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We are confident that this CPD Section of the Irish Journal of Psychological Medicine will prove to be a valuable resource for consultant psychiatrists, psychiatric trainees and all journal readers. We welcome feedback from readers and, especially, any suggestions for topics to be covered in future CPD modules. Suggestions should be emailed to: [psychological@medmedia.ie](mailto:psychological@medmedia.ie)

## Recent advances in the biological treatment of mood disorders

Gary McDonald, Brian Hallahan

Mood disorders are common conditions associated with significant disability. Depression and bipolar disorder are the 3rd and 12th most common causes of moderate to severe disability worldwide as measured by global burden of disability (GBD) and disability adjusted life years (DALYs), with depression predicted to become the leading cause of disability worldwide by 2030.<sup>1</sup> Despite this, both of these disorders are potentially treatable in a large proportion of cases. In this review article, we will discuss recent evidence and advances in relation to biological treatments for both depression and bipolar disorder and discuss both well known and novel therapeutic options available for treating these disorders.

### Depression and standard antidepressant agents

Several studies have demonstrated that tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have comparable efficacy in the treatment of depression,<sup>2,3</sup> although baseline remission rates with both are noted to be as low as 30%,<sup>4,5</sup> and either alternative or additional agents are thus

often required. A number of studies have demonstrated subtle differences in efficacy between agents, with venlafaxine perhaps exhibiting a marginal benefit over other SSRIs.<sup>4,7</sup> Furthermore, a recent meta-analysis of "new-generation" antidepressants found venlafaxine, escitalopram, mirtazapine and sertraline superior in efficacy to other SSRIs, SNRIs (including milnacipran, presently not licensed in Ireland) and reboxetine (which was inferior in efficacy to all 11 other antidepressant agents studied).<sup>8</sup> Furthermore, differential efficacy in relation to individual symptoms has been demonstrated between agents even where comparable overall efficacy was noted, with a recent study demonstrating a drug-specific advantage favouring escitalopram compared to nortriptyline for mood and cognitive symptoms and a drug-specific advantage favouring nortriptyline over escitalopram for neuro-vegetative symptoms.<sup>9</sup>

The evidence in relation to the treatment of depression including refractory depression has substantially improved due to the Sequenced Treatment Alternatives to Relieve Depression programme (STAR\*D).<sup>5,10</sup> This pragmatic effectiveness programme explored various treatment pathways in depression and evaluated symptom response and remission rates for each treatment. In brief, all patients were initially commenced on citalopram for 14 weeks with individuals not achieving remission, either switched to an alternative antidepressant (bupropion, venlafaxine, or sertraline), or augmented with bupropion or buspirone. Individuals not in remission at this stage, were then either switched to mirtazapine or nortriptyline, or augmented with lithium or

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tri-iodothyronine (T3). The final stage for those still not in remission involved a switch of medications to either tranylcypromine or to a combination of mirtazapine and venlafaxine. Cumulative remission rates at each stage were 33%, 57%, 63%, and 67%, with the authors suggesting that their results demonstrated both significant difficulties in successfully attaining remission for individuals with major depression, and that response to medications were not predicted by drug pharmacology or previous initiated treatments.<sup>10,11</sup> Pharmacotherapeutic options that demonstrated efficacy in the STAR\*D programme, but are seldom administered in clinical practice at present, included nortryptiline alone, and bupropion, buspirone and T3 as augmentation agents.

Given these results, the approach to treating individuals with depression is probably best decided on an individuals' clinical and medication history, drug toxicity and patient acceptability of the planned treatment regime.

### Subtypes of depression

#### Atypical depression

Monoamine oxidase inhibitors (MAOIs), and in particular phenelzine, have consistently demonstrated increased efficacy compared to TCAs in treating atypical depression,<sup>12</sup> however superiority of MAOIs compared to the other antidepressants including SSRIs is less clear due to a paucity of studies in this area with SSRIs demonstrating comparable efficacy to MAOIs in some studies.<sup>13,14</sup> Based on current evidence, MAOIs should be considered as a viable therapeutic option for individuals with atypical depression not responding to other antidepressants including SSRIs.

#### Psychotic depression

The response rates for treating psychotic depression with antidepressants are significantly inferior to non-psychotic depression.<sup>15</sup> The combination of an antidepressant and an antipsychotic agent is the most effective pharmacological therapy, and has consistently been shown to be superior in efficacy to antidepressant or antipsychotic treatment alone.<sup>16-18</sup> However the most effective biological treatment remains electroconvulsive therapy (ECT).<sup>17,18</sup>

One novel therapeutic option is the type II glucocorticoid receptor antagonist mifepristone, which has demonstrated superior efficacy compared to placebo in a randomised controlled trial (RCT),<sup>19</sup> and an open-label trial,<sup>20</sup> however its principal beneficial effect was in reducing psychotic rather than depressive symptoms, thus further studies are required in relation to the efficacy of mifepristone in psychotic depression.

