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Review
Ανασκόπηση

Pharmacological agents under research for the maintenance treatment in bipolar disorder

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The treatment of bipolar disorder is a current challenge for clinicians and despite progress in psychopharmacology, options remain limited and results are often unsatisfactory. Current research focuses on finding new pharmaceutical agents for all phases of bipolar disorder, i.e. mania, bipolar depression and maintenance. Particularly, relapse prevention and long-term stabilization is a major therapeutic target. Combination treatment and polypharmacy are the most common choices concerning relapse prevention. Furthermore, during maintenance phase patients often experience residual mood symptoms, cognitive deficits and functional decline, which altogether illustrate the inadequate effectiveness of existing treatments and the need for new, targeted, effective and safe treatments for bipolar disorder. This review focuses on active agents for maintenance treatment in bipolar disorder investigated during the last 5 years. The compounds under investigation have been tried or tested either as monotherapy or as an add-on treatment in clinical trials that have progressed up to phase 3 or in preclinical models of bipolar disorder. While awaiting the completion of many ongoing studies, the results so far indicate that paliperidone and pregabalin may have a position in the maintenance treatment of bipolar disorder. Additionally, dextromethorphan, which acts primarily as a NMDA antagonist, may be an interesting compound for further study. However, results on memantine, another NMDA antagonist, were not encouraging. The effects of omega-3 fatty acids and cytidine were not superior to placebo, although they both have neurotrophic and neuroprotective properties. Eslicarbazepine, which has antiepileptic action, provided some evidence of efficacy as monotherapy. Regarding preclinical studies in experimental models, the pharmacological agents under investigation seem to follow the neurobiological pathways related to mechanism of action of lithium, which is still the "golden standard" for preventing recurrence in bipolar disorder. Major therapeutic targets are synthetic glucose kinase 3 (GSK-3) and the path of phosphoinositol (IMP), both probably involved in the action of lithium. Furthermore, the

role of circadian rhythms maintenance is being studied in preclinical and clinical trials investigating the efficacy and safety of compounds CK-01 and ramelteon, respectively. Research also focuses on pharmacological agents based on epigenetic changes and gene expression modulation, as the inhibitor of histone deacetylase (HDAC). Of note, the development of valid and reliable experimental models for bipolar disorder, which currently remains quite controversial, will contribute to the understanding of the pathogenic mechanisms and the development of new effective treatments. Improving methodology aspects of clinical trials, such as diagnosis, clinical heterogeneity, monitoring time, gender differences and comorbidities, may promote research. Current studies seem promising for the development of novel pharmacological agents in the near future, although there are methodological limitations in the search for the maintenance treatment in bipolar disorder. New therapeutic targets include not only the already known mechanisms of action, but also novel pathophysiological pathways, probably implicated in bipolar disorder.

Key words: Bipolar disorder, maintenance treatment, novel therapeutic targets, new pharmaceutical agents.

Introduction

Bipolar disorder (BD) is a chronic disease with potentially serious negative impact on patients' functioning and characterized by recurrent episodes of mania or hypomania (BD I and II type respectively) and depression. Difficulties and clinical embarrassment regarding its treatment arise from the very nature of the disease –chronic and recurrent– and other clinical characteristics, such as heterogeneity and frequent comorbidity with other mental disorders (personality disorders, substance abuse, anxiety disorders).[1]

BD treatment is a challenge for modern clinician and despite progress in psychopharmacology, options remain limited and results are often unsatisfactory. Current research focuses on finding new pharmaceutical agents for all phases of BD, i.e., antimanic, antidepressive and maintenance treatment. Especially, relapse prevention and long-term stability is a major therapeutic goal as in many cases the disorder is resistant to all first line mood-stabilizing drugs available. Augmentation strategies and polypharmacy are the most common choices for relapse prevention,[2] although it is postulated that polypharmacy does not significantly improve prognosis concerning symptom chronicity and functional impairment.[3] Moreover, patients under maintenance therapy that do not exhibit mood episode, often suffer from residual mood symptoms,[4] cognitive decline[5] and poor psychosocial functioning.[6] All the above mentioned problems concerning BD treatment demonstrate the insufficient effectiveness of existing treatments –at least for a large proportion of patients– and the need for new, targeted, effective and safe treatments that will enrich the pharmaceutical armamentarium for the complete remission of symptoms and better stabilization of BD patients. This review studied all pharmaceutical agents that have been tested, both in a clinical and a preclinical level, as potential effective maintenance treatment options.

