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An update on adjunctive treatment options for bipolar disorder

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**Abstract**

**Objectives:** Bipolar disorder is a complex illness often requiring combinations of therapies to successfully treat symptoms. In recent years there have been significant advancements in a number of therapies for bipolar disorder. As such, it is timely to provide an overview of current adjunctive therapeutic options for treating clinicians to inform their patients and work towards optimal outcomes.

**Methods:** Publications were identified from PubMed searches on bipolar disorder and pharmacotherapy, nutraceuticals, hormone therapy, psychoeducation, interpersonal and social rhythm therapy, cognitive remediation, mindfulness,

e-Health and brain stimulation techniques. Relevant articles in these areas were selected for further review. This paper provides a narrative review of adjunctive treatment options and is not a systematic review of the literature.

**Results:** A number of pharmacotherapeutic, psychological and neuromodulation treatment options are available. These have varying efficacy but all have shown benefit to people with bipolar disorder. Due to the complex nature of treating the disorder, combination treatments are often required. Adjunctive treatments to traditional pharmacological and psychological therapies are proving useful in closing the gap between initial symptom remission and full functional recovery.

**Conclusions:** Given that response to monotherapy is often inadequate, combination regimens for bipolar disorder are typical. Correspondingly, psychiatric research is working towards a better understanding of the disorder’s underlying biology. Therefore treatment options are changing and adjunctive therapies are being increasingly recognised as providing significant tools to improve patient outcomes. Toward this end, this paper provides an overview of novel treatments that may improve clinical outcomes for people with bipolar disorder.

**Keywords:**

bipolar disorder; nutraceuticals; hormones; psychological therapies; cognition; e-health; transcranial magnetic stimulation; neuromodulation techniques

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# Introduction

The lifetime prevalence of bipolar disorder is between 0.1 percent and 4.4 percent [[1,](#_bookmark22) [2].](#_bookmark23) Bipolar disorder may be associated with poor symptomatic, physical and psychosocial outcomes and is generally considered a lifelong condition [[3].](#_bookmark24) As such, patients are often prescribed a combination of therapy types, all aiming to improve functional outcomes for the individual. Thus, the aim of treatment is to reduce the frequency, duration and severity of active episodes and increase time spent in remission.

While there has been some recent developments in modified drugs for bipolar disorder (e.g., divalproex), and using anti-epileptic and antipsychotic medications as adjuvants (e.g., lamotrigine, quetiapine), no novel agents have significantly al- tered the pharmacological landscape over the last decade. Lithium remains the most common treatment and persistent bipolar depression remains difficult to treat [[4,](#_bookmark25) [5].](#_bookmark26) Similarly, while there is efficacy with psychological therapies, these are mainly adjunctive and there is still a paucity which are specific to bipolar disorder and ef- fective as monotherapy [[6].](#_bookmark27) Finally, there is the option of exploring electroconvulsive therapy (ECT), used predominantly as a ‘last line’, which can have profound im-

provements, but also severe side-effects, with efficacy predominantly in depression and a waning effect that does not appear to last over the longer term [[7].](#_bookmark28)

Therefore, there has been a renewed search for novel approaches to treatments for bipolar disorder. It has resulted in an number of therapies undergoing evaluation through investigator-initiated studies, encompassing pharmacological, psychologi- cal and neuromodulation approaches [[8].](#_bookmark29) This review provides an update on novel adjunctive treatment options for bipolar disorder to assist clinicians in working towards better functional recovery for patients.

# Treatments

Repurposed agents

There is now significant evidence implicating inflammation, altered antioxidant de- fense and mitochondrial dysfunction in the pathophysiology of bipolar disorder [[9].](#_bookmark30) A multitude of novel trials have utilized this new biological understanding to trial agents that specifically target these pathways [[10].](#_bookmark31) By utilising existing agents with known safety profiles and repurposing them for psychiatric indications, the devel- opment of a new therapy can be accelerated compared to *de novo* drug discovery. N-acetyl cysteine, traditionally used as an antidote to paracetamol overdose, has been an agent successfully repurposed for bipolar depression [[11].](#_bookmark32) There have been several randomized controlled trials, aggregated in a recent meta-analysis [[11],](#_bookmark32) show- ing benefits of N-acetyl cysteine as an adjunctive therapy for bipolar depression. To date, the dosing has been 2000 mg/day in addition to treatment as usual, with minimal side-effects and no apparent interactions with usual treatment [[12].](#_bookmark33)