#### Post-stroke depression

Post-stroke depression occurs in approximately 30-40% of individuals,<sup>21</sup> and is associated with several factors including female sex, prior personal history of depression, positive family history of depression, and somatic co-morbidity other than stroke.<sup>22</sup> Due to the high incidence of post-stroke depression, prophylactic treatment with antidepressants has thus been proposed.<sup>23</sup>

Pharmacological treatments recommended in post-stroke depression include SSRIs and nortryptiline,<sup>24</sup> however considerable caution is required when prescribing anti-depressant agents due to potential physical morbidity and drug interactions. In relation to physical morbidity, individuals treated with SSRIs have an increased risk of gastro-intestinal and uterine bleeding, probably

due to decreased platelet uptake of serotonin and consequent interference with platelet aggregation.<sup>25,26</sup> Therefore, a possible increased risk of further strokes may be present with SSRI treatment and is important to consider when prescribing in this patient cohort, although some authors have found no such association.<sup>26</sup> SSRIs have differential effects on the cytochrome p450 system with sertraline, and in particular citalopram demonstrating minimal potential for interaction with other pharmacological agents.<sup>27</sup> Citalopram is thus the antidepressant of choice for individuals with post-stroke depression on warfarin treatment.

#### Other options for refractory depression

Several other agents in recent studies have demonstrated a possible benefit in the treatment of refractory depression including lithium, T3, atypical antipsychotic agents, lamotrigine, and pindolol. Lithium has demonstrated a significant benefit in the treatment of refractory depression in several studies,<sup>28,29</sup> however the recent STAR\*D programme noted only a modest response for lithium augmentation, equivalent to T3 but with greater side-effects.<sup>30</sup> T3 has, like lithium, been used for many years as an augmentation agent for refractory depression, with varying results,<sup>31,32</sup> however careful thyroid function test monitoring is required with its use. Various atypical antipsychotics including olanzapine<sup>33</sup> and ziprasidone,<sup>34</sup> have shown efficacy in the adjunctive treatment of unipolar depression, with particular promise recently being noted with the aripiprazole.<sup>35-37</sup> Lamotrigine has also demonstrated benefits in refractory depression, particularly in individuals with co-morbid anxiety or chronic pain syndromes.<sup>38</sup> The addition of pindolol to serotonergic agents has demonstrated some benefit in refractory depression with a recent meta-analysis finding a reduction in depressive symptoms in an initial four week period,<sup>39</sup> although longer-term studies are necessary. Combinations of more standard antidepressants such as venlafaxine and mirtazapine,<sup>40</sup> SSRIs and bupropion,<sup>41</sup> or high dose venlafaxine,<sup>42</sup> have all been found to ameliorate refractory depression.

### Novel pharmacological treatments

#### Bupropion

Bupropion is a noradrenaline and dopamine reuptake inhibitor (NDRI) which was first licensed as an antidepressant in the United States of America in 1985. It was withdrawn in 1986 due to its propensity to induce seizures, however it was re-released in 1989 after guidelines were drawn-up in relation to its maximum dosage, as seizures were found to be dose dependent.<sup>43</sup> Bupropion has demonstrated equivalent antidepressant efficacy compared to both SSRIs and SNRIs in several studies,<sup>44-46</sup> and has a low propensity to cause side-effects such as sexual dysfunction and sedation,<sup>47</sup> and thus presents a viable antidepressant option.

#### Agomelatine

Agomelatine is a melatonin analogue (chronobiotic) initially developed to treat disturbed circadian rhythms, however it has been shown to exhibit a significant antidepressant effect – superior to placebo,<sup>48</sup> and comparable to venlafaxine.<sup>49</sup> Agomelatine is a novel antidepressant agent acting as a potent agonist of melatonin 1 (MT1) and melatonin 2 (MT2) receptors, and in contrast to other melatonin analogues, also has antagonistic properties on 5-HT<sub>2c</sub> receptors. Putative reasons for agomelatine's antidepressant effect include the hypothesis that disrupted

circadian rhythms are important aetiological factors in mood disturbance,<sup>50</sup> and not merely a symptomatic consequence of this, and therefore resetting such rhythms (using agomelatine) could exert a potential antidepressant action. Furthermore studies on individuals with depression and significant sleep disturbance (treatable by agomelatine) have demonstrated that the introduction of rhythm therapy or hypnotics for insomnia can “break a lack of response” and consequently increase the rapidity of recovery.<sup>51,52</sup> Agomelatine’s specificity of action probably results in its low incidence of side-effects, with dizziness the only adverse effect found at greater than placebo levels.<sup>53</sup> It is due to receive its Irish license in the next couple of months and should present a viable alternative for the pharmacological treatment of depression.

