Psychiatria Danubina, 2019; Vol. 31, Suppl. 3, pp 595-603 *Conference paper*

PHARMACOLOGICAL THERAPIES IN BIPOLAR DISORDER: A REVIEW OF CURRENT TREATMENT OPTIONS

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SUMMARY

Background: *Bipolar disorder is a mental illness characterised by periods of elevated mood alternating with periods of depression. Long-term relapse prevention in bipolar disorder is challenging, with a significant number of patients relapsing following the initial stabilisation of mood. Initial treatment of the condition is complex and usually occurs in secondary care. Whilst there is no known cure for bipolar disorder, several therapies have been found to be effective in both managing acute episodes and sustaining long-term remission. The key pharmacological therapies in bipolar disorder are lithium salts, antiepileptics and antipsychotics and these will be the focus of this review.*

Aim: *This review seeks to outline the key common pharmacological therapies used in the treatment and relapse prevention of this condition.*

Methods: *A MEDLINE search was performed, and the available literature was subsequently analysed, including meta-analyses, reviews and original clinical trials.*

Results: *Management strategies can be subdivided into treating acute presentations of mania and depression and maintaining long-term remission. The extensive side effect profile of several antipsychotics means that there are certain patient groups for whom they may be intolerable or contraindicated. Lithium emerges as a highly efficacious maintenance therapy but retains the burden of therapeutic drug monitoring. Antiepileptics play a crucial role in maintaining remission but are linked to serious, albeit rare, side effects.*

Conclusion: *Despite the efficacy of the medications discussed in this article, their underlying mechanisms of action remain to be fully elucidated. Nonetheless, these key therapies continue to be essential tools in the management of bipolar disorder.*

Key words: *bipolar disorder - lithium - antiepileptics – antipsychotics -relapse prevention*

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INTRODUCTION

Bipolar disorder is a severe mental illness characterised by periods of elevated mood (mania or hypomania), depression and mixed episodes. It affects 1-2% of the population worldwide, transcending nationality, ethnicity and socioeconomic status (Grande et al. 2016).

Bipolar disorder comprises several subtypes. Bipolar I disorder is characterised by at least one manic episode with or without a history of depressive episodes. Bipolar II disorder is characterised by one or more episodes of depression and by at least one episode of hypomania, but no evidence of mania (NICE 2018). Hypomania differs from mania in several ways: symptoms need only last 4 days; there are no psychotic features; there is no significant impairment in occupational or social functioning; and hospitalisation is not required. Episodes may also be mixed, in which depressive and manic or hypomanic symptoms co-exist or rapidly alternate. In addition, rapid-cycling bipolar disorder is defined as the experience of 4 or more mood episodes within a 12-month period. These may be depressive, manic, hypomanic or mixed.

The management of bipolar disorder can be divided into two distinct phases: management of an initial episode (which may precipitate the diagnosis of bipolar disorder) and long-term management to prevent relapses. These two phases require different treatment strategies and coordination between primary and secondary care. This distinction is also important when the different pharmacological therapies used to treat bipolar disorder are considered.

The oldest and, arguably, the most effective of these therapies is lithium. Salts of lithium (lithium carbonate and lithium citrate) have been used for 70 years in bipolar disorder. Initially they were observed to have an antimanic effect, only becoming established as a maintenance therapy twenty years later. Whilst the efficacy of lithium is established, its popularity has declined more recently. As lithium is a naturally-occurring substance, it cannot be patented by pharmaceutical companies. It is believed by some that this lack of commercial incentive has been a key factor in its decline (Bauer 2018). Another stumbling block with lithium is the necessity for therapeutic drug monitoring, which must occur three-monthly as a minimum once the drug has been titrated accordingly (NICE 2018).

