patients with greater cognitive impairment[158]. Similarly, *post-hoc* analyses of phase 2 trials of BI 425809, a glycine transporter inhibitor under investigation for cognitive dysfunction in schizophrenia, indicated greater response to drug in patients receiving not more than one concurrent antipsychotic, with more negative symptoms and not receiving concurrent benzodiazepines, and with the 10 mg dose in females and in patients aged 38 years or younger, a schizophrenia illness duration of 5-10 years, and worse baseline cognition[68]. Such data create decision points as to whether a trial programme should always target the entire population with a given illness, where the effect size may be diluted, or whether it would not be safer and, ultimately, more cost-effective to obtain approval for a more restricted subsample with the greatest chance of success. If data indicate viability of the treatment for the entire or a more expanded patient sample, such trials could be performed afterwards.

Moreover, enrichment designs can base their randomization on previous response, as occurs in trials conducted in stabilized patients who are randomized to continuation of study drug or a switch to placebo. Duration and degree of stability and related placebo relapse rates are important considerations when designing such trials, as shorter durations and less complete remission increase the likelihood of relapse, particularly in the placebo arm. However, one also needs to guard against spurious relapses due to rebound and withdrawal phenomena upon rapid drug discontinuation[159], which naturally occur less readily the longer the half-life of a given medication is[160]. Furthermore, in bipolar disorder, illness polarity of the pre-stabilization illness phase is largely predictive of the polarity of the next episode[161], which needs to be considered when designing relapse prevention trials. Although such enrichment has been criticized as a limitation[162], it matches and informs clinical care where those patients are continued on maintenance therapy who have responded to and tolerate the medication.

In addition to the adaptive randomiza-

tion outlined above, an additional strategy for randomization of patients is having a lead-in phase with single-blind placebo, open-label medication or double-blind placebo, basing randomization on response during this lead-in phase. In the placebo run-in stage, patients are treated with placebo, and then only those not responding to placebo are randomized to either placebo or active treatment. This design has been implemented in augmentation studies of antidepressants with second-generation antipsychotics for patients with major depression and suboptimal response to antidepressants[163], in which those improving too much during the single-blind dose optimization phase were excluded from the randomization.

While a large number of trials adopted the single-blind placebo lead-in period as a form of full enrichment of the trial in placebo non-responders, this enrichment has failed to show benefits, as suggested by a meta-analysis of 101 antidepressant trials[164] and recently replicated in a meta-analysis of 347 antidepressant trials, of which 174 used a single-blind placebo run-in period[165]. Single-blind placebo and open-label medication lead-in phases are inferior to other enrichment study designs, such as sequential parallel design[166], and have longer duration and higher costs. Accounting for costs, sample size, and duration of trials, the sequential parallel design may to be more effective for phase 3 trials aiming to regulatory approval[166].

As we have seen in the previous overview of clinical trials on major depressive disorder, sequential parallel comparison is a study design that attempts to overcome limitations of placebo lead-in stages[167-171]. Trials are structured in two stages, and can be conducted with one randomization, if the trial has two arms, or two randomizations if three arms are used (one active, two placebo). Participants are first randomized to placebo (stage 1). Then, non-responders to placebo are re-randomized again to the two treatment options (stage 2), in case of two arms trials. If a three arms trial is conducted (one active arm, two placebo arms), placebo non-responders of both placebo arms are assigned to active treatment, or placebo. Data are analyzed from the first randomization, as well as from the second randomization[172], and they are pooled in the same analysis generating one p value. It has been estimated that with this design it is possible to keep the same level of power conducting trials with 20% to 50% fewer individuals[173].

Finally, "adaptive seamless designs" are trial designs that attempt to conduct one multi-phase trial, as opposed to multiple separate learning and confirmatory trials. This design can reduce the time from phase 1 to phase 3 trials aiming to regulatory approval, implementing continuous recruitment, with intense monitoring and data analysis that can inform adaptive dose, randomization, and sample size. However, there are concerns regarding the risk of type I error in this type of design[174].