Material and method

This review focuses on new pharmacological agents tested as BD maintenance treatment, from experimental models until phase 3 clinical trials during the last 5 years, i.e. from 2010 till April 2015. The identification of preclinical and clinical studies was conducted using databases of NIH (National Institutes of Health; http://www.clinicaltrials.gov/), EMA (European Medicines Agency; https://www.clinicaltrialsregister.eu/ctr-search/search) and WHO (World Health Organization International Clinical Registry Platform; http://apps.who.int/trialsearch). Moreover, articles from PubMed and PLOS ONE were taken into account in order to identify relevant preclinical studies and open trials. Concerning selection

criteria, compounds or pharmacological agents tested in children, adolescents or the elderly (>65 years) with BD were excluded from our study. Likewise, studies that focused exclusively on the treatment of bipolar depression, manic episode or cognitive deficits or comorbidity in BD patients, were not included. Active compounds that had progressed to phase 4 were not included in this review. The clinical trials included in this review were either completed or ongoing or were recently (from 2014 onwards) terminated for financial reasons, though they might seem promising. Pharmacological agents were further determined based on the current study phase, the type of expected therapeutic approach (monotherapy or adjunctive treatment), their mechanism of action and existing results. Regarding preclinical trials, given the lack of reliable experimental animal model for BD, only those who reported efficacy in both models of mania and depression were included in this review.

Clinical trials for maintenance treatment in BD

Our search revealed 9 completed studies (with or without announced results) and 9 ongoing studies for a total of 15 pharmacological agents tested from phase 1 to 3.

Completed studies

Seven out of 9 completed studies had reported results, 3 with favorable clinical efficacy and one with positive results for tolerability and safety, one with some evidence for efficacy, 2 did not show any significant effect, while for the remaining 2 results had not been announced at the time of writing this report (table 1).

Dextromethorphan

Dextromethorphan is widely used as a cough suppressant, but has been reported to have neuroprotective effects on dopaminergic neurons and anti-inflammation properties associated with neuronal degeneration in both experimental models and clinical trials.[7,8] In addition, as it shares pharmacodynamic properties similar to ketamine,[9] mainly as a NMDA-receptor antagonist and σ1 and σ2 opioid-receptor agonist, its possible use as antidepressant is under investigation.[9] In a recent phase 3 trial, dextromethorphan was studied for 12 weeks as an adjunctive treatment (30 mg and 60 mg) to 309 BD patients who had been receiving valproate, while 123 healthy subjects were used as controls (receiving valproate and placebo).[10] The study showed good efficacy for those taking dextromethorphan as an add-on treatment in terms of measuring YMRS (Young Mania Rating Scale) and HDRS (Hamilton Depression Rating Scale).[10] This finding encourages further research into the potential therapeutic role of dextromethorphan in maintenance treatment of BD.

Pregabalin

The use of pregabalin as an antiepileptic drug and in the treatment of generalized anxiety disorder and neuropathic pain is known. Pregabalin's chemical structure is considered to be analogous to GABA and binds with the a-2δ subunit of the voltage-dependent calcium channel. The possible use of pregabalin as an add-on treatment was addressed in an open label study[11] in 58 refractory BD patients. In 41% of patients (acute responders) that were administered an average dose of 72±69 mg/d, significant improvement was noticed in CGI scale (Clinical Global Impression) after two months. In these patients pregabalin demonstrated either antidepressant (29%), or antimanic (21%) or stabilizing properties (50%), while 42% continued to receive it after 3 years.[11] These results indicate that pregabalin might have a role in maintenance therapy.

Paliperidone

Paliperidone belongs to the class of atypical antipsychotics, acting primarily as a dopamine and serotonin receptor antagonist, indicated for the treatment of schizophrenia and schizoaffective disorder. In one study,[12] bipolar patients (n=152), who had recently achieved remission taking paliperidone ER (extended release), were compared to patients treated with placebo after the recession (n=148) in the maintenance phase. The results of this study at 41 months follow-up assessment con-

Table 1. Completed studies of pharmacological agents under research for maintenance treatment in bipolar disorder.