Other anti-inflammatory agents have also been trialled and some efficacy has been shown with adjunctive celecoxib treatment. A randomized controlled trial of participants experiencing mixed or depressed bipolar episodes (and undergoing ECT) found that 200 mg twice a day (i.e., 400 mg/day) of adjunctive celecoxib attenuated increases in TNF-alpha levels. No other changes were noted. In a more

recent study, adjunctive celecoxib (400 mg/day) was effective in mania over six weeks of treatment [[13].](#_bookmark34) There is current interest in a variety of other adjunctive anti-inflammatory agents in varying stages of clinical trials. Adjunctive minocy- cline has been shown to improve symptoms in a case report of bipolar depression. Following a week of minocycline treatment (150 mg/day), the patient was noted to have improved symptoms [[14].](#_bookmark35) A randomized controlled trial is currently un- derway to provide definitive evidence of minocycline’s potential in bipolar disorder (ClinicalTrials.gov: NCT01429272) [[15].](#_bookmark36) There are also a number of other

psychiatric minocycline trials, including a trial in patients with major depressive disorder which was shown to be positive on functional and quality of life outcomes [[17](#_bookmark38), [16]](#_bookmark37). In addition, ketamine is currently being explored as an adjunctive therapy for bipolar disorder. A recent meta-analysis suggested adjunctive ketamine in combination with ECT is not ef- ficacious [[18].](#_bookmark39) However, when explored as an adjunct to any other therapy and specifically for bipolar depression, adjunctive ketamine has been found to be useful [[19].](#_bookmark40) Given the lack of targeted therapies for bipolar depression, such treatment options in this domain need to be seriously considered.

Nutraceuticals

There has been an explosion in the field of nutritional psychiatry recently [[20].](#_bookmark41) Several nutraceutical agents have been trialled as adjunctive therapies to improve treatment for the symptoms of bipolar disorder (e.g., N-acetyl cysteine, also con- sidered a health supplement [[21].](#_bookmark42) While there is growing popularity in the commu- nity for the use of Omega-3 fatty acids, varying efficacy has been found in bipolar disorder [[22].](#_bookmark43) Overall, it appears that adjunctive Omega-3 treatment favours im- provement in bipolar disorder, however methodological issues remain such as trial design and sample size, which make definitive statements difficult [[23].](#_bookmark44) Similar find- ings have been reported with adjunctive inositol, with one study finding statistical

improvements, but another two studies showed only small effects which did not reach statistical significance on the primary outcomes. These results leave the utility of inositol for bipolar disorder in doubt [[24].](#_bookmark45) Folic acid has also been trialled as an adjunctive treatment for bipolar disorder, although only two trials have been published to date. An early study found no improvement in people with bipolar depression (n=17) who were taking lithium following adjunctive folate treatment (200 µg/day) [[25].](#_bookmark46) However, the study also included individuals with unipolar depression (in which some benefit was shown) and the sample size may have been a significant limiting factor. More recently, a study of 88 participants showed benefits of high-dose folic acid (3 mg/day) as an adjunct to sodium valproate for bipolar mania [[26].](#_bookmark47) Magnesium, melatonin and choline have also been suggested as potentially useful adjunctive agents, but only small trials have been conducted and further work is required [[23].](#_bookmark44) There is also current interest in investigating combinations of adjunctive nutraceutical agents [[10](#_bookmark31), [27](#_bookmark48), [28]](#_bookmark49). However, results from randomised controlled trials are required.