Despite adaptive designs, trials often fail. The worst-case scenario, which is far from rare, is recruiting a quite large amount of participants, e.g. 500 patients, exposing them to experimental medications, with potential safety issues and important costs, but ultimately observing no significant differences between medication and placebo. Stopping for futility is an important design that can terminate trials prematurely as soon as there is evidence of no significant effect of the interventions versus the control[175]. Several methods have been proposed to *a priori* define optimal futility thresholds, that can be applied to different study designs, including sequential trials with one or more endpoints[176,177]. Stopping for futility trials based on issues with the drug, selected doses, target population or assessments, allows to terminate trials early that are bound to ultimately fail, protecting many patients from potential adverse events of experimental medications, and saving cost and time in case the failed trial informs an improved study design and/or trial conduct[178].

A recent study investigating the potential of adaptive design trials has been submitted to the European Medicines Agency (EMA). Out of 59 adaptive design trials, 30 actually started, 23 were concluded, nine had a significant treatment effect, and four led to a market authorization[175]. Importantly, only 18 trials actually implemented the adaptive elements, which might suggest challenges in implementation of these elements. On the other hand, of these 18 trials, 11 were concluded, and six had significant findings, which points to the potential of adaptive designs[175]. Most frequently adapted elements were dose selection, sample size re-assessment, and stopping for futility[175].

Placebo response and drug-placebo difference

While the ingredients driving placebo effect can be studied and have the potential to identify safe therapeutic elements that can be exported into clinical care[35], high placebo response is a plague that affects RCTs across different mental disorders[32,38,39]. In fact, it has been suggested that some major pharmaceutical companies have diminished their investment in developing medications for mental disorders because of the challenges in signal detection due to higher than expected placebo responses.

Many regulatory agencies (such as the FDA and the EMA) as well as researchers have taken the position that to assess the efficacy of a new treatment for many mental disorders is not possible without a placebo-controlled design. Needless to say, this guidance has had enormous impact on drug development. Consequently, every psychotropic medication that has been approved for the treatment of a mental disorder in either the US or Europe in the past 30 years has been assessed in placebo-controlled clinical trials.

This practice has been challenged by the increasing reluctance of clinicians[179] and patients[180,181] to participate in such studies. In addition, ethical committees in many countries are making it increasingly difficult to conduct placebo-controlled clinical trials. Of course, when these studies are allowed, risk minimization procedures must be in place. At the same time, studies in recent years have found large dropout rates in trials utilizing placebo controls[182], as well as a decrease of the placebo-drug difference[183-186], largely driven by increasing placebo effects without similar degrees of increased drug effects.

The placebo response has increased over a period of many years in conditions such as depression, while the drug response has not[187]. In an analysis that included 167 dou-

ble-blind RCTs with 28,102 (mainly chronic) participants, it was reported that, of the response predictors analyzed, 16 trial characteristics changed over the decades[188]. However, in a multivariable meta-regression, only industry sponsorship and increasing placebo response were significant moderators of effect sizes. Drug response remained stable over time.

The magnitude of placebo effect is larger in trials on depressive disorder, bipolar depression and mania, and smaller in trials on schizophrenia[38,39]. Nevertheless, placebo effect has been increasing not only in depression[38] but also in schizophrenia over the past 24 years[189], and is a major obstacle for developing novel medications[32]. Indeed, placebo response is particularly high in trials sponsored by the industry[38]. For example, analyses of schizophrenia trials indicated an increase in total psychopathology improvement over 45 years of 12.3 points for placebo, while the increase was of merely 1.2 points for antipsychotic agents[188]. Similarly concerning increases in placebo response in regulatory schizophrenia trials have been reported by the FDA, indicating that dropout rates also increased in parallel, with greater dropout rates in US-based studies[190].

Having a large placebo response fatally reduces the chances of finding significant differences with the experimental arm. In pharmacological clinical trials of depression, it has been shown that critical placebo response rates are 30% and 40% for monotherapy and augmentation, respectively[191]. Above these thresholds, chances of positive trials dramatically worsen[191].