Pharmacological agent/Compound	Study identifier	Phase	Treatment as	Main mechanism of action	Results
Dextromethorphan	NCT01188265	Phase 3	Add-on	Antagonism of NMDA receptors, agonism of σ1 and σ2 opioid receptors	Significant improvement compared to placebo in YMRS and HDRS
Pregabalin	Open Label	Phase 2	Add-on	Binds to the a-2-delta subunit of voltage-dependent calcium channel	Improvement in CGI-BP scale
Paliperidone	NCT00490971	Phase 3	Monotherapy	Antagonism of dopamine and serotonin receptors	Significant improvement compared to placebo for prevention of manic but not depressive episodes
Eslicarbazepine	NCT01825837	Phase 2	Monotherapy	Blockade of voltage-gated sodium channels	No significant differences in CGI-BP or relapse prevention. Evidence of efficacy in stabilizing after manic episode
Memantine	NCT01188148	Phase 2–3	Add-on	Antagonism of NMDA receptors	No significant differences compared to placebo in YMRS and HDRS
Cytidine and omega 3 fatty acids	NCT00854737	Phase 2	Add-on	Neurotrophic/ neuroprotective action	Not superior to placebo
Cariprazine	NCT01059539	Phase 3	Monotherapy	Partial agonism of D2, D3 receptors	Efficacy in safety and tolerability
Taurine	NCT00217165	Phase 2	Add-on	Antioxidant activity, cell membrane stabilization, calcium signalling modulation	No results available
Antibodies to digoxin	NCT00550576	Phase 2	Add-on	Action against endogenous digitalis-like compounds	No results available

CGI-BP: Clinical Global Impression – Bipolar Version; YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale

cerning relapse for any major mood episode (depressive or manic) showed that the average time to relapse in subjects who received paliperidone was 558 days compared to 283 days for those receiving placebo. However, this finding was statistically significant regarding the prevention of manic but not depressive episodes.[12]

Eslicarbazepine

Eslicarbazepine, chemically similar to oxcarbazepine, is used in the treatment of partial seizures by blocking voltage-gated sodium channels. Its possible role as a mood stabilizer was recently examined in a phase 2 study in 85 BD patients who had

recently achieved remission after manic episode. Patients were randomized into three groups receiving eslicarbazepine as monotherapy at doses of 300 mg, 900 mg and 1800 mg respectively, and were assessed for six months. The results of this study did not show statistically significant efficacy for any of the three groups in terms of clinical improvement (as measured by the Clinical Global impression scale) or relapse prevention (as measured by the number of subjects who developed manic or depressive episode). However, secondary efficacy measurements showed that eslicarbazepine in a dosage of 300 mg to 900 mg was significantly more effective than placebo in achieving normothymia after manic episode. Eslicarbazepine was also found generally safe and well tolerated.[13]

Memantine

Memantine is indicated for the treatment of moderate to severe Alzheimer's disease, by acting as an NMDA-receptor antagonist. Although there is some data indicating a possible synergic role of memantine as mood stabilizer, possibly in the context of neuroprotection/neurogenesis,[14] as both antidepressant[15] and antimanic[16] agent, there has been no strong evidence in favor of these hypothetically therapeutic actions. In a 12 week, phase 2–3, double-blind study, memantine was compared to placebo as an add-on treatment in patients taking valproate without any significant difference in terms of efficacy.[17] However, studies of memantine continue to be conducted with the expectation of more favorable results.[18]

Cytidine and omega 3 fatty acids

Cytidine and omega 3 fatty acids as natural dietary supplements have neurotrophic and neuroprotective action. Their role in BD is not clear, with ambiguous evidence concerning efficacy.[19–21] In a four month, double-blind study, groups of BD patients receiving as an add-on treatment: (a) omega 3 fatty acids and (b) omega 3 fatty acids and cytidine were compared with a group receiving placebo in terms of relapse prevention. Among the compared groups no difference was noticed either in preventing relapse or improving symptoms as measured by scales of mania and depression.[22]

Cariprazine

Cariprazine is a new atypical antipsychotic with a novel pharmacological profile, acting as a D2, D3 receptor partial agonist. Studies have shown good tolerability and safety but also effectiveness in the treatment of manic, mixed episode,[23,24] while there are positive indications for bipolar depression.[25] A two week, phase 3 study in 402 BD patients was conducted in terms of examining safety and tolerance. This study showed promising results for its administration in longer term, as main side effect was akathisia (32.6%), but this resulted in discontinuation in only 4.7% of people who presented it.[26]

Taurine

Taurine is an amino-acid found in the human brain, showing antioxidant activity with a possible role in cell membrane stabilization and calcium signaling modulation. It potentially presents antidepressant activity, as shown by testing in experimental models,[27] and antiepileptic properties.[28] Its possible place in BD maintenance treatment is investigated in a phase 2 trial, but no results have yet been reported.