### Tianeptine

Tianeptine is the first selective serotonin reuptake enhancer (SSRE) available on prescription and acts in direct contrast to SSRIs by promoting the pre-synaptic neuronal reuptake of serotonin from the synapse. Despite this apparent paradox in relation to a possible antidepressant effect, an increasing evidence base in relation to tianeptine’s effectiveness in depression has been noted, with a meta-analysis of five RCTs demonstrating equivalent antidepressant efficacy to SSRIs.<sup>54</sup> Some aspects of tianeptines’ actions are, however, similar to those of SSRIs; for example, both have been associated with down-regulation of the hypothalamic-pituitary-adrenocortical (HPA) system to normal levels,<sup>55</sup> – dysregulation of the HPA axis is one of the most consistent findings in neurobiological studies of depressive disorder.

Tianeptine has a licence for the treatment of depression in several European countries, including France, as well as in several countries in Asia and South America, but to our knowledge, there are no plans to grant tianeptine a licence to for treating depression in Ireland in the near future, although it is currently available on prescription on a named patient basis. Tianeptine has a benign side effect profile, however, in contrast to other antidepressants (except tranylcypromine),<sup>56,57</sup> there are reported problems with dependence, with features of increased tolerance and withdrawals noted.<sup>58</sup>

This has consequently led to restrictions in its use in several countries, including psychiatrist-only prescribing in Singapore, and its classification as a controlled substance in Bahrain. Tianeptine has also been abused intravenously in the Russian federation to counteract opiate withdrawal symptoms.<sup>59</sup> Therefore, while tianeptine may represent a viable antidepressant option, significant concerns regarding its risk of inducing dependence need to be considered.

### Bipolar affective disorder (BPAD)

As with depression, there is a burgeoning body of evidence in relation to the pharmacotherapy of bipolar disorder, with many recent studies emanating from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) – a large National Institute of Mental Health (NIMH) clinical research programme designed to study treatment effectiveness with both naturalistic and randomly assigned treatment protocols across 22 sites in the US and including over 4,000 patients with well characterised bipolar disorder. In the following section we discuss various pharmacological treatments for bipolar disorder with several studies from the STEP-BD referred to.

### Traditional mood stabilising agents

Lithium, valproate and carbamazepine have been used for many years as mood stabilisers, with lithium the most established mood stabiliser. However, several other agents including many atypical antipsychotics and other anti-epileptics have been utilised in the treatment of BPAD in recent years. In relation to lithium, recent evidence suggests greater efficacy for preventing manic rather than depressive episodes, although efficacy for both is noted,<sup>60,61</sup> with the number needed to treat quite large, at 10 and 14 respectively.<sup>60</sup> A significant benefit of lithium administration is the finding that long-term treatment reduces mortality from suicide to levels found in the general population,<sup>62,63</sup> and reduces significantly rates of deliberate self-harm.<sup>64</sup> However, prior to commencing an individual with BPAD on lithium several important factors should be considered. In addition to its many side-effects, recent evidence suggests that intermittent treatment with lithium can significantly worsen the course of BPAD increasing both manic and possibly depressive episodes,<sup>65,66</sup> with this risk of relapse somewhat ameliorated by a gradual discontinuation of lithium over a time-period in excess of one month.<sup>67</sup> Lithium is therefore probably best suited to individuals who have good treatment concordance, are not being treated with other medications that significantly interact with lithium (diuretics, non-steroidal anti-inflammatory drugs, ACE inhibitors etc.) and who will require and are willing to accept lithium therapy for at least three years.<sup>68</sup>

Valproate and carbamazepine are the other well established “traditional” mood stabilisers, however significant caution is also required with these agents. Particular care is required when prescribing valproate to women of child bearing age and should be avoided. The risk of foetal malformations is 7.2%, much of which due to neural tube defects.<sup>69</sup> If valproate cannot be avoided in this patient group, adequate contraception should be ensured and prophylactic folate prescribed. Carbamazepine similarly requires caution with prescribing due to its adverse effect profile, and its potent inducing properties on the hepatic cytochrome P450 enzymes with consequent reduction of plasma levels of most antidepressants, antipsychotics, benzodiazepines, some cholinesterase inhibitors, methadone, thyroxine, theophylline and oestrogens.<sup>24</sup> Furthermore, drugs that inhibit the CYP3A4 enzyme (cimetidine, diltiazem, verapamil, erythromycin, SSRIs etc.) can significantly increase carbamazepine levels, precipitating toxicity.<sup>24</sup> Therefore, as with lithium, significant consideration of the disadvantages of these agents is required and thus many other agents are now frequently considered for the treatment of bipolar disorder.