Hormone treatments

Recent evidence indicates that the selective estrogen receptor modulator — ta- moxifen, a protein kinase C (PKC) inhibitor — may confer some benefit in reduc- ing manic symptomatology [[29].](#_bookmark50) It has been postulated that alongside its PKC- inhibiting effects, tamoxifen may stimulate ovarian steroid genesis which increases estrogen levels [[30].](#_bookmark51) Several studies have demonstrated mood-symptom improve- ment as a result of tamoxifen augmentation [[31,](#_bookmark52) [32,](#_bookmark53) [33,](#_bookmark54) [34].](#_bookmark55) For example, Amrol- lah and colleagues [[35]](#_bookmark56) recently showed the effectiveness of adjunctive tamoxifen compared to lithium alone for the rapid reduction of manic symptoms in 40 in patients with bipolar disorder. This potential effect — coupled with known differ- ences between men and women in the clinical course of bipolar disorder and an increased risk for relapse in women at times corresponding to major reproductive

events — suggests that estrogen may play a role in bipolar disorder symptomatol- ogy. Correspondingly, Kulkarni et al. observed that adjunctive augmentation with the progestin medroxyprogesterone (MPA) had a modulating effect on manic symp- tomatology in comparison to tamoxifen or placebo [[36].](#_bookmark57) Although the reason for the lack of effect with tamoxifen is unclear, the anti-manic effect of MPA was postulated as being related to its estrogenic effect. At this point understanding the effects of estrogen in bipolar disorder remains limited, but there is at least some evidence that it may play some role in the disorder’s pathophysiology [[30].](#_bookmark51) Further work exploring the efficacy of tamoxifen and MPA is thus required.

Psychoeducation

Psychoeducation as an adjunctive therapy for bipolar disorder has

evolved from providing patients with information exclusively related to

a biological understanding of disorder and related pharmacological treatments to

an integrative approach emphasising illness and symptom awareness, treatment adherence,

self-management, the importance of regular habits, avoiding drug misuse and

promoting good physical health [[39](#_bookmark60), [40]](#_bookmark61). Although the active ingredients of this

treatment are yet to be clearly established, it is speculated that psychoeducation

helps individuals recognise early signs and symptoms and adopt behavioural

measures to prevent a full-blown episode [[39](#_bookmark60), [41](#_bookmark62), [42]](#_bookmark63). The superiority of group

psychoeducation over individual psychoeducation further suggests that the opportunity

to share personal experiences and insights in a supportive peer setting confers

additional benefit [[43](#_bookmark64), [44](#_bookmark65), [45]](#_bookmark66).

Psychoeducation as an adjunctive treatment has shown encouraging results in both bipolar I and bipolar II disorder and across a range of therapeutic targets. Studies show that

psychoeducation increases adherence to medication and other elements of treatment

[[43](#_bookmark64), [47](#_bookmark68), [38](#_bookmark59), [48](#_bookmark69), [49](#_bookmark70), [41](#_bookmark62)] and reduces time spent in manic, hypomanic, mixed and depressive episodes[[51](#_bookmark72), [52](#_bookmark73), [38]](#_bookmark59). Long lasting improvements in overall relapse rates, time spent ill, hospitalisation readmission and number of hospitalisation days have also beendemonstrated [[43](#_bookmark64), [51](#_bookmark72), [55](#_bookmark76), [54]](#_bookmark75). Recent studies report that

psychoeducation is associated with increased perceptions of control [[49](#_bookmark70)] and reduced

self-stigma among people with bipolar disorder [[56]](#_bookmark77).

 Evidence suggests that the efficacy of psychoeducation ~~, it is~~ diminishes as the number of episodes increase, highlighting the importance of delivering this treatment as early as possible [[57](#_bookmark78), [41]](#_bookmark62). Ideally, psychoeducation should be delivered when patients are euthymic and are best able to comprehend and retain the information, however patients with mild depressive episode can also benefit [[58]](#_bookmark79).

Overall, psychoeducation is a clinically and cost-effective [[59](#_bookmark80)] adjunctive therapy

for bipolar disorder and is increasingly considered a standard component of care.

Further research is needed to identify the causal mechanisms in psychoeducation that lead to positive outcomes, clarify the optimal dose and mode of delivery, and understand how to best

personalise treatment. In the following sections, we review the novel psychological therapies available that have been investigated for bipolar disorder.