Antipsychotics have come to the fore in more recent years following the discovery of the atypical antipsychotic, clozapine. This drug was a valuable advance in the field as it had a far lower incidence of extrapyramidal side effects (EPS) than its predecessors. A family of second-generation atypical antipsychotics have since become common treatments in bipolar disorder. Whilst these are very efficacious drugs, their multimodal mechanism of action confers an extensive side-effect profile. The tolerability of this group of drugs to the individual patient thus becomes an essential consideration.

Antiepileptics are the third class of drug that are commonly used in the management of bipolar disorder. They share a common mechanism of action by inhibiting sodium signalling in CNS neurons and therefore dampen global neurotransmission. The two key antiepileptics valproate and lamotrigine are widely used as mood stabilisers and are able to maintain remission in a variety of patient groups. They also show efficacy in managing other facets of bipolar disorder, with valproate demonstrating antimanic properties while lamotrigine is useful in managing bipolar depressive states. These benefits, however, must be balanced against their off-target activity, which can be life-threatening in a small minority of cases.

LITHIUM

History

Since its introduction in 1949, lithium has become a mainstay of psychopharmacology. Some have even hailed it the 'aspirin of psychiatry'. As well as its antimanic and prophylactic actions, it also displays antidepressant, anti-suicidal and neuroprotective effects (Bauer 2018). As such, it could be argued it more closely resembles a psychiatric 'cure-all'! Indeed, this is cemented by its status as the longest standing psychotropic medication in clinical practice.

Lithium carbonate was first used in 1949 by John Cade to treat mania. He initially noted the calming effect of the drug and other behavioural changes in laboratory animals, before going on to test his hypothesis on ten patients (Tondo et al. 2019). Its main use however, as a maintenance therapy for bipolar disorder, was not realised until 1968. Two Danish psychiatrists, Schou and Baastrup were pioneers in establishing its safety and its widespread use in the modern-day treatment of various psychiatric disorders.

Psychopharmacology

Its mechanism of action is thought to be derived from its ability to disrupt magnesium binding sites on proteins. Many proteins are regulated by magnesium binding and this confers a plethora of potential mechanisms through which lithium may operate (Kato 2019). Inhibition of inositol monophosphate (IMP) and the subsequent depletion of inositol from neurons is thought by many to be its key mechanism of action. This reduces signalling through the inositol phospholipid pathway. This theory has been supported with both in vitro and in vivo experiments. For example, in IMAP2 knockout mice experiments, the affected mice showed behavioural changes and an increase in rearing behaviours compared to the control group. Another popular theory is that lithium acts through inhibition of glucose synthase kinase 3β (GSK-3β). GSK-3β has many substrates on which it acts and so the possibilities with regards to lithium's mechanism of action are equally broad. Both theories are well-evidenced, and one can reasonably speculate that they may be working in tandem. Alternatively, another candidate protein that is regulated by magnesium binding could feasibly underlie lithium's effects.

Indications

It is interesting to note that the primary use of lithium today is long-term relapse prevention in bipolar disorder, whereas other drugs have superseded it as an antimanic agent. It can be used as an adjunct in mania where two different antipsychotic medications have failed to adequately control symptoms (NICE 2018).

Efficacy

Lithium's evidence base in terms of its efficacy as a maintenance therapy is well-established. A network meta-analysis (Miura et al. 2014) also showed lithium to be the most effective maintenance treatment and supported its continued use as the first-line drug. This is reflected by its status as the first-line drug in many guidelines internationally. These include not only the NICE guidelines, but also the CANMAT, CIND and Japanese Society of Mood Disorders guidelines (Kato 2019). There is also a strong body of evidence that lithium has robust anti-suicidal properties. A meta-analysis of studies investigating suicide rates found that suicide was 82% less frequent whilst on lithium treatment in terms of suicides per 100 patient-years (Tondo et al. 2001).