The use of these ‘traditional’ mood stabilisers however, continues to exhibit a beneficial effect for patients, with the recent STEP-BD program also noting that individuals on these medications had a less complex overall pharmacological regime.<sup>70</sup>

### Atypical antipsychotics

Atypical antipsychotics are frequently used agents for the management of acute mania, particularly when psychosis is present, and have also become increasingly utilised in BPAD prophylaxis, both in combination with ‘traditional’ mood stabilisers and alone. Several antipsychotics (olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, clozapine) have demonstrated efficacy in the treatment of bipolar mania although less evidence has been documented for their use in bipolar depression.

Table 1: Evidence base for various medications in bipolar disorder

|                           | Strength of evidence  |   |   |
|---------------------------|---|---|---|
|                           | Strong  | Weak  | Minimal   |
| <b>Mania</b>              | Lithium<br>Olanzapine<br>Valproate<br>Quetiapine<br>Clozapine | Carbamazepine<br>Risperidone<br>Ziprasidone<br>Lamotrigine  | Topiramate<br>Levetiracetam                               |
| <b>Depression</b>         | Lamotrigine<br>Quetiapine                                     | Lithium<br>Valproate<br>Olanzapine + Fluoxetine<br>Antidepressants<br>Clozapine<br>Modafanil<br>Inositol<br>Pramipexole | Olanzapine<br>Topiramate<br>Levetiracetam<br>Mifepristone |
| <b>Rapid Cycling BPAD</b> | Valproate + lithium<br>Lamotrigine                            | Quetiapine<br>Lithium alone<br>Carbamazepine  | Levetiracetam   |

Olanzapine is probably the most widely used atypical antipsychotic agent at present, with evidence suggesting superior efficacy over placebo,<sup>71</sup> and either superior or equivalent efficacy over valproate,<sup>72,73</sup> and lithium,<sup>74,75</sup> for bipolar mania. Olanzapine has not demonstrated efficacy for bipolar depression alone,<sup>75</sup> however the combination of olanzapine and fluoxetine (marketed as “Zyp-Zac” in the United States of America and licensed there for the treatment of bipolar depression), has demonstrated superior efficacy compared to placebo,<sup>76</sup> to olanzapine alone,<sup>77</sup> and possibly compared to lamotrigine.<sup>78</sup>

Evidence for the use of other atypical antipsychotic agents in bipolar disorder has also been demonstrated. Atypical antipsychotics such as aripiprazole have shown efficacy in preventing manic but not depressive relapse in BPAD;<sup>79</sup> however a small open-label study from the STEP-BD program noted a benefit for treating resistant bipolar depression,<sup>80</sup> with another open-label study detecting a small benefit in rapid-cycling bipolar disorder,<sup>81</sup> suggesting that aripiprazole may also have a role in bipolar disorder not restricted to manic episodes. Quetiapine more convincingly has demonstrated efficacy in reducing relapses for both bipolar mania and depression,<sup>82,83</sup> and recently (March 9, 2009) attained a licence in Ireland for the treatment of bipolar depression, in addition to its current licence for bipolar mania.

Clozapine has demonstrated a beneficial treatment effect in refractory bipolar disorder, especially for the treatment and prophylaxis of mania,<sup>84,85</sup> however barriers to prescribing include rigorous white cell count monitoring and off-licence use.

Thus, despite advantages of atypical antipsychotics over “traditional” mood-stabilisers in not requiring serum level monitoring and a reduced potential for drug interactions, the side-effect profiles of atypical antipsychotic agents are significant, and consequently as with “traditional” mood stabilisers, cautious prescribing practices are required, particularly when poly-pharmacy is being employed. Furthermore, in contrast to “traditional” mood stabilisers, an evidence base is only now emerging in

relation to their efficacy in BPAD, with further studies required, particularly in relation to their use in bipolar depression and rapid cycling BPAD.