Trial design, treatment, population and study conduct characteristics that are associated with placebo effects have been extensively studied, and several variables have been identified as being consistently associated with increased drug-placebo difference across different mental disorders. These factors should be considered carefully when designing trials aiming to increase the likelihood of success, i.e., separation from placebo. For example, an open-label lead-in phase before double-blind randomization increases placebo effect[38]. A second factor is poor recruitment with invalid baseline assessment and caseness ascertainment. On the other hand, more severe symptoms at baseline are associated with lower placebo response and greater drug-placebo difference in trials testing antidepressants for depressive disorders[192] as well as in schizophrenia trials, independent of year of the study[32]. However, when aiming for adequately high baseline symptom severity, one needs to consider artificial baseline symptom severity inflation due to wash-out or rebound phenomena, or to rater bias aiming to include patients above a certain minimum illness severity[189,193,194].

Greater improvement versus placebo in acutely exacerbated and more severe cases may be achieved more quickly, allowing for shorter trials to separate from placebo[195,196]. On the other hand, separation from placebo regarding negative symptoms, remission of symptoms or functional recovery may require longer trial designs. Therefore, the targeted outcome needs to be taken into consideration when setting symptom severity and trial duration parameters for trials.

Since some factors that increase the placebo response may also increase response to the experimental arm, ultimately having no net effect on the chances of a trial success, or may even increase drug response to a greater degree, it is most important to assess factors from the viewpoint of decreasing or increasing the drug-placebo difference. The largest evidence synthesis to date has shown that factors moderating larger drug-placebo differences in schizophrenia trials were smaller sample size, less study sites, less active study arms, more patients randomized to placebo, use of the Brief Psychiatric Rating Scale (BPRS) instead of the later introduced PANSS, longer wash-out period, longer study duration, shorter duration of illness, and younger age[188,197]. In multivariable meta-regression analyses, the only remaining predictors of greater drug-placebo difference included lower placebo response and non-industry sponsorship, which is associated with a lower likelihood of having trial design features that have been associated with greater placebo effects[197]. The fact that placebo response is inflated when randomizing more patients to the active arm and less to the placebo arm, as shown in depression[198] and schizophrenia[193], is probably due to expectations of improvement[172].

Population, recruitment

The results of every clinical trial apply to the population represented by the sample, not beyond. For instance, the results of an RCT conducted in patients with early-stage Alzheimer's disease do not necessarily apply to the prevention of that disease in at-risk individuals or those with minimal cognitive impairment, or to those at middle or late stages of the disease. For ethical reasons, one cannot include those unwilling to consent to participate, or patients who are likely to be harmed by participation. Otherwise, to which population the RCT researchers intend their conclusions to apply determines inclusion/exclusion criteria, clearly stated and consistently applied.

Moreover, the results of any RCT do not necessarily apply to every subgroup of the population sampled. If a treatment is shown highly effective in the population sampled, there may yet be a minority subgroup in which the treatment is ineffective or toxic. If an RCT detects little or no treatment versus control difference, the population may split into two subgroups, in one of which treatment is more effective and safe, while in the other control is more effective and safe, cancelling each other in the total population[200].

Patients included in trials for schizophrenia are usually not representative of the real-world population seen in everyday clinical practice. Moreover, trial and population characteristics have changed over time[188]. For instance, patients with schizophrenia that are typically eligible in trials have less physical comorbidities, less psychiatric comorbidities, and less suicidal behaviors[156]. Overall, only one patient out of five real-world patients with schizophrenia would be eligible to be recruited in a randomized controlled trial[156].

Such limited representativeness of phase 2 and 3, placebo-controlled trials in the field of schizophrenia applies also to other conditions, including mood disorders[201] and substance use disorders, due to similarly restricted inclusion criteria and also to the fact that patients need to be capable of giving informed consent. This limited representativeness puts emphasis on the importance of well-designed phase 4 studies that aim to test not if, but in whom and under which circumstances a medication

works. It would be helpful if certain regulatory minimal standards and requirements for phase 4 studies could be attached to approval of a new medication. While current post-approval requirements are generally restricted to additional indications (e.g., relapse prevention trials, pediatric trials) or safety assessments/risk mitigation measures, it would be desirable and welcome if a set of standards for phase 4 trials aiming at testing generalizability or utility in certain patient subgroups could be developed and applied.