Specific digoxin antibodies (FAB)

As endogenous digitalis-like central nervous system compounds are involved in the pathogenesis of mood disorders,[29] a phase 2 trial has examined the safety and efficacy profile of specific digoxin antibodies (FAB) in BD patients, without any announced outcome measures as yet.

Ongoing clinical trials for maintenance treatment in BD

Our search revealed 9 clinical ongoing trials, recruiting or active (not recruiting - analysis phase) investigating 6 pharmacological agents (table 2) that had not announced results at the time of writing this report.

Inositol Hexaphosphate (IP6)

IP6 is involved in the intracellular system of second messenger phosphatidylinositol, with potential antidepressant role in bipolar depression, as small studies indicate.[30] In an ongoing phase 1 trial, IP6 will be

Table 2. Ongoing clinical trials for maintenance treatment in bipolar disorder.

Pharmacological agent/Compound	Study identifier	Phase	Treatment as	Main mechanism of action	Results (to be announced)
Inositol Hexaphosphate (IP6)	NCT02081287	Phase 1	Add-on	Neuroprotective action	November 2015
ELND005 (Scyllo-Inositol)	NCT01674010	Phase 2	Add-on	Blockade of Amyloid-beta (Aβ) development	Recently terminated
Ramelteon	NCT01467713	Phase 3	Add-on	Agonist of MT1 and MT2 receptors	Recently terminated
Lurasidone	NCT01358357 NCT01575561 NCT01986114	Phase 3	Add-on Monotherapy	Antagonism of dopamine, serotonin and noradrenalin receptors	April 2015 July 2015 September 2017
Asenapine	NCT01396291	Phase 3	Monotherapy	Antagonism of D2, 5-HT_2A receptors	June 2015
Aripiprazole	NCT01567527 NCT01710709	Phase 3	Monotherapy	Partial agonist of D2, 5-HT_2A receptors	April 2017 February 2016

studied for safety and effectiveness as an adjunctive treatment to lithium and will be compared with lamotrigine regarding their antidepressant and stabilizing properties.

ELND005 (Scyllo - Inositol)

ELND005 is an experimental compound for Alzheimer's disease treatment as it appears to act as an amyloid-β aggregation inhibitor. A double-blind phase 2 clinical trial for ELND005 as an add-on treatment in BD maintenance therapy was recently stopped by the sponsoring company for financial reasons.

Ramelteon

Ramelteon binds to melatonergic receptors MT1 and MT2 and beyond its use as hypnotic, it can play a role in the regulation of circadian rhythms, whose maintenance is particularly important for preventing recurrence of BD episodes. While a phase 4 study announced efficacy of ramelteon as maintenance therapy,[31] a phase 3 trial for its sublingual form, aiming at alternative ways of administration, was recently suspended due to financial reasons.

Lurasidone

Lurasidone is a new atypical antipsychotic that has been approved for the treatment of bipolar depression, either as monotherapy or as an add-on treatment.[32] Regarding relapse prevention, lurasidone is studied in three phase 3 trials (table 2), a double blind, one open-label as an add-on treatment and one open-label as monotherapy for 28, 12 and 52 weeks respectively. Results of these studies are expected.

Asenapine

Asenapine is an atypical antipsychotic for the treatment of schizophrenia and manic/mixed episode. Besides bipolar depression,[33] asenapine is studied as monotherapy in a double-blind trial, compared to placebo for mood episode prevention.

Aripiprazole

Aripiprazole is used as monotherapy or adjunctive treatment for manic/mixed episode and maintenance treatment, while it is controversial whether it is effective in bipolar depression.[34–36] For the time being, two phase 3 trials are investigating the use of

long acting injectable aripiprazole for 52 weeks for BD maintenance therapy.