Side Effects & Contraindications

Lithium is associated with a variety of initial side effects including tremor, nausea, fatigue, increased appetite, increased white blood cell count, polydipsia and polyuria. Some of these side effects (thirst and tremor) tend to subside over the initial few weeks of treatment (Tondo et al. 2019). However, the narrow therapeutic index of lithium may be considered to be its main drawback. This is the ratio of the toxic concentration of a drug to its therapeutic concentration (and is approximately 3 for lithium). This makes lithium toxicity, which can be life-threatening, a realistic concern where therapeutic drug monitoring is not employed effectively. Blood lithium concentration must be measured one week after starting therapy, one week after every dose change and weekly until levels are stable. Thereafter, levels must be measured three-monthly. BMI, kidney function, calcium and thyroid function tests must be measured six-monthly. In addition, lithium prescription must always be by brand name and with a consistent salt-form, as the bioavailability of each preparation varies widely (NICE 2018).

Owing to its near-complete renal excretion (minor contributions include sweat and faeces), lithium is contraindicated in those with clinically significant renal

impairment (NICE 2018). Equally, those with low sodium levels should not receive lithium as the kidneys treat lithium similarly to sodium (Hedya & Swoboda 2019). Sodium depletion can lead to excessive lithium reabsorption and subsequent toxicity. In the same way, diabetes insipidus is a contraindication for lithium therapy as the kidneys cannot produce a concentrated urine.

Lithium also has multiple effects on the physiology of the thyroid gland. Most important among them is the inhibition of the synthesis and release of the thyroid hormones, namely tri-iodothyronine (T3) and thyroxine (T4). This reduction in thyroid hormone secretion increased the production of thyroid-stimulating hormone (TSH), causing thyrocyte proliferation and goitre (Kibirige et al. 2013). Goitre is observed in approximately 40% and hypothyroidism in 20% (Lazarus 2009). However, treatment with levothyroxine is effective and hypothyroidism is not an absolute contraindication to lithium therapy. Whilst those that develop hypothyroidism upon commencing lithium can continue the drug, those with untreated or untreatable hypothyroidism cannot be prescribed it for these reasons.

Lithium is also contraindicated in patients with cardiac disease associated with rhythm disorders. This can be explained by the similarity of lithium to other cations such as sodium and potassium which govern the membrane potential of excitable cells. Regression analyses of electrocardiography parameters have shown that long-term lithium use was associated with atrial and ventricular instability (even at therapeutic doses) compared to healthy controls (Altinbas et al. 2014). Understandably, Brugada syndrome (which can cause ventricular arrhythmias) is an absolute contraindication to lithium therapy. A literature review of the use of drugs in Brugada syndrome patients lists lithium as a class IIa drug. Class IIa drugs are defined as those drugs in which the weight of evidence is in favour of a pro-arrhythmic activity (Postema et al. 2009). Additionally, it is thought that lithium can unmask Brugada syndrome, even at subtherapeutic doses (Chandra & Chandra 2009).

Overall, lithium is a very effective drug but is inappropriate for many patients due to its wide-ranging physiological effects. Perhaps another important factor limiting its use is a lack of incentive for pharmaceutical companies to promote it due to the fact is a natural substance and therefore cannot be patented. Newer, trendier compounds have overtaken it in the US. Additionally, some authors have described a 'lithium stigma' due to the perception that lithium is only a drug for the severely mentally ill, with antipsychotics and anti-epileptics being less taboo (Tondo et al. 2019). However, the efficacy of lithium in relapse prevention cannot be understated. As well as there being an international consensus on its use, it has also stood the test of time, continuing to be the first-line drug as a maintenance therapy 70 years since its inception.

ANTIPSYCHOTICS

History

It is widely attributed that Paul Ehrlich's quest fora novel antimalarial in the late 19th Century brought to light the clinical significance of early phenothiazine derivatives (Zirkle 1973). Their utility as negative psychomotor modulators, however, did not become apparent until the advent of chlorpromazine in the late 1950s. Initially explored for its actions at histamine receptors, it was subsequently found to have drastic tranquilising effects on acutely manic patients (Winkelman 1954).