Another relevant problem is inflation of symptoms at baseline. This can derive from several factors. First, symptoms do vary through the natural course of a disease, and can be reactive to stressful stimuli, such as routine disruption or anticipation of novel scenarios. Participating in a clinical trial can certainly come with stress, and so at the baseline assessment a person might show inflated symptoms, that can then regress to the mean once the trial environment and visits have become the new "normal". Another explanation can be the need of sites to recruit patients, that can produce, even not deliberately, higher symptoms ratings at baseline.

Several strategies can be implemented to optimize patient representativeness, and reduce symptom inflation at baseline. First, to reduce the risk of including "professional" trial participants, chronically unstable instead of acutely exacerbated patients, or those with unclear diagnosis and treatment history, it may be advisable to require medical records documenting at least the recent past in those not recruited from regular clinical care settings. Second, relaxing to some degree inclusion criteria, without increasing risk to study participants or the integrity of the study, by allowing participants with a certain set of physical or psychiatric comorbidities, would make recruitment easier, and the trial more pragmatic and clinically useful, potentially decrease placebo response, and allow greater adherence to equity, diversity and inclusion principles[202-205].

Retention is also part of recruitment, i.e., the continual "recruitment" of patients into staying in the study. Retention is crucial to minimize loss of data, that may actually be missing not at random, and to retain sufficient statistical power needed to test the hypothesis. Of note, exit strategies and lined trial phases may affect retention vs. dropout from the trial. For example, if exit strategies are too lenient or have too much appeal (e.g., open extension study with free treatment), more patients than necessary may drop out. If, on the other hand, exit strategies are too strict, patients may be kept in the study longer than they should. Thus, it is important to balance the desire for low dropout with need for patient safety by permitting more rescue strategies within the study that are transient and/or do not compromise the outcome. However, one may want to limit rewarding dropout and roll-over options into next/additional study phases.

Sites

Trials are typically conducted across multiple sites, to allow timely recruitment of sufficiently large samples. However, having a high number of sites does not come without downfalls. First, sites are frequently incentivized to recruit, and have pressure to recruit, which can lead to inclusion of inappropriate patients with regards to diagnosis, duration of exacerbation, or baseline severity. The more sites participate in a trial, the higher the heterogeneity, the higher the chance of poor quality of trial procedure compliance, including randomization, blinding and ratings, and the harder the quality control.

Dropping sites with poor recruitment early, as well those sites showing abnormal placebo response, can mitigate the impact of this heterogeneity. Second, sites should be certified, re-certified, and strictly monitored, with rater retraining being offered or raters being dropped in case of signs of inconsistent ratings. Third, since the number of sites moderates larger placebo response, having fewer highly efficient and high-quality sites as opposed to many poorly efficient sites is preferable. Moreover, in situations where multiple trials with multiple molecules are being conducted at similar times, competition over eligible patients can be a problem. In such situations, it is possible that patients required for trials with more restrictive criteria regarding illness duration or severity, comorbidities or comedications are steered preferentially toward those trials, so that some of such patients are removed from the other trials.

Lacking objective "laboratory" tests and biomarkers, we rely on the participant's subjective report, and on the training of assessors as well as their reliability with other assessors in the same trial. Given the number of sites often involved in such trials, how realistic is it to expect true inter-rater reliability to be established and maintained? Yet, inter-rater reliability contributes to statistical power.

Reliability training is almost always performed only on the ratings of interviews conducted by an expert with a model patient, thereby creating an ideal situation that allows for time-efficient rater training. The skill to elicit the information that is to be rated is left out, which can create serious issues with the actual elicitation of valid data. Thus, raters should also be trained and assessed in the elicitation, not only the rating procedures. Furthermore, as there can be rater drift over time, trainings need to be repeated throughout often long trial programmes.