Preclinical studies for maintenance therapy for bipolar disorder

Our search for the last 5 years found 5 eligible studies corresponding to equal number of pharmacological agents (table 3), that showed efficacy in experimental models of both mania and depression. This inclusion criteria was considered more accurate, since there is no valid and reliable animal model of BD, due to difficulty to reflect the phenotype of switching symptoms of mania and depression at the same model.[37]

CK01

The compound CK01 inhibits the function of the casein kinase 1 (CK1) ε/δ, which is believed to be involved in the modulation of the molecular clock and therefore circadian rythm.[38] CLOCK mice, carry a mutation in one of the essential proteins associated with maintaining circadian rhythm and present significant disruption of it along with a behavioral profile resembling a phenotype similar to human mania. In one study, CK01 was administered to CLOCK mice and then compared to lithium's action. Results showed reversal of anxiety-hyperactivity behavior (as lithium) and partial reversal of the phenotype of depression forced-swim test model.[39] The above results suggest that pharmaceutical agents that inhibit CK1, may have therapeutic value for BD.

Ebselen

Ebselen is a compound with significant antioxidant properties that inhibits monophosphatase inositol (IMP). It was observed that it mimics the action of lithium, probably because via the common neurobiological pathway of inositol recycling inhibition, exhibiting similar efficacy in preclinical stage.[40] It has been found to be effective in both depression[41] and

Table 3. Preclinical trials for maintenance treatment in bipolar disorder.

Compound	Animal model Mania/Depression	Mechanism of action	Results Mania/Depression model
CK01	CLOCK mice	CK1 ε/δ inhibition	Reversal of stress behavior - hyperactivity/partial reversal of depression phenotype
Ebselen	Model: amphetamine-induced hyperactivity/forced swim test and tail suspension test in mice	IMP inhibition	Similar to the action of lithium: Reduction of the observed behavior of rearing and hyperactivity/reduction of immobility time
Peptide TAT – KLCpCDK	Model: amphetamine-induced hyperactivity/forced swim test and tail suspension test in mice	GSK-3 inhibition of KLC2 phosphorylation and AMPA glutamate receptors modulation	Similar to the action of lithium: Reduction of the observed behavior of amphetamine-induced hyperactivity/reduction of immobility time
Cpd-60	Model: amphetamine-induced hyperactivity/forced swim test in mice	HDAC ½ inhibition	Reduction of the observed behavior of amphetamine-induced hyperactivity/reduction of immobility time
Sodium butyrate (SB)	Model: AMPH-induced hyperactivity in Wistar rats/maternal deprivation and chronic mild stress	HDAC inhibition	Reversal of mania/depression phenotype respectively

CK: Casein kinase, IMP: Monophosphatase inositol, GSK-3: glycogen synthase kinase-3, KLC-2: kinase light chain 2, AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazole propionate, HDAC: Histone Deacetylase

mania[40] models, and therefore a candidate agent for further study in treating BD.

Peptide TAT – KLCpCDK

This peptide has been found to have lithium-like properties, inhibiting glycogen synthase-3 kinase (GSK-3), while additionally shows effectiveness in both models of depression and mania.[42] Although results of this study were announced in 2010, there have not been since then, known to us at least, further clinical trials for this agent in BD.

Cpd-60

Cpd-60 acts as a selective 1/2 histone deacetylase (HDAC 1/2) inhibitor, modulating chromatin and gene expression in mouse brains. Evidence of its efficacy has been found in both mania and depression models.[43] Inhibition of HDAC may be a candidate target for the development of epigenetic acting agents that would have a therapeutic role in BD.

Sodium Butyrate (SB)

This compound, similarly to Cpd-60, inhibits HDAC and simultaneously exhibits neurotrophic activity. SB administration in experimental models of mania[44,45] and depression[44,46] resulted in amelioration of behavioral patterns, indicating a possible mood stabilizing role.

Current limitations and prospects in maintenance treatment of BD

The need to develop new treatments for BD is beyond any doubt. There are therapeutic difficulties in BD, especially in preventing depressive episodes or depressive residual symptoms or treating BD II in the long-term.[47] Lithium may be the golden option for relapse prevention, but, as noted above, a proportion of BD patients will not respond (non-responders)[48] or be fully protected, regarding mixed or rapid-cycling type, and often will present side effects,[49] which impede therapeutic process. Moreover, many patients are treatment resistant,[50] presenting with residual symptoms during maintenance phase[51] and therefore ongoing treatment is considered inadequate. The phenomenon of polypharmacy[2] is also frequent in order to achieve stabilization and treat residual symptoms. Finally, new pharmaceutical agents which are developed based on the mechanism of lithium action or other pathophysiological pathways may contribute to the understanding of the underlying neurobiological substrates of BD.[52]