Interpersonal and social rhythm therapy

The main therapeutic goals of interpersonal and social rhythm therapy (IPSRT) are to regulate social and circadian rhythms, maintain regular routines, promote positive social relationships and social roles, and to reduce interpersonal conflict [[60].](#_bookmark81) Given such rhythms are often dysregulated in bipolar disorder, this line of therapy could be useful [[61].](#_bookmark82) This approach has shown some efficacy in bipolar disorder, with significantly higher regularity of social rhythms and a significant reduction in the likelihood of mood recurrence [[60].](#_bookmark81) A more recent pilot study comparing IPSRT to quetiapine for people with bipolar II disorder showed promising results [[62].](#_bookmark83) Both groups had significant improvements in depression and mania rating scores over 12 weeks, had high satisfaction ratings, and there were no differences in treatment preferences of participants, suggesting IPSRT could be effective as a standalone treatment for bipolar II. These results show that IPSRT plays an important role in the psychosocial treatment of this illness.

Mindfulness

Mindfulness is a form of cognitive awareness that focuses on stress reduction by improving concentration and encouraging relaxation [[63].](#_bookmark84) This approach promotes the conscious awareness of distressing thoughts and feelings, and aims to provide in- dividuals with the ability to disengage from these thoughts and feelings rather than counter them [[64].](#_bookmark85) When used as a psychological therapy tool, mindfulness is often incorporated into cognitive therapy (i.e., mindfulness-based cognitive therapy, or MBCT). MBCT was first used as a psychological intervention for anxiety disorders [[63],](#_bookmark84) and has since been applied to a range of mental health conditions, including bipolar disorder. Results of MBCT in bipolar disorder have been positive over- all, ranging from significant improvements in executive functioning, memory, task completion, and attentional readiness [[65,](#_bookmark86) [64],](#_bookmark85) to significant decreases in depres- sion scores, anxiety scores, and dysfunctional attitudes on achievement [[66,](#_bookmark87) [67,](#_bookmark88) [68].](#_bookmark89)

These findings are promising, however it is not yet clear how long-lasting the effects of MBCT are in bipolar disorder.

Cognitive remediation

Over the last two decades, there has been an increased focus on the neurocognitive profile of bipolar disorder. There is now significant evidence indicating people with the illness have substantial impairments in cognitive function, ranging from lower- order deficits in processing speed to higher-order deficits in executive functioning [[69,](#_bookmark90) [70,](#_bookmark91) [71].](#_bookmark92) Cognitive abnormalities have been consistently demonstrated in patients

during both symptomatic and euthymic mood states as well as during the first BD

episode [[72](#_bookmark93), [73]](#_bookmark94), with recent evidence also suggesting that cognitive impairments

may be present prior to illness onset in some individuals [[74](#_bookmark95), [75]](#_bookmark96). These findings

— coupled with growing research indicating individuals at increased genetic risk for

the disorder also exhibit neuropsychological impairment in certain cognitive domains —

suggest that aberrant cognition may represent a trait-like endophenotype for the illness

[[76](#_bookmark97), [77](#_bookmark98), [78]](#_bookmark99).

To this end, an emerging theme in the bipolar disorder literature is the use of cognitive remediation therapy (CRT) [[79].](#_bookmark100) CRT seeks to remediate cognitive dys- function through lasting, generalizable improvements in neuropsychological, and subsequently, psychosocial ability [[80].](#_bookmark101) Given that cognitive processes are under- pinned by structural and functional brain mechanisms known to be dynamic in nature, cognitive remediation partially draws on the principle that the brain is plastic and capable of change [[81].](#_bookmark102) In practical terms, it is a behavioural inter- vention designed to improve attention, memory, executive functioning and other neuropsychological processes through the use of computer-based and face-to-face training programs which teach drill and practice, and adaptive and compensatory strategies, usually over a period of 10 sessions or more.