The benefits of chlorpromazine and similar traditional antipsychotics however was countered by the high incidence of tardive dyskinesia and unwanted dystonic reactions (Denham & Carrick 1961). This problem was only answered several decades later by the development of clozapine, an atypical drug which displayed markedly reduced incidence rates of extrapyramidal effects in comparison to traditional antipsychotics (Baldessarini & Frankenburg 1991). The success of clozapine has spurred the development of several novel second-generation drugs which are routinely used in the management of bipolar disorder today.

Psychopharmacology

While the molecular mechanisms of bipolar disorder are slowly being unravelled, there still exists a large gap between the neurobiological understanding of the condition and the mechanism of action of antipsychotics. Atypical antipsychotic drugs are believed to be effective in the management of mania by primarily antagonising the effects of dopamine at D2 receptors, an effect shared with typical antipsychotics (Seeman 2004). However, neuroimaging studies have demonstrated that the atypical drugs clozapine and quetiapine display low affinities for the D2 receptor and only engage the receptor for brief periods of time, which is believed to contribute to their lower incidence rates of EPS (Seeman & Tallerico 1999).

Several atypical drugs also display antagonism at multiple receptor sites, giving an incredibly complex mechanism of action. Olanzapine has been shown to display antagonism at 5-HT2A, 5-HT2C, H1 and muscarinic receptor subtypes (Bymaster & Felder 2002, Reynolds 2011, Yatham et al. 2005). Both 5-HT2A and 5-HT2C receptors have been shown to play crucial roles in the regulation of mood, and as such it is postulated that this antagonism underpins the efficacy of several atypical drugs in ameliorating depressive episodes (Berg et al. 2008).

Indications

The UK's National Institute for Clinical Excellence (NICE) advocates the use of atypical antipsychotics

for the management of all aspects of bipolar disorder including acute manic episodes, mixed episodes, depression and maintenance regimes (NICE 2019). As per the guidelines, a choice of either the typical antipsychotic haloperidol or one of three atypical drugs (olanzapine, quetiapine, or risperidone) is deemed an appropriate first line treatment (Anderson et al. 2012) (Table 1).

Table 1. Summary of NICE guidance on the use of antipsychotics in the management of bipolar disorder

Condition	Preferred antipsychotic treatment
Acutemania and mixed episodes	Haloperidol OR Olanzapine OR Risperidone OR Quetiapine
Depression	Quetiapine OR + Olanzapine OR Olanzapine + Fluoxetine
Relapse prevention (min. 4 weeks after manic episode)	Haloperidol OR Olanzapine OR Risperidone OR Quetiapine
Acute mania while on antidepressant	Antidepressant should be terminated, then treat as per acute manic episode

Efficacy

A significant body of research lends weight to the notion that both typical and atypical antipsychotics display therapeutic benefits over placebo in the treatment of mania (Derry & Moore 2007, Smith et al. 2007). In comparison to monotherapy with mood-stabilisers, there appears to be a greater role for atypical antipsychotics in the management of mania. In particular, the atypical drug olanzapine has been shown to exhibit superior antimanic effects over lithium without the need for regular blood monitoring (Niufan et al. 2008). The typical antipsychotic chlorpromazine, however, only showed a clear benefit over lithium in more severe cases (Prien et al. 1972).

It should be noted that current NICE guidance also permits the use of the first-generation antipsychotic haloperidol in the management of acute mania. A meta-analysis by Scherk and colleagues found that haloperidol was more effective than both olanzapine and quetiapine in providing symptomatic relief in acutely manic patients. This was demonstrated by measurable differences in the Young mania rating scale (YMRS) scores between the two drug classes, the main parameter used to quantify the degree of mania experienced during the study. However, the overall efficacy between atypical and typical antipsychotics was deemed similar due to the higher incidence of adverse effects leading to increased trial non-compliance in the haloperidol group (Scherk et al. 2007). As such, it is important that clinicians take tolerability into account when deciding commencing initial treatment for mania.