Centralized raters were introduced with the goal of addressing these issues, by utilizing live, two-way videos to vastly reduce the number of required raters and enable ongoing calibration of reliability[206,207]. In addition, providing such external assessment and adjudication of patient eligibility is intended to help reduce misaligned incentives in determining patient eligibility and the phenomenon of baseline inflation[208]. Although such methods can provide advantages, there are limitations as well, including the lack of information gathered in a direct encounter.

The introduction of new technologies holds enormous promise for making such processes more reliable, continuous, applicable in the real world, and cost-effective. For example, language processing and speech analysis[209,210] and analyses of facial expression[211] could be very informative in conditions such as schizophrenia, mania and depression, or even in such domains as agitation and negative symptoms. At the same time, ecological momentary assessment can provide repeated sampling of subjects' current behaviors and experi-

ences in real time, in their natural environments[212,213]. Such a strategy can minimize recall bias and maximize ecological validity. The use of smartphones and wearable devices can provide objective information on geolocation, activity levels, frequency and timing of social interactions, sleep and other measures of interest to clinical trialists[214], including medication assumption[215,216].

The integration of digital phenotyping, as well as symptom efficacy and tolerability surveillance using passively collected data, have been underexploited in both the selection of adequate patients as well as the ongoing assessment of outcomes throughout clinical trials and drug discovery and development in psychiatry. These modern technologies provide unprecedented opportunities and need to be explored as supportive, key secondary, or even primary outcomes for regulatory approval trial programmes. Moreover, as patient-reported outcomes as well as functional endpoints gain traction, digital assessments are going to provide more continuous, reliable and real-world data that can be used to assess the value of a new treatment versus the appropriate control condition.

Assessment and outcomes

Raters should administer scales and measures that are clinically relevant, that are meaningful for the patient, that are not too time consuming, and that are broadly used in the field (also to allow evidence synthesis efforts). Special attention should be given to the time of the assessment, in particular – but not only – with cognitive symptoms, due to diurnal variation of the performance[217].

Assessment should be ideally repeated over time, to feed analyses with richer data. For example, to compare treatment vs. control on change in severity over eight weeks, one could measure only the endpoint, or the change in severity between baseline and the endpoint, or the slope of severity over the eight weeks, or one could dichotomize any of these possibilities, which would all be valid choices. Using the endpoint or pre-post change is generally not the best choice, as, with dropout, the endpoint is the time point most likely to be missing. Instead, the slope (say, over weeks 0, 1, 4, 8) is a better choice, since this is a linear combination of the repeated severity measures, which increases the reliability of the outcome measure (hence power). The availability of repeated measures over time also improves imputation, better protecting validity. However, requiring measures, say, daily over eight weeks, rather than only at four time points, may erase such advantages by encouraging dropout and missing data. A balance between the burden on patients and the needs of the research must always be considered and tailored to the research question at hand.

More than one outcome in a trial is desirable, as one outcome only can hardly provide a comprehensive clinical picture, yet adjusting for multiple comparisons in the statistical analyses is needed in case that more than one primary outcome is being assessed or in case that inferential statistical testing is desired even of key secondary outcomes. For secondary and exploratory, hypothesis-generating outcomes and those requiring a lot of multidimensional data, such as for functioning, modern tools including digital phenotyping and ecological momentary assessment can be of great value and should be progressively introduced in assessment of trials[218-228]. Digital phenotyping and ecological momentary assessments can be repeated multiple times, and can be even continuous in case of passive monitoring. To what degree interactive digital phenotyping may affect placebo response is still unclear, and whether a digital outcome parameter could become a primary outcome leading to approval of a medicine will need to be seen, but is not beyond the realms of feasibility and validity. Additionally, monitoring of physiologic parameters is a potential candidate tool to facilitate measurement of objective response, biomarkers of subgroups with better response, or target engagement.

Beyond secondary and exploratory outcomes that can be manifold but should be assessed with minimal patient time and burden, the most salient problem, however, is multiplicity for the primary outcome measures in an RCT. The goal of an RCT is to recommend *one* treatment over the other in the population sampled: *one* decision. Having multiple primary outcome measures that give conflicting answers undermines the purpose of the RCT. With one primary outcome, the chance of a false positive with usual approaches is less than 5%. With two independent primary outcomes, the chance of one or more false positives is 10%; with three it is 14%, ever increasing the chance of a misleading conclusion. If there is adjustment for multiple testing, using a significance level lower enough for each outcome, so that the overall chance of a false positive result is less than 5%, there is a loss of power, a greater risk of a failed RCT, and still, conflicting results on the multiple tests.