CRT has been studied increasingly in the context of psychotic disorders [[82].](#_bookmark103) Rel- atively few cognitive remediation studies have been carried out in bipolar disorder, although preliminary research indicates that some of the same cognitive improve- ments seen in psychosis may also apply [[79].](#_bookmark100) A systematic review by Anaya and colleagues [[83]](#_bookmark104) reported a significant, moderate pooled effect size for pre- to post- intervention change in cognitive performance in an aggregate sample of bipolar disorder and unipolar disorder subjects (i.e., combined across seven small studies). Importantly, one of the studies included in the analysis also indicated reductions in depressive symptoms, and improvements in occupational and general psychosocial functioning [[84].](#_bookmark105) Furthermore, recent investigation in a group of euthymic bipolar disorder-I subjects showed that compared to treatment as usual, functional reme- diation (where improvements in functional endpoints are emphasized) had an effi- cacious effect on daily functioning [[85].](#_bookmark106) Other evidence suggests that this form of remediation may also be efficacious for individuals with euthymic bipolar disorder-II [[86].](#_bookmark107) Moreover, neuroimaging studies suggest it may have measurable implications for brain changes, as improvements in working memory and indirect changes in functional brain activation were observed in individuals with unipolar/bipolar de- pression after 10 weeks of computer-assisted cognitive remediation [[87].](#_bookmark108) One caveat to note is that ”euthymic” state is hard to define and thus studies are difficult to compare. Moreover, there may be residual effects that last a long time after the last episode. Thus, it may be difficult to disentangle inter-episode improvement from therapeutic effects.

e-Health approaches

A number of internet-based programs for mental health have been developed based on successful face-to-face psychological therapy approaches. These online interven- tions are becoming increasingly common and have shown significant efficacy across a variety of mental health conditions [[88].](#_bookmark109) It has been suggested that in bipolar dis-

order, online programs may help people to overcome a number of barriers commonly faced when attempting to access self-management programs [[89].](#_bookmark110)

Few internet-based interventions have been evaluated for use as adjunctive treat- ments for bipolar disorder, and the results for these programs have been varied [[90].](#_bookmark111) While some interventions have found no significant improvements in outcomes when compared with control conditions [[91,](#_bookmark112) [49,](#_bookmark70) [92],](#_bookmark113) one study have found significant re- ductions in mania symptom severity [[93].](#_bookmark114) Other programs have also shown promise when evaluated in pilot studies [[94,](#_bookmark115) [95]](#_bookmark116) and further evaluations of these programs are anticipated.

Nearly all of the existing online programs for bipolar disorder have incor- porated elements of psychoeducation and cognitive behaviour therapy (CBT) [[93,](#_bookmark114) [96,](#_bookmark117) [49,](#_bookmark70) [91,](#_bookmark112) [97,](#_bookmark118) [92].](#_bookmark113) One program has utilized social rhythm therapy [[95]](#_bookmark116) (a key element of IPSRT), while the most recent program was based on mindfulness [[94].](#_bookmark115) A recent review of optimization strategies for the delivery of e-health interventions in bipolar disorder suggested the inclusion of peer support, such as discussion forums and peer coaching, could help to improve program engagement [[89].](#_bookmark110) Two studies have suggested peer coaching can significantly improve program adherence [[97,](#_bookmark118) [98],](#_bookmark119) however further research is required to determine the impact of discussion forums in online interventions for bipolar disorder. Programs developed for bipolar disorder

to date have focused on self-help interventions with minimal therapist assistance,

however therapist-guided interventions are also an option. Based on the current literature, it is unclear which therapeutic approach works best in online programs for the disorder.

More recently, a number of smartphone-based applications (or apps) have been developed for use as self-management tools for bipolar disorder. While many of these apps are available on the commercial market [[99],](#_bookmark120) research into the efficacy of this approach appears to be ongoing [[100].](#_bookmark121) A recent systematic review reported

that while a number of apps for bipolar disorder were commercially available, the quality of these apps is very poor [[99].](#_bookmark120) The review found the content provided within informational apps was not in line with practice guidelines and core psychoeducation principles, and information sources were rarely cited. This review also reported that the majority of symptom monitoring apps failed to monitor key areas such as sleep and medication intake, and screening apps did not use validated screening measures [[99].](#_bookmark120)

To date, only one smartphone app has been evaluated by a randomized controlled trial. Results showed no significant improvements in symptoms of both depression and mania in those using the smartphone app for daily mood monitoring [[101].](#_bookmark122)

In addition to smartphone apps, other portable electronic devices such as mobiles phones and personal digital assistants (PDAs) have been utilized in a number of ways as adjunctive treatment tools for bipolar disorder. Face-to-face psychoedu- cation followed by mobile phone-based mood monitoring has been shown to sig- nificantly improve symptoms of depression when compared with paper-based mood monitoring in people with bipolar disorder [[102].](#_bookmark123) Pilot data on an ecological momen- tary intervention delivered via PDA also showed a significant decrease in depression symptoms, as well as high rates of treatment adherence [[103]](#_bookmark124).