Depressive episodes are one of the most common presenting complaints of bipolar disorder and as such form a cornerstone symptom in the aetiology the disease (Cruz et al. 2010). Unlike mania, however, only two antipsychotics are licensed in the UK for combating bipolar depression. Both quetiapine and olanzapine have been shown to have significant positive impacts in alleviating and maintaining remission of depressive episodes in bipolar patients (Gao et al. 2005). This beneficial effect also extends to patients with treatment-resistant unipolar depression but is inferior to the therapeutic effect of antidepressants for non-refractory cases of major depressive disorder (Amato et al. 2018).

Selective serotonin reuptake inhibitors (SSRIs) may also feature in the overall management of bipolar depression when combined with an atypical antipsychotic. A growing body of work has highlighted that dual therapy with olanzapine and fluoxetine produces measurable improvements in overall mood beyond those provided by monotherapy with olanzapine alone (Tohen et al. 2003). Animal studies have found that this combination therapy is able to significantly enhance catecholamine signalling in the prefrontal cortex, however the resultant effect of this in ameliorating mood in human subjects remains to be explored (Zhang et al. 2000).

Side Effects & Contraindications

While initially designed to combat the debilitating, extrapyramidal symptoms experienced by patients taking traditional antipsychotics, the multimodal mechanism of action of the atypical drugs has invariably led to novel off-target effects.

Atypical antipsychotics are believed to cause greater metabolic dysregulation than their traditional counterparts, leading to higher rates of truncal obesity and weight gain in patients taking these drugs (Reynolds & Kirk 2010). Indeed, several studies have noted that olanzapine and clozapine are associated with the worst metabolic profile, with this undesirable effect being positively correlated with the length of treatment and lack of previous antipsychotic exposure (Bak et al. 2014, Correll et al. 2015). In contrast, aripiprazole has been consistently associated with a low incidence of weight disturbance and may even be beneficial in inducing weight loss in a select subset of bipolar patients (Barzman et al. 2004).

Various mechanisms have been proposed for this action, including the modulation of NPY signalling and 5-HT2 antagonism in the feeding centres of the hypothalamus (Kirk et al. 2006, López-Alonso et al. 2007). The latter is supported by the notion that 5-HT2deficient mice have been shown to demonstrate voracious eating and rapid weight gain (Tecott et al. 1995). The role of the H1 receptor in satiety has also received significant attention in recent years and was

explored in a landmark study by Kim and colleagues. Strikingly, the study detailed that the satiety-inducing effects of leptin are reduced upon administration of atypical antipsychotics, with the degree of dampening being correlated with the affinity of the drug with H1 receptors (Kim et al. 2007). This is believed to occur despite an increase in circulating leptin levels, thus reflecting the propensity of these drugs to concurrently induce a degree of leptin resistance which further fuels weight gain (McIntyre et al. 2003).

Atypical drugs are largely contraindicated in those with evidence of cardiac conduction anomalies. This is attributable to the ability of the drugs to lengthen the cardiac QTcinterval, which can be detected withregular ECG monitoring (Zemrak & Kenna 2008). The mechanism for this prolongation is yet to be fully elucidated but is believed to involve antagonism of a type of inwardly-rectifying potassium channel (hERG) which plays a critical role in myocyte repolarisation (Nachimuthu et al. 2012). Antagonism of these ion channels may lead to a sudden death by inducing a broad-complex polymorphic ventricular tachycardia (Ray et al. 2009). Ziprasidone has been shown to have the worst cardiac profile and as such care should be exercised when combining it with other treatments known to prolong the QT interval such as SSRIs (Vieweg 2003).