#### Other anti-epileptic agents

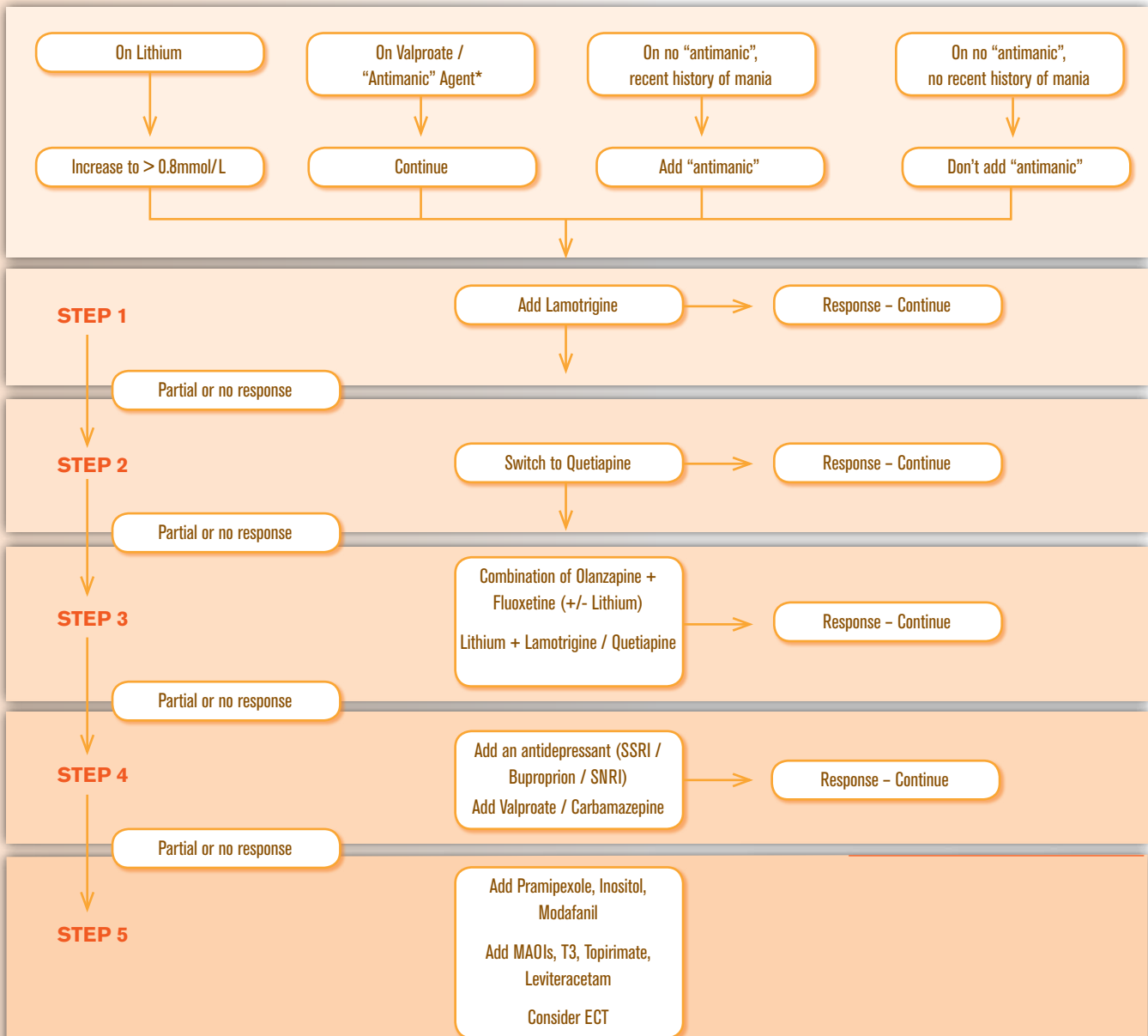
Lamotrigine is the other anti-epileptic agent most frequently used and studied in BPAD, although other anti-epileptic agents including gabapentin, topiramate, zonisamide and levetiracetam have also been proposed as treatment alternatives.