Delivering psychotherapeutic material at a distance comes with a range of

unique ethical considerations and safety concerns. Ensuring appropriate user safety

monitoring, maintaining secure data privacy controls, and clearly communicating

the adjunctive nature of an intervention is crucial [[104]](#_bookmark125). Online and mobile

technologies provide a number of solutions to these issues through automated safety

assessments, password protected and encrypted data files, and automated reminder

notifications to seek face-to-face care when required [[104]](#_bookmark125).

Considering the rate at which technology continues to advance, it is likely that incorporating technologies such as computers and smartphones into treatment will continue to be a focus of research for the foreseeable future.

Repetitive transcranial magnetic stimulation

While ECT was introduced almost a century ago as the first form of therapeutic brain stimulation, the last two decades have been momentous for the advancement of brain stimulation techniques. Undoubtedly, the most significant has been the establishment of repetitive transcranial magnetic stimulation (rTMS) on the left dorsolateral prefrontal cortex (DLPFC), as a safe and efficacious treatment for depression with a low side-effect profile [[105,](#_bookmark126) [106,](#_bookmark127) [107].](#_bookmark128)

The first of these trials provided evidence that high-frequency rTMS on the DLPFC (the most common of depression rTMS treatment protocols) was effica- cious for bipolar depression [[108].](#_bookmark129) In contrast, a subsequent trial that also applied high-frequency rTMS on the left DLPFC, found rTMS was not significantly bet- ter than sham for treating bipolar depression [[109].](#_bookmark130) It is relevant to note, however, that this study adopted more conservative treatment parameters; that is, a lower frequency of stimulation and a much shorter duration of treatment course com- pared with the previous study as well most studies in the depression literature. Notwithstanding, Fitzgerald and colleagues (2016) [[110]](#_bookmark131) employed a more inten- sive treatment protocol with sequential bilateral DLPFC stimulation, but similarly showed no significant benefit of active compared with sham rTMS in the largest trial to date (n=49). This study importantly provided a basis for the authors to carry out post-hoc power analysis, which revealed that a sample of 157 would be required to show therapeutic effects. Thus, all the aforementioned studies were underpow- ered and their results should be interpreted with caution. Notably, a large-sample naturalistic study (n=240) recently provided evidence that rTMS is similarly effec- tive for bipolar depression compared with unipolar depression, and taken together

with findings of sham-controlled trials, this work indicates further investigation into rTMS treatment for bipolar depression is warranted [[111].](#_bookmark132)

In evaluating rTMS treatment for bipolar depression, it should be recognized that the confounding effects of limitations in study design are likely to be important. In the rTMS for depression literature, a progressive overall pattern of improved ther- apeutic benefit of rTMS for depression is apparent, and a meta-analysis has shown that effect sizes reported in more recent studies are larger than in older studies [[112].](#_bookmark133) More recent studies were better designed, and in turn, likely contributed to their superior effect size findings. For instance, recent studies recruited larger sam- ples and employed more intensive treatment protocols providing 20 (or more) rTMS sessions, whereas earlier smaller-sample studies typically adopted a more conserva- tive number of sessions (e.g., 10). It is also plausible that patients selected in later studies may have been less treatment-resistant, a feature that has been shown to correspond with better rTMS response [[113].](#_bookmark134)

It is possible that further research into rTMS for bipolar depression has been deterred due to the reports of induction of hypomania/mania in this population [[114].](#_bookmark135) However, it has been shown that the risk of developing mania is low, not significantly different when comparing active or sham rTMS, and not higher when compared to antidepressant treatment [[115].](#_bookmark136) This evidence suggests that switching to hypomania/mania is a change in clinical status that may or may not occur dur- ing the course of rTMS treatment and an appropriate level of clinical management is advisable (for further information see Fitzgerald and Daskalakis, 2013) [[114].](#_bookmark135) Despite being extremely uncommon, it is critical to consider seizure induction as a possible adverse event, which has been documented in depression and healthy patients during or immediately after rTMS [[116].](#_bookmark138) Reports of seizures with rTMS occurred in cases where stimulation exceeded established TMS safety guidelines

1. or patients with existing neurological disorders (e.g., epilepsy, multiple sclero-

sis) [[116].](#_bookmark138) It is therefore strongly advisable that the provision of rTMS to patients with neurological disorders is carefully and appropriately considered.