ANTIEPILEPTICS

History

The marketing of phenobarbital as an anti-seizure drug in the early 19th century hailed the beginning of a long era of antiepileptic drug discovery (Smith et al. 2007). Since then, the creation of the antiepileptic drug development programme (ADD) has enabled several conventional therapies to come to the forefront of mainstay medical treatment. Within this programme, novel compounds are tested against a battery of animal seizure models to determine their overall efficacy and suitability in clinical practice (Kupferberg 1989).

Modern-day antiepileptics were developed around the turn of the millennium with the aim of reducing the amount of off-target effects and drug-drug interactions with prevalent medications (Porter et al. 1984). An example of this new class of antiepileptic includes lamotrigine, which alongside the older anticonvulsant valproate plays a crucial role in the management of bipolar disorder.

Psychopharmacology

Sodium valproate follows a characteristic pharmacokinetic profile, displaying near-complete absorption upon oral administration (Perucca et al. 1978). The drug then rapidly equilibrates between CSF and blood before being eliminated through both urine and faeces (Schobben et al. 1980, Woodbury 1980). In a similar fashion, administration of lamotrigine leads to maximal plasma concentrations within three hours of ingestion with an estimated bioavailability of 98% (Goa et al. 1993).

Both drugs exert therapeutic effect by modulation of voltage-gated sodium channels. The open-channel inhibition displayed by lamotrigine is believed to stabilize the resting membrane potential of presynaptic glutamergic neurons, leading to reduced excitatory neurotransmitter signaling (Stahl 2004). In contrast, valproate-induced inhibition of sodium channels has been shown to reduce neuronal burst firing and induce long term adaptive changes in overall ion channel levels (McLean & Macdonald 1986, Yamamoto et al. 1997). Furthermore, animal models have highlighted the secondary effect of valproate in increasing inhibitory GABA transmission, which may play a role in reducing the severity of bipolar symptoms (Johannessen 2000). One proposed mechanism for this effect is by inhibition of succinic semialdehyde reductase, an enzyme that plays an important role in the degradation of GABA (Ghodke-Puranik et al. 2013).

Indications

As per the NICE guidelines for the management of bipolar disorder, both lamotrigine and valproate are indicated as mood stabilizing treatments to prevent future relapses. Valproate is further licensed as a third-line treatment for the management of mania where antipsychotics and lithium have shown poor efficacy or are contraindicated. Conversely, lamotrigine is also indicated as monotherapy for the management of bipolar depression and unlike valproate does not require regular blood tests to assess hepatic function (Calabrese et al. 1999).

Efficacy

There exists a significant body of evidence to support the efficacy of both valproate and lamotrigine as mood stabilizing agents. Lambert and colleagues highlighted that when compared to the traditional mood stabilizer lithium, valproate maintained a similar rate of illness remission over an 18-month timeframe (Lambert & Venaud 1995). Similar results have been shown by lamotrigine, which is also able to maintain remission in pregnancy with minimal teratogenic activity (Newport et al. 2008).

Several meta-analyses have highlighted the antimanic properties of valproate (Macritchie et al. 2003). This effect is believed to be synergistic with antipsychotics, with a similar rate of adverse effects as antipsychotic monotherapy alone (Müller-Oerlinghausen et al. 2000). Furthermore, work by McElroy and colleagues highlighted that orally loading valproate in acutely manic patients significantly improved overall outcomes. It is thought that this effect is due to a rapid reduction in the time taken to reach the effective therapeutic concentration by administering high doses of the drug (McElroy et al. 1993).

Conversely, lamotrigine has been proven to be successful in the management of bipolar depressive states. Dose-dependent improvements in the Hamilton Rating Scale for Depression (HRSD) and Montgomery-Asberg Depression Rating Scale (MADRS) upon lamotrigine administration is well documented in the literature (Calabrese et al. 1999). This benefit is believed to be correlated with the magnitude of the depressive episode, as patients that displayed a more severe phenotype showed a greater response to lamotrigine treatment (Geddes et al. 2009).