From this review it appears that three active compounds (dextromethorphan, pregabalin, paliperidone) and possibly eslicarbazepine have shown some positive evidence for BD maintenance therapy. Considering, however, the methodology of these and other ongoing trials, there are marked differences in the definition of maintenance therapy, the required time for long-term prophylaxis and how efficacy of each intervention is evaluated. Measuring clinical levels of functioning or residual symptoms (mania or depression) does not seem to ensure long-term prevention. Regarding study design, it may be preferable to use days to relapse (for any major mood episode) or the number of individuals who will finally relapse as primary outcome measures and the longest, possible, follow-up time period for which a prophylactic treatment will be considered adequate. Methodological issues, such as diagnosis, clinical heterogeneity, gender differences and comorbidity,[53] should also be addressed in order to promote research.[52] Finally, regarding preclinical trials, there are important limitations in developing a reliable, valid BD model that will present both the pole of mania and depression in a single behavioral phenotype.[37]

Based on the above concerning studies design, paliperidone seems to have favorable profile for further study as a mood stabilizer, although, for the moment, it seems to be effective only in the prevention of manic episodes. Cariprazine is another antipsychotic that presents with a novel mechanism of action and has shown good tolerability and safety. Results on the efficacy of cariprazine in maintenance treatment are expected, as well as from other atypical antipsychotics, namely lurasidone, asenapine and long-acting aripiprazole. Study results on the efficacy of NMDA receptors inhibitors, dextromethorphan and memantine, are so far mixed, although there is preliminary positive evidence for dextromethorphan. Pregabalin

and eslicarbazepine are anticonvulsants with prospects of further study in BD maintenance treatment. Trials of pharmaceutical agents with neuroprotective and/or neurotrophic properties, such as omega-3 fatty acids and cytidine, did not reveal positive results. Studies on the therapeutic benefit of modulating circadian rhythms in both experimental models and clinical trials, with CK01 and ramelteon respectively, have yielded encouraging results. In preclinical level, neurobiological pathways of GSK-3 and IMP inhibition, both related to the therapeutic effects of lithium, are known and important targets for the development of pharmaceutical agents for BD.[52,54] Pharmacological agents based on epigenetic changes and gene expression modulation, such as the inhibitor of HDAC, are earning more ground in modern research for BD.[52,54,55]

Φαρμακολογικοί παράγοντες υπό μελέτη για τη θεραπεία συντήρησης στη διπολική διαταραχή

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Η θεραπεία της διπολικής διαταραχής αποτελεί πρόκληση για τον σύγχρονο κλινικό και, παρά την πρόοδο της ψυχοφαρμακολογίας, οι επιλογές παραμένουν περιορισμένες και τα αποτελέσματα συχνά μη ικανοποιητικά. Η σύγχρονη έρευνα επικεντρώνεται στην ανεύρεση νέων φαρμακευτικών παραγόντων για όλες τις φάσεις της διπολικής διαταραχής, για την αντιμετώπιση μανιακών και καταθλιπτικών επεισοδίων και τη θεραπεία συντήρησης. Ιδιαίτερα η πρόληψη των υποτροπών και η μακροπρόθεσμη σταθεροποίηση συνιστά μείζονα θεραπευτικό στόχο. Οι συνδυαστικές θεραπείες και η πολυφαρμακία αποτελούν την πλέον συχνή τακτική επιλογή στη πρόληψη των υποτροπών. Επιπλέον, στη φάση συντήρησης οι ασθενείς βιώνουν συχνά υπολειπόμενα συμπτώματα από τη διάθεση, παρουσιάζουν γνωστικά ελλείμματα και λειτουργική έκπτωση, κάτι που καταδεικνύει τη μη επαρκή αποτελεσματικότητα των υπαρχουσών θεραπειών και την ανάγκη για νέες, στοχευμένες, αποτελεσματικές και ασφαλείς θεραπείες για τη διπολική διαταραχή. Η παρούσα ανασκόπηση εστιάζει σε δραστικές ουσίες για τη θεραπεία συντήρησης που διερευνώνται την τελευταία 5ετία. Οι υπό έρευνα ουσίες έχουν δοκιμαστεί ή δοκιμάζονται είτε ως μονοθεραπεία είτε ως θεραπεία ενίσχυσης σε κλινικές δοκιμές που έχουν προχωρήσει έως την φάση 3 ή σε προκλινικά μοντέλα διπολικής διαταραχής. Ενώ αναμένεται η ολοκλήρωση πολλών τρεχουσών μελετών, τα μέχρι τώρα αποτελέσματα δείχνουν ότι η παλιπεριδόνη και η πρεγκαμπαλίνη ίσως έχουν θέση στη θεραπεία συντήρησης της διπολικής διαταραχής. Επιπρόσθετα, η δεξτρομεθορφάνη, που δρα κυρίως ως NMDA ανταγωνιστής, παρουσιάζεται ως ενδιαφέρουσα ουσία για περαιτέρω μελέτη. Ωστόσο η μεμαντίνη που είναι επίσης NMDA ανταγωνιστής δεν έχει δώσει ενθαρρυντικά αποτελέσματα. Από την άλλη πλευρά, οι μέχρι τώρα δοκιμές ω-3 λιπαρά οξέα και κυτιδίνη δεν έδειξαν ανώτερη αποτελεσματικότητα σε σχέση με το εικονικό φάρμακο, παρόλο που έχουν τόσο νευροτροφικές όσο και νευροπροστατευτικές ιδιότητες. Η αντιεπιλη-