Lamotrigine is licensed for the treatment and prophylaxis of BPAD, with efficacy consistently demonstrated for treating bipolar depression. Increased efficacy compared to placebo,<sup>86,87</sup> and lithium,<sup>87</sup> and comparable efficacy to citalopram,<sup>88</sup> has been demonstrated in bipolar depression. Furthermore, marginally superior outcomes were noted for lamotrigine as an augmentation agent in bipolar depression compared to both risperidone and inositol in the STEP-BD Program.<sup>89</sup> However, lamotrigine's efficacy in relation to the treatment and prophylaxis of manic episodes remains limited.<sup>87</sup> A particular advantage of lamotrigine compared to antidepressant agents in the treatment of bipolar depression is its lack of association with inducing either (hypo) manic episodes or a rapid cycling mood state.<sup>90</sup> Lamotrigine has also demonstrated a treatment effect for individuals with rapid cycling BPAD compared to placebo,<sup>91,92</sup> although this has not been rigorously investigated, and to date is not definitively superior to lithium treatment.<sup>93</sup>

Evidence in relation to other anti-epileptics in the treatment of BPAD remains preliminary. Whilst a number of studies have found a treatment effect for topiramate in both bipolar depression and mania,<sup>94</sup> several recent studies have not corroborated these findings.<sup>95,96</sup> There have also been a number of studies demonstrating a putative mood stabilising effect with other anti-epileptics including gabapentin,<sup>97</sup> and levetiracetam;<sup>98</sup> however well designed RCTs of these agents are required before any definitive statement in relation to their efficacy can be made.

## CPD: Module 1

Figure 1: Algorithm for the treatment of Bipolar Disorder – Currently Depressed



\*Antimanic agents are considered in this algorithm to include lithium, valproate, carbamazepine, olanzapine, quetiapine or other antipsychotic agents.

### Other treatments for bipolar depression

#### Antidepressants

As discussed previously, antidepressants have been associated with the induction of (hypo)manic episodes or a rapid-cycling state, when used to treat individuals with bipolar depression,<sup>90</sup> although predicting individuals who will switch mood state remains difficult.<sup>90</sup> Furthermore a number of recent studies now suggest that antidepressants exhibit no benefit in bipolar depression, including the STEP-BD program which demonstrated that recovery from depression in individuals with bipolar disorder was independent of the addition of antidepressant agents.<sup>100,101</sup>

#### Other agents

Several other medications have been studied in relation to BPAD, including modafanil, inositol, mifepristone and pramipexole, however further RCTs are required in relation to all of these agents. RCTs have demonstrated benefits for modafanil,<sup>102</sup> and inositol in bipolar depression.<sup>103</sup> However, as discussed earlier,

a recent study from the STEP-BD Program found inositol less efficacious than lamotrigine.<sup>99</sup> Evidence for a treatment effect with mifepristone in bipolar depression remains limited but promising.<sup>104</sup> Pramipexole, a dopamine agonist, widely used in Parkinson's disease has demonstrated a treatment effect when used as an augmentation agent in two RCTs in bipolar depression without inducing switching to (hypo)mania or a rapid cycling state,<sup>105,106</sup> however both studies had relatively low power. A summary of the strength of evidence in relation to the various pharmacological treatments in relation to BPAD is presented in *Table 1* and a proposed algorithm for the treatment of bipolar depression is presented in *Figure 1*.

### Other oral compounds in mood disorders

There are several herbal and nutritional compounds with reputed beneficial effects in mood disorders. In the following section we discuss essential fatty acids (EFAs) and St John's wort, which have a substantial evidence base in this regard.

### Essential fatty acids (EFAs) and mood disorders

EFAs are divided into two groups, omega-3 ( $\omega$ -3) and omega-6 ( $\omega$ -6) fatty acids depending on their biochemical structure and are predominantly (a weak metabolic pathway does exist) attained by dietary intake.  $\omega$ -3 EFAs are attained via seafood, and the principal CNS-related EFAs are eicosapentanoic (EPA) and docosahexaenoic (DHA) acids. These are important components of phospholipids, integral to cell membrane structure and if unavailable are replaced by non-EFAs,<sup>107</sup> changing the behaviour of the phospholipid molecules and affecting the tertiary and quaternary structures of membrane-bound receptors and associated neurotransmitters.<sup>108</sup> The presence or absence of EFAs has also been associated with cell-signalling systems,<sup>109</sup> and the production of various eicosanoids (including prostaglandins, thromboxanes, prostacyclins and leukotrienes).<sup>110</sup> Due to these effects, EFAs have been studied in a variety of neuropsychiatric disorders including depression and bipolar disorder. RCTs have demonstrated varied results in relation to major depression with several studies demonstrating a therapeutic benefit,<sup>111-113</sup> however this finding is not universal.<sup>114, 115</sup> The distinguishing feature of studies where  $\omega$ -3 EFA supplementation has ameliorated depression is that EPA was given in a dose of 1-2g; with only one study in depression utilising this dosage not detecting a benefit over placebo.<sup>116</sup> In bipolar disorder, no consistent results have been attained – in particular in relation to a possible anti-manic effect, with both positive,<sup>117</sup> and negative results noted,<sup>118</sup> although EPA administration has been more consistently associated with improved mood in bipolar depression.<sup>119,120</sup> These results suggest that  $\omega$ -3 EFA supplementation has a potential antidepressant effect but not an anti-manic effect.