Side Effects & Contraindications

The side effect profile of sodium valproate is well defined and extensive. Of note, excessive weight gain plays an important factor in valproate discontinuation and poor treatment adherence. While the mechanism surrounding this unfavourable effect is unknown, it is hypothesized to involve both increases in insulin secretion and deficiencies in components of the fatty acid metabolism cycle (Breum et al. 1992, Kanemura et al. 2012). A rare but potentially serious complication of valproate is that of hyperammonemic encephalopathy. This condition is characterized by a raised plasma ammonia level, falling GCS and vomiting and is thought to be attributable to the inhibition of urea cycling by valproate metabolites (Brusilow 2002, Coulter & Allen 1980). Early treatment with L-carnitine has been shown to improve outcomes in patients with valproate-induced encephalopathy (Segura-Bruna et al. 2006).

Unlike valproate, the modern anticonvulsant lamotrigine is not associated with excessive changes in body mass (Biton et al. 2001). Instead, cutaneous side effects on the toxic epidermal necrolysis spectrum form a significant proportion of the unwanted effects of the drug. Of these, Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are regarded as the most serious dermatological complications. Both SJS and TEN form a continuum of disease, with SJS being characterized by mucosal blistering lesions with ≤10% cutaneous desquamation while TEN is defined by a ≥30% detachment of the skin (Messenheimer 1998). The pathogenesis of these type IV hypersensitivity reactions remains to be fully elucidated, however it is postulated that aberrant lymphocytic activity plays a crucial role in their aetiology (Sánchez-Borges 2008).

Pregnant females and females of child bearing potential serve as important contraindications to the administration of valproate due to the risk of foetal malformations (Vajda & Eadie 2005). Valproate is believed to exert its teratogenic effect through inhibition of foetal histone deacetylase (HDAC), a key enzyme involved in the storage of DNA (Lloyd 2013). Other notable contraindications to valproate include severe hepatic failure and hematological malignancies (Coyle et al. 2005, Peterson & Naunton 2005). In a similar fashion to lithium, lamotrigine serves as a relative contraindication in patients with Brugada syndrome, largely due to its ability to inhibit cardiac sodium channels at high doses (Strimel et al. 2010). Clinicians should therefore be aware of the risks of lamotrigine in patients with a familial history of sudden death and adjust the therapeutic dose accordingly.

CONCLUSION

This paper has sought to highlight the key aspects of the key major bipolar disorder treatments while also attempting to unravel the complex mechanisms surrounding their therapeutic effect. It is clear that lithium and antipsychotics have a crucial role in the management of bipolar disorder and display tremendous efficacy as the primary maintenance and antimanic treatments respectively. Lamotrigine and anti-psychotics have also been shown to combat bipolar depression as monotherapies, with the latter also being used in combination with an antidepressant. Of course, these beneficial effects should always be balanced against any off-target effects to ensure high levels of patient compliance. Regular blood monitoring for patients undergoing lithium therapy is also essential to closely monitor drug levels and thus prevent toxicity. The antiepileptic valproate is effective as a mood stabiliser and as an antimanic agent however is contraindicated in females of reproductive age due to its teratogenic profile. The adverse effects of weight gain and hepatotoxicity associated with valproate can be diminished by switching to lamotrigine, however this must be balanced with an increased risk of cutaneous syndromes. Alternative pharmacotherapies and psychotherapy are likely to play a greater role in patients with co-existing arrythmias, which serves as a relative contraindication for all three drug classes. As new treatments develop, further study will be needed to integrate them with the current first-line drugs discussed in this review.

Acknowledgements:

We would like to thank Dr Mark Agius for his continued support, guidance and advice during the synthesis of this piece of literature.

Conflict of interest: *None to declare.*

Contribution of individual authors:

Amol Joshi: background research and writing of conclusion, antiepileptic and antipsychotic sections.

Alexander Bow: background research and writing of abstract, introduction and lithium sections.

Mark Agius: background research for antiepileptic, lithium and antipsychotic sections. Guidance on structure and components of article.

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