# Discussion

Effective treatment of bipolar disorder is an ongoing challenge for patients and clinicians. Given that many people do not respond adequately to monotherapy and combination regimens are the rule rather than the exception [[118],](#_bookmark140) it is imperative that clinicians and patients are provided with up-to-date information on novel tools for bipolar disorder management. Indeed, with mental healthcare resources being limited and ongoing advances in technology, the use of self-directed learning and treatment in the online space is gaining momentum [[119].](#_bookmark141) Furthermore, the departure from large-scale pharmaceutical company investments in mental health treatments has been paralleled by a significant expansion of investigator-initiated research leading to the development of novel therapies. It is imperative that information on novel interventions are widely disseminated given the critical need for new effective therapies, the shift towards treatment in the primary care setting, and the paucity of marketing resources in investigator-initiated studies.

By bringing together all the available information, clinicians can more readily identify potential new treatment options for their patients. Some of these new therapies are more patient-centred, especially in the context of internet-based therapies. It shifts the focus back onto the patient and enables a greater sense of direction and control in the management of their illness. Such patient-directed care also facilitates individualized tailored healthcare, thus maximising the opportunity for full recovery. Indeed, the inclusion of adjunctive therapies to conventional treatment regimens has been one very useful pathway to fill the shortfall towards full functional recovery for patients.

With enormous growth in biology psychiatry research over recent years, a plethora of novel agents have focused on biologically relevant pathways, some of which have

Shown efficacy in bipolar disorder. There has been particular interest in bipolar depression in the field because it is a condition that has the greatest unmet need in terms of

treatment outcomes. Adjunctive agents are being used more commonly by clinicians and this review should assist in informing both clinicians and patients in the mental health space of what is available and what has been found to be useful.

Advances in brain stimulation techniques has provided an alternate strategy for targeting aberrant neurobiological pathways in bipolar depression; that is, high- frequency rTMS applied to the left DLPFC. Although efforts into rTMS treatment specifically for bipolar depression to date has been scant, it is a promising, relatively safe and low-risk treatment bipolar depression. Given bipolar depression patients are included in most rTMS treatment for depression studies and the shared diathesis between bipolar and unipolar depression, there is clearly further potential for rTMS to be established as a treatment of bipolar depression. However, studies utilising larger sample sizes with more advanced treatment protocols are required before the efficacy of rTMS for bipolar depression can be better determined.

In regard to psychological therapies, while more research is required into the potential benefits of CRT for people with bipolar disorder, current evidence suggests that it is imperative for treating team members to recognize that cognitive deficits may be present in individuals with the illness. Indeed, the assessment of cognitive ability in clinical practice is an area that has been largely ignored thus far. Yet in the context of persistent functional impairments that remain even beyond symptom remission [[120],](#_bookmark142) it is a major impediment to holistic disease management. Progress toward rectifying this issue will no doubt require increased dissemination of research knowledge from scientists to clinicians and greater collaboration between primary healthcare providers, neuropsychologists, psychiatrists and moreover policy makers.

While advances in technology may provide new opportunities to enhance treatment, they also present an interesting challenge for clinicians. The internet is be-

coming an increasingly acceptable source of information, with 21% of US adults using the internet to search for mental health information [[121].](#_bookmark143) While a number of evidence-based e-health and m-health tools for bipolar disorder exist, so too do commercially driven products with little regard for clinical guidelines [[99].](#_bookmark120) With rapid growth in this area, it is becoming increasingly important for clinicians to stay up-to-date and technologically savvy so they can recognize poor quality tools and information, and best advise their patients accordingly.

# Conclusion

In conclusion, current treatments for bipolar disorder can reduce episode frequency. It is a promising time for new therapies to be produced. A more complete understanding of how bipolar disorder develops and persists may lead to improved prediction of episodes, new approaches for treatment-resistant patients and even curative interventions. There are a range of updated tools, summarized in this re- view, that provide new options for the treatment of bipolar disorder and may help to improve functional health outcomes for patients.

**Competing interests**

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