### St. John's wort (*Hypericum perforatum*)

St. John's wort contains at least 10 compounds, including hypericins, flavonoids and xanthenes.<sup>121</sup> The active ingredients and mechanisms of action remain unclear, however hypotheses in relation to its putative antidepressant action relate to MAO inhibition,<sup>122</sup> serotonin and noradrenaline reuptake inhibition,<sup>123</sup> and up-regulation of the serotonin receptors.<sup>123</sup> Much evidence now exists to demonstrate an antidepressant effect for St John's wort,<sup>121,124</sup> however this antidepressant effect in severe depression remains disputed.<sup>125</sup> Although in general St John's wort is well tolerated with minimal adverse effects, it has been associated with hypersensitivity reactions;<sup>126</sup> is an inducer of the CYP3A4 enzyme; has been associated with reducing plasma concentrations of many medications including digoxin, indinavir and warfarin;<sup>127-129</sup> and has precipitated hypomanic or manic episodes in individuals both with and without a history of bipolar disorder.<sup>130,131</sup> There is minimal or no evidence to suggest that St John's wort has a role in the treatment of bipolar disorder to date. St John's wort has been available on a prescription only basis in Ireland since January 1st, 2000.

### Non-pharmacological treatments for mood disorders

#### Electroconvulsive therapy (ECT)

Despite advances in pharmacotherapy, and well documented difficulties in relation to short-term memory problems, ECT remains an important treatment option in major depressive disorder and in particular in catatonia,<sup>132</sup> depression requiring a rapid treatment response,<sup>133</sup> treatment resistant depression<sup>134,135</sup> (although not all studies have demonstrated a benefit),<sup>136</sup> and

in depression associated with pregnancy, where it has proven safety to mother and baby in all trimesters.<sup>137,138</sup> Evidence also suggests a therapeutic benefit in resistant mania.<sup>139,140</sup> ECT is recommended by the Royal College of Psychiatrists for consideration as a first-line treatment in cases where a rapid response is required.<sup>141</sup>

#### Psychosurgery and brain stimulation

While psychosurgery is now rarely performed, there has been a resurgence of interest in other surgical interventions for individuals with intractable mood disorders, with lesional procedures now more sophisticated and localised, and other brain stimulation approaches, such as repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS) and deep brain stimulation (DBS) also been studied.

#### Repetitive transcranial magnetic stimulation (rTMS)

Repetitive transcranial magnetic stimulation (rTMS) delivers a magnetic pulse focally to the human cortex and is achieved using a hand-held stimulating coil applied directly to the head, where a magnetic pulse is delivered underlying the point of application. In depression, rTMS has predominantly been applied to the left dorsolateral prefrontal cortex, a brain area implicated in major depressive disorder.<sup>142</sup> Reports on the efficacy of rTMS in depression have been largely inconsistent. For example, a systematic review and meta-analysis of randomised double-blind placebo controlled trials of rTMS stimulation demonstrated a benefit of rTMS after just two weeks of treatment using the Hamilton Depression Rating Scale but not the Beck Depression Inventory (BDI),<sup>143</sup> with no benefit with either scale noted at one or two weeks after treatment application was discontinued.<sup>143</sup> Thus the authors concluded that there were significant flaws in many of the previous studies and suggested that a thorough randomised multi-centre study involving large numbers of individuals was required to further elucidate any possible antidepressant effect of rTMS. Recent studies are also largely inconsistent with both superior and inferior efficacy for rTMS over sham rTMS,<sup>144,145</sup> and predominantly inferior efficacy for rTMS compared to ECT demonstrated.<sup>146</sup> While rTMS is approved for use in depression in the US and has minimal if no side-effects, there is insufficient evidence to support its use in depression at present.

In relation to BPAD, there have been fewer studies evaluating the effect of rTMS. A recent randomised controlled trial applying a rapid pulse (or sham) to the right prefrontal cortex demonstrated a significant benefit for manic symptoms,<sup>147</sup> and these findings are supported by an open-label study conducted in a similar fashion.<sup>148</sup> Despite further evidence from several case reports of a possible beneficial effect for both bipolar mania and depression (not all case reports demonstrate a treatment effect), further RCTs are required to elucidate if rTMS is of potential benefit in bipolar disorder.

