Web-appendix 3:
Detailed algorithm for the treatment of Bipolar disorder

1. Treatment of acute mania/hypomania

First step:

- Discontinue treatment with antidepressants
- In rapid cycling patients start with aripiprazole or quetiapine monotherapy. In non-psychotic cases valproate is also an option, but the therapist should take into consideration the previous history of psychotic features in making the choice.
- In non-rapid cycling patients start with aripiprazole, cariprazine, paliperidone, quetiapine or risperidone monotherapy. Valproate and asenapine monotherapy are first choice only if psychotic features are not present. The therapist should take into consideration the previous history of psychotic features in making the choice.
- If mixed features are present (concomitant depressive symptoms), then start with quetiapine or risperidone monotherapy.
- If a full blown mixed episode according to DSM-IV criteria is present, then start with combination of olanzapine plus valproate or maybe lithium
- If the patient is already under one of the above 'first step' monotherapy or under combination therapy of any kind and response is unsatisfactory, switch into another 'first step' monotherapy.
- In case the personal history of the patient suggests this is not an option, proceed to next step and switch to the closest second step treatment option.

Second step:

- In rapid cycling patients prefer olanzapine or lithium monotherapy
- In non-rapic cyclers use monotherapy with haloperidol, lithium, olanzapine or ziprasidone or combination treatment of lithium or valproate with aripiprazole, haloperidol or olanzapine. Lithium combination with allopurinol* is also an option. Another combination is valproate plus an FGA.
- If psychotic features are not present, this step could also include monotherapy with carbamazepine or the combination of valproate plus celecoxib*, but the therapist should take into consideration the previous history of psychotic features in making the choice.
- If mixed features are present (concomitant depressive symptoms), then the choice should be olanzapine monotherapy
- If a full blown mixed episode according to DSM-IV criteria is present, then the choice should be monotherapy with olanzapine, aripiprazole or carbamazepine.

Third step:

- Combination treatment of lithium or valproate with quetiapine or risperidone
- If a full blown mixed episode according to DSM-IV criteria is present, then the choice should be valproate monotherapy

Fourth step:

- Apply ECT on top of pharmacological treatment
- Monotherapy with chlorpromazine, pimozide or tamoxifen.
- Combination of lithium or valproate plus tamoxifen or the combination of risperidone or oxcarbazepine plus lithium.
- If a full blown mixed episode according to DSM-IV criteria is present, then the choice should be OFC or ziprasidone monotherapy.

Fifth step:

- Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist. ECT if not applied earlier

Not recommended:

- Monotherapy with eslicarbazepine, gabapentin, lamotrigine, licarbazepine, TMS, topiramate, verapamil
- Combination therapy of lithium or valproate plus paliperidone, ziprasidone, gabapentin or topiramate, carbamazepine plus Free and Easy Wanderer Plus (FEWP) and the combination of allopurinol plus a mood stabilizer (other than lithium) or an FGA (other than chlorpromazine or haloperidol). Also not recommended medroxyprogesterone plus a mood stabilizer.
- If mixed features are present (concomitant depressive symptoms), monotherapy with aripiprazole, carbamazepine, cariprazine, haloperidol, lithium, tamoxifen, