National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Psychiatry

Medication name: Olanzapine and Fluoxetine combination

Date of review: March 2015

Indication: Treatment with depressive episodes in patients with bipolar disorder.

Executive summary:

Introduction and contextualization:
Bipolar disorder is a psychiatric illness characterised by episodes of recurrent mania or hypomania and major depression. The depressive phase is considered extremely debilitative to the patient. There is thus a need for adequate treatment options for controlling and preventing these episodes. [1]

The current Adult Hospital Level Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) 2012 recommends the following:[2]

Depressive episodes in bipolar patients

First line

- Lithium, oral, 5 mg/kg/dose 12 hourly.
  - This takes some weeks to work and during this period, review the patient at least weekly, and ensure a supportive/reliable environment.
  - Target trough plasma levels 0.4–0.8 mmol/L.
  - Dosing in patients with renal impairment is complex and should be done using therapeutic drug monitoring in consultation with a specialist.

AND/OR

- Valproate, oral, 600 mg daily.
  - Increase dose to 20 mg/kg/day 6–8 hourly.

Second line

ADD

- Fluoxetine, oral, 20 mg daily. In consultation with psychiatrist.

Note:
Do not use antidepressants as monotherapy in bipolar patients. Failed second line: refer.

The olanzapine - fluoxetine combination (as well as quetiapine) are approved for the indication of bipolar depression, and form part of the first line regimen in a number of Bipolar depression

guidelines.[3,4] On review of the 2012 STGs/EML, it was suggested that olanzapine-fluoxetine be included for the first line therapy for bipolar depression.

Evidence synthesis and quality:

The evidence evaluating the efficacy and safety of Olanzapine and Fluoxetine in bipolar disorder - depressive episodes are as follows:

- Meta-analysis of randomised, placebo-controlled trials evaluating the treatment options for bipolar depression.
- Systematic review of randomised, double-blind, placebo-controlled trials and a meta-analysis for the efficacy of therapeutic options for the management of acute bipolar depressive episodes.

There is limited research on bipolar depression pharmacotherapy options, particularly with regard to head-to-head comparisons of efficacy and safety. The evidence is mainly confined to placebo-controlled trials, with extrapolated superiority of these agents gained from meta-analysis data.

Evidence synthesis:

Efficacy

A meta-analysis performed by Selle V et.al. evaluated the treatment options for bipolar depression. Randomised, controlled trials with mood-stabilising anticonvulsants, second-generation antipsychotics and lithium salts were included.[5] The standard mean drug-placebo difference (SMD) for apparent efficacy ranked the evaluated agents as follows: Olanzapine-fluoxetine > valproate > carbamazepine > lurasidone > quetiapine > olanzapine > lamotrigine > lithium > ziprasidone> aripiprazole.

Table 1 indicates the findings of the meta-analysis in terms of NNT, response rate ratios, and SMD.

Table 1:

Treatment	NNT	Response-rate ratios [95% CI]	Standard Mean Difference (drug-placebo) [95% CI]
Olanzapine-fluoxetine	1.8	1.84 [1.44-2.36]	0.453 [0.211-0.695]
Carbamazepine	3.4	1.84 [1.01-3.34]	0.209 [-0.291-0.709]
Valproate	4.4	2.08 [1.18-3.65]	0.452 [0.114-0.790]
Lurasidone	4.6	1.72 [1.33-2.22]	0.318 [0.128-0.508]
Quetiapine	5.9	1.36 [1.24-1.46]	0.373 [0.284-0.462]
Lamotrigine	10*	1.25 [1.07-1.46]	0.131 [-0.018-0.280]
Olanzapine	11*	1.25 [1.08-1.44]	0.187 [0.072-0.302]
Lithium	15*	1.12 [0.92-1.44]	0.142 [-0.099-0.383]
Ziprasidone	87*	1.02 [0.90-1.17]	0.103 [-0.036-0.241]
Aripiprazole	>100*	0.88 [0.74-1.04]	0.077 [-0.072-0.227]

**non-significant separation of drug and placebo related response*

A review by Ketter TA et. al. of randomised, double-blind, placebo-controlled trials and meta-analysis, evaluated the efficacy of pharmacotherapies for acute bipolar depressive episodes.[6] The efficacy

variable measured was number needed to treat (NNT) for acute response as compared to placebo. Table 2 highlights the review findings.

Table 2:

Treatment	NNT	[95% CI]
Olanzapine-fluoxetine	4	[3-8]
Quetiapine	6	[5-9]
Olanzapine	11	[6-113]
Lamotrigine	12	[8-41]
Antidepressants	29	infinite

Safety

Ketter et. al [6]

Treatment	NNH	[95% CI]
Olanzapine-fluoxetine	6 (weight gain)	[4-10]
Quetiapine	5 (sedation / somnolence)	[4-5]
Olanzapine	5 (weight gain)	[4-6]
Lamotrigine	37 (sedation / somnolence)	Infinite
Antidepressants	200	Infinite
Lithium	10-20	

In an RCT comparing olanzapine-fluoxetine, olanzepine and placebo, found that the adverse effects for olanzpine-fluoxetine combination were similar to olanzapine monotherapy. Weight gain was higher in patients treated with olanzapine than those on placebo, mean+/- SD, 2.59 +/- 3.24kg versus -0.47 +/- 2.62kg ($p < 0.001$), over an 8 week period. [7]

For the current STG/EML first line recommendations for bipolar depression, Lithium and Valproate:

- In a meta-analysis looking at the long-term management of bipolar disorder with lithium compared to placebo, lithium was commonly associated with nausea and diarrhoea (absolute risk 20%, 95% CI 1.07-2.92 and 1.35-4.10 respectively, as well as somnolence (Absolute risk 8%, 95% CI 1.02-3.84) and hypothyroidism (Absolute risk 4%, 95% CI 0.52-168.91).[8]

- A meta-analysis and systematic review evaluating valproate versus in the treatment of acute bipolar depression, found that there were no significant differences in adverse effects. [9]

Summary:

Olanzapine-fluoxetine combination and quetiapine are the only registered agents available in South Africa for the treatment of Bipolar Depression.

The efficacy of Olanzapine-fluoxetine combination in terms of response rate and standard difference as compared to placebo has been shown to be superior in extrapolated meta-analysis superiority random effects model (NNT 1.8 - 4). Olanzapine-fluoxetine has a high incidence for weight gain, NNH 6.

In contrary, the current agents, lithium or valproate, display higher NNTs, however their propensity for harm is less.

Recommendations:

Olanzapine with fluoxetine be added to the Adult-Level STG/EML for the first line treatment of Bipolar Depression.

References

[1] Frye MA. Bipolar Disorder - A focus on Depression. The New England Journal of Medicine. 2011;364:51-59.

[2] National Department of Health. Adult Hospital Level - Standard Treatment Guideline and Essential Medicines List 2012.

[3] Geddes JR et.al. Treatment of bipolar disorder. Lancet. 2013; 381:1672-1682.

[4] National Institute for Health And Care Excellence (NICE). Bipolar disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care. September 2014.

[5] Selle V, et.al. Treatments for Acute Bipolar Depression: Meta-analysis of Placebo-controlled, Monotherapy Trials of Anticonvulsants, Lithium and Antipsychotics. Pharmacopsychiatry. 2014;47:43-52.

[6] Ketter TA. Balancing benefits and harms of treatments for acute bipolar depression - Review. Journal of Affective Disorders. 2014. 169;S1:S24-S33.

[7] Tohen M, et. al. Efficacy of Olanzapine and Olanzapine-Fluoxetine Combination in the Treatment of Bipolar I Depression. Arch Gen Psychiatry. 2003;60:1079-1088.

[8] Geddes JR, et. al. Long-term Lithium Therapy for Bipolar Disorder: Systematic Review and Meta-analysis of Randomised Controlled Trials. American Journal of Psychiatry. 2004; 161: 217-222.

[9] Smith LA. et. al. Valproate for the treatment of acute bipolar depressio: Systematic review and meta-analysis. Journal of Affective Disorders. 2010; 112 (1-2): 1-9.