πτικής δράσης εσλικαρβαζεπίνη είχε κάποιες ενδείξεις αποτελεσματικότητας ως μονοθεραπεία. Όσον αφορά στις μελέτες σε προκλινικά, πειραματικά μοντέλα, οι υπό έρευνα ουσίες φαίνεται να ακολουθούν το νευροβιολογικό μονοπάτι του λιθίου, που εξακολουθεί να είναι η «χρυσή επιλογή» για την πρόληψη υποτροπών στη διπολική διαταραχή. Κύριοι θεραπευτικοί στόχοι είναι η συνθετική κινάση της γλυκόζης 3 (GSK-3) και το μονοπάτι της φωσφοϊνοσιτόλης (IMP), που υποστηρίζεται ότι εμπλέκονται στη δράση του λιθίου. Επιπλέον, η διατήρηση των κιρκάδιων ρυθμών εξετάζεται σε προκλινικές και κλινικές μελέτες με τη διερεύνηση της αποτελεσματικότητας και ασφάλειας των ουσιών CK-01 και ραμελτεόνης αντίστοιχα. Η έρευνα εστιάζει επίσης σε φαρμακευτικά μόρια που σχετίζονται με επιγεννητικές μεταβολές ή τη ρύθμιση της γονιδιακής έκφρασης, όπως η ιστόνη της δεακετυλάσης (HDAC). Θα πρέπει επίσης να επισημανθεί ότι η ανάπτυξη έγκυρων και αξιόπιστων πειραματικών μοντέλων διπολικής διαταραχής, που προς το παρόν παραμένει αρκετά αμφιλεγόμενη, θα συμβάλει στην κατανόηση των παθογενετικών μηχανισμών της αλλά και στην ανεύρεση κατάλληλων και αποτελεσματικών θεραπειών. Επίσης, η βελτίωση των μελετών σε μεθοδολογικά ζητήματα όπως η διάγνωση, η κλινική ετερογένεια, ο χρόνος παρακολούθησης, οι διαφορές ανάμεσα στα φύλα και η συννοσηρότητα, μπορεί να προαγάγουν την έρευνα. Οι τρέχουσες μελέτες αφήνουν περιθώρια για την ανάπτυξη νέων δραστικών ουσιών στο άμεσο μέλλον, μολονότι υπάρχουν μεθοδολογικοί περιορισμοί στην έρευνα για τη θεραπεία συντήρησης στη διπολική διαταραχή. Οι νέοι θεραπευτικοί στόχοι περιλαμβάνουν όχι μόνο τους ήδη γνωστούς μηχανισμούς δράσης αλλά και νέα παθοφυσιολογικά μονοπάτια που πιθανώς εμπλέκονται στη διπολική διαταραχή.

Λέξεις ευρετηρίου: Διπολική διαταραχή, θεραπεία συντήρησης, νέοι θεραπευτικοί στόχοι, νέοι φαρμακολογικοί παράγοντες.

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