An RCT should have *one and only one* primary outcome measure, but that may be a composite measure. Ideally, with that measure presented for two patients in the population, clinicians should be able to unequivocally recognize which (if either) had the better clinical outcome. For example, the decrease of symptoms over treatment might be an acceptable outcome measure. However, if patients develop serious health problems due to treatment or control, that is not a sufficient primary outcome measure. Ideally, the appropriate outcome measure should reflect a benefit-to-harm balance. If there are several independent benefits and several independent harms of concern, the outcome of treatment is the cumulative effect on the patient of whatever the benefits and harms experienced[229]. Benefits and harms ideally should somehow be considered jointly, with the effect of treatment indicated by the total effect on the patient, not the separate effects on multiple outcome measures[230]. By the same token, if symptom severity is measured weekly over, say, eight weeks of treatment, the impact of treatment should not be separately assessed at each week, but some composite measure (e.g., the trend of the severity over time) should be used.

Finally, dichotomization of an ordinal outcome is always a poor choice. For example, if "success" were defined by a ≥50% decrease in symptoms over the eight weeks, a patient with a 51% decrease in symptoms has the identical outcome to another with a 100% decrease, while a patient with a 49% decrease is considered the same as one with 0% decrease or an increase. Moreover,

two patients, one with 49% and one with 51% decrease, are considered as different from each other as one with 0% and another with 100% decrease. Consequently, there is a significant risk for misclassification and a major loss of power with dichotomization[231]; sample sizes may have to be doubled or tripled to have the same power as that from using the ordinal or continuous outcome. To make matters worse, different choices of cut-point may change the conclusions. The "costs of dichotomization" have long been recognized[232], but are often ignored. However, it is possible to turn a dichotomized outcome, such as response or relapse, into a scaled outcome, by estimating the time to an event. Although this approach increases the statistical power, nevertheless, the decision about the specific definition and cut-points involved in the definition of the categorical outcome remain.

Statistical analyses

The success of a trial, and approval of a medication to treat a given disease, also largely depend on the results of the statistical analyses. These analyses, if wrong, even in presence of a sound design, can jeopardize a large amount of work and investments. Hence, adopting appropriate statistical approaches that minimize type I and II error chances is paramount.

One of the aspects in statistical analyses is how they are adjusted for multiple testing. One commonly used method is the most conservative Bonferroni correction, that divides the alpha=0.05 by the number of statistical tests. However, a number of related and different methods exist that should be considered[233]. Such methods also include hierarchical testing in case multiple secondary outcomes are subjected to inferential statistics, whereby outcomes are ordered based on importance or likelihood of success and then each tested at $p<0.05$, stopping all further testing once the next *a priori* selected outcome does not reach that statistical threshold.

Another important aspect in statistical analyses is how covariates are handled. Baseline factors that identify subgroups in which treatment effects are different are "moderators of treatment outcome" in that population[234]. What the results of an RCT demonstrate is what would happen if everyone in the population sampled were given treatment rather than control. If there are moderators known *a priori*, that affects sampling decisions. For example, if it is already known from previous research that a treatment is effective only for women and not for men, further research on that treatment would focus on women. If there is only suggestive evidence that sex might moderate treatment outcome, the RCT might be stratified by sex, with adequate representation of males and females, to test the *a priori* hypothesis that sex moderates treatment outcome and to estimate separate effect sizes for women and for men.

Some researchers would throw sex in as a covariate in a linear model "just in case". If sex is irrelevant to the outcome, the treatment effect tested and estimated is exactly the same one as when the covariate is not included, but with a loss of power and precision. Conversely, if sex moderates treatment outcome, and the interaction term is omitted (as it often is), the effect size tested and estimated is uninterpretable. Only if it is known *a priori* that the treatment vs. control effect is the same for males and females, is the treatment effect size meaningful, representing the common effect size for males and females in that population.

The situation worsens when there are multiple covariates entered into a linear model "just in case", that are correlated with each other (collinear), and the interactions of each covariate with the treatment or with each other are incorrectly assumed to be zero, or it is incorrectly assumed that each has a linear effect on the outcome. If any of these assumptions is wrong, the RCT validity and power will be compromised. Yet, many published RCTs enter multiple covariates into their models without a rationale or justification, under a misapprehension that "controlling for" factors by adding in covariates "just in case" improves RCT results. Instead, each covariate to be used in a RCT analysis should be explicitly mentioned in the *a priori* hypothesis and registration, and the rationale and justification for each should be presented in both the proposal and the resulting paper. How covariates are to be included must be specified and justified in the analysis plan, and the sample size increased to accommodate the consequent loss of power.

Another important aspect of statistical analyses is imputation. Imputation is needed to conduct intention-to-treat or modified intent-to-treat analyses where patients are included who have treatment exposure and at least one post-baseline assessment. Intention-to-treat analyses are more representative of the overall efficacy/acceptability ratio of an experimental treatment, as opposed to "completer" analyses that are conducted on selected "ideal" patients who likely benefitted the most from that medication. In fact, completer analyses violate the randomization principle and are to be avoided.

Various imputation methods exist to handle missing data. The simplest method is last-observation-carried-forward. However, this method assumes no further change after dropout and disadvantages the group in which there is earlier and more discontinuation in terms of efficacy, but also reduces the time for cumulative adverse effects in that study arm. A now frequently used alternative is the mixed model for repeated measures (MMRM), a popular choice for randomized trials with longitudinal continuous outcomes. In MMRM analyses, the results from patients staying in the study longer are used to model the estimated change after study discontinuation based on trajectories of patients with similar initial symptom change. However, as patients completing trials on placebo may be systematically different from those who do not, especially if they drop out for inefficacy, MMRM models may overestimate placebo effects, which may be another reason for increasing placebo effects in more recent years, when MMRM analyses have become the standard data method in RCTs.

Another potentially important issue is whether the assumption that data are missing at random, which underlie all standard data analytic techniques, is true. Given that efficacy and tolerability differences between study arms may significantly affect missingness of data, especially in longer-term studies with higher dropout rates, non-random missingness can significantly affect the results. Thus, it is important to check if data are in fact missing at ran-

dom and to employ different data analytic techniques if this assumption is violated, such as selection models or pattern mixture models[235-237], which is rarely done, but which can affect the results and interpretation of the study.

DISCUSSION

Clinical trials are the cornerstone of current evidence-based medicine. The field has evolved, and increasingly complex as well as simplified clinical trial designs have been developed. Designs range from effectiveness trials with maximized internal validity but limited external generalizability, to large simple trials that maximize external validity but have reduced precision. In the case of non-randomized trials, large nationwide database studies can aid hypothesis generation, but are insufficient to allow making causal inferences. Data analytics have equally evolved and are now very sophisticated, and it has become increasingly important to choose the most appropriate statistical analysis plan for a given trial design, research question and attempt at minimizing type I and/or type II error.

In drug development and for regulatory approval purposes, randomized, placebo-controlled, parallel-design trials are the main vehicle. They include placebo-controlled trials for the approval of acute treatments as well as placebo substitution trials for the approval of maintenance interventions. Increasingly, an active control (not comparison) arm is included in order to test the integrity of the study, which enables to distinguish between negative trials (the established medication does separate from placebo, while the experimental drug does not) from failed trials (neither the experimental nor the established medication separate from placebo). Moreover, comparison with an established "common comparator", either as part of the placebo-controlled phase 3 trial programme or of phase 4 studies, will gain traction to go beyond common symptom and adverse effect outcomes to include also quality of life and/or functional endpoints, on which the new medication can demonstrate statistically and clinically relevant advantages. Indeed, patient-reported subjective well-being and quality of life, caregiver/observer reports and functional outcomes, which may be captured more objectively and comprehensively in the living world environment via digital assessments, have become increasingly relevant.