#### Vagal nerve stimulation (VNS)

VNS has been approved for the treatment of refractory depression since 2005 in the US, after several studies assessing its use in epilepsy demonstrated a beneficial effect on depressed mood.<sup>148,150</sup> VNS involves the implantation of an electrical impulse generator (about the size of a pocket watch) below the clavicle, which connects to electrodes wrapped around the left vagus nerve (avoiding the right vagus nerve to minimise interference with cardiac innervation).<sup>151</sup> The exact mechanism of VNS's

antidepressant action remains uncertain, however vagal sensory information is relayed to several mood regulatory areas in the brain (eg. the reticular formation in the medulla, the amygdala, the forebrain via the parabrachial nucleus and locus coeruleus, and the hypothalamus),<sup>152,153</sup> and stimulation leads to increased elevated levels of gamma aminobutyric acid (GABA),<sup>154</sup> which may be associated with depression of thalamic excitatory activity,<sup>155</sup> and down-regulation of the HPA axis, with a potential mood regulatory effect.<sup>55</sup> In refractory depression, benefits have been noted both in acute<sup>156</sup> and maintenance treatment,<sup>157</sup> however not all studies demonstrating an improvement in depressed mood have noted a rapid response.<sup>158</sup> Furthermore, several adverse effects have been described, including pain (29%), coughing (14%), voice alteration (13%), chest pain (12%), nausea (10%) and less frequently vocal cord palsies (1%) and lower facial muscle paralysis (1%), with some adverse effects including voice alteration persisting with continued treatment.<sup>159</sup>

Evidence for a treatment effect of VNS in bipolar disorder is less extensive, however a number of studies have found equivalent beneficial effects in both bipolar depression and unipolar depression.<sup>160,161</sup> Furthermore, a small open-label trial in rapid-cycling BPAD noted a benefit for VNS,<sup>161</sup> although there are reports of rTMS induced hypomania and mania.<sup>157</sup>

### Deep brain stimulation (DBS)

DBS was initially developed for treating movement disorders such as Parkinson's disease and involves inserting electrodes into the "desired" brain region, with these electrodes connected to an implanted pulse generator. DBS potentially exerts its effects by astrocytic release of adenosine triphosphate, and subsequent accumulation of adenosine, and adenosine A1 receptor activation, leading to depression of thalamic excitatory transmission.<sup>162</sup> This inhibitory effect on thalamic function has similar consequences to ablative procedures, but with the advantage of remaining reversible.

The evidence base for DBS remains limited, with only a few studies of small numbers, but results are promising,<sup>163,164</sup> with five brain regions identified as potentially responsive (ventral striatum/nucleus accumbens, subgenual cingulate cortex, inferior thalamic peduncle, rostral cingulate cortex and the lateral habenula).<sup>165</sup> However, DBS has also been associated with both depression and (hypo)mania<sup>165,167</sup> when used in the treatment of movement disorders, although others have found no mood alterations with long-term DBS,<sup>168</sup> perhaps suggesting the importance of accurate electrode placement.<sup>167</sup>

### Psychopharmacogenetics

Several research groups are now examining gene polymorphisms and their associations with treatment options in neuropsychiatric disorders (including mood disorders), with the aim, as stronger associations are identified and gene testing becomes more cost-effective, of determining the treatment option best suited on an individual basis. In the STAR\*D study, various polymorphisms of different genes were compared with tolerance and predictability of response to citalopram. Significant findings were noted in the FKBP5 gene,<sup>169</sup> five pharmacokinetic genes (CYP2D6, ABCB1, CYP2C19, CYP3A4, and CYP3A5),<sup>170</sup> and the GRIK4 gene.<sup>171</sup> An association between the HTR2A gene (coding for the serotonin 2A receptor) and citalopram response has also previously been noted.<sup>172</sup> Thus, psychopharmacogenetics may potentially enable psychiatrists in the future to treat

individuals on presentation with the pharmacotherapeutic agent that has the greatest chance of ameliorating their symptoms.

### Summary

In both depression and BPAD, there are a large number of biological treatment options available, with many more likely to attain a license in the coming years. In this review article, we have attempted to summarise recent evidence and advances in relation to many therapeutic options and also discuss some of the more novel options available. Novel antidepressant agents demonstrating efficacy with few associated adverse effects include bupropion and agomelatine. In BPAD, despite the expanding list of agents available, few demonstrate superiority in efficacy over "traditional" mood stabilisers, although both lamotrigine and quetiapine have demonstrated efficacy for both bipolar depression (particularly bipolar depression) and for rapid-cycling BPAD. Perhaps psychopharmacogenetic research will enable us in the future to predict the treatment option with the greatest chance of ameliorating mood disorders at an individualised level.

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