However, in mental health, novel psychopharmacological mechanisms of action that effectively and safely treat common and often severely impairing mental disorders have remained extremely scarce, and many initially promising trial programmes ultimately failed. Clinical trials in psychiatric disorders have been challenged by issues around recruitment of a sufficiently large and representative sample of patients, within a reasonable amount of time, fulfilling strict inclusion criteria to answer a given question. However, sample sizes have increased, especially in phase 3 trials, due to a disproportionate increase in placebo response with relatively little increase in drug response over the past few decades.

When targeting outcomes beyond symptoms, including quality of life and functionality in multiple relevant domains – self-care, social interactions, leisure time activities, and educational/work performance – medications mostly "only" prepare the brains of people with mental disorders to have the potential to function better, without putting their increased or restituted "capacity" into action. In order to translate the improved symptomatic status into action and also improve measurable "performance", designs that combine drugs with psychosocial interventions may need to be considered more, especially when targeting complex cognitive, behavioral and functional outcomes. As a matter of fact, when seeking approval for the pharmacological treatment of cognition in schizophrenia, a functional co-primary outcome is required demonstrating that the statistically significantly improvement in cognitive performance has real-world impact on behavior and functioning.

The rapid evolution of widely available and scalable digital technology holds enormous promise to enhance the precision and granularity as well as the temporal coverage of the assessment of symptoms and behavior in people before and during treatment with a tested pharmacological entity or its control. Such digital phenotyping can be helpful to measure symptoms more comprehensively and with more precision and ecological validity, including their variability over time and in relationship to internal and external contexts. Moreover, digital tools can provide more reliably and objectively assessments of cognitive, academic, behavioral and social functioning. Inasmuch as passive instead of interactive digital monitoring in applied, concerns about increased placebo effects via digital engagement should be mitigated.

The overview of ongoing phase 2 and 3 trials that we present in this paper has some limitations. First, although we attempted to be inclusive in the identification of pharmacological agents with novel mechanisms of action, or already known agents targeting a currently unapproved mental condition, we may have missed some agents. The exclusion of eligible agents may have been due to our restricting the search to the US and European clinical trials registers, so that agents and trial programmes not registered yet may have been missed. Moreover, there may be trial programmes and agents in other than the US and European trial registries that we did not survey. Additionally, some agents that might have been approved for another condition or age group may have been classified as phase 4 trials and missed. Furthermore, as the field of psychopharmacology is a highly dynamic and evolving one, new agents and targets may have been identified since our last search date. Second, we may have listed drugs and targets that have since been dropped and trial programmes that have been discontinued. However, as clinical trial registries are updated on a voluntary basis, this information may have been actually not available. On-time updating of the records by sponsors would be desirable. Third, although we attempted to classify the mechanisms of action of emerging and newly tested psychopharmacological agents, for some of them insufficient information was available, so that they may not have been classifiable or may even be (partially) incorrectly classified. Hence, as further information about the specific mechanisms of action of individual pharmacological treatments emerge, our classifications may need to be updated or corrected.

In conclusion, the development and approval process for new pharmacological

agents that target medical conditions is complex, and this complexity and the related perils of failure may be even enhanced when targeting mental disorders. The information contained in this paper aims to provide practical knowledge on issues related to clinical trial methodology and implementation that need to be considered and weighed, with their relative pros and cons, serving as a roadmap that targets successful approval of new agents for the treatment of mental disorders.

Additionally, in taking stock of the current drug development targets and related mechanisms of action aimed at the treatment of the main mental disorders in adults, we aimed to provide an overview of the most promising molecules that the field should observe, learn from and, possibly, pursue further, should specific agents under development successfully progress through their phase 2 and 3 programs and, ultimately, lead to regulatory approval.

It is hoped that, in ten years from now, multiple new drug targets will become available, ideally for each of the reviewed main mental disorders, allowing clinicians to improve outcomes of many patients who are currently still only sub-optimally managed with the currently available agents, so that not only impact on symptoms and tolerability are increased, but also subjective well-being, quality of life and social functioning can be improved more and in sustainable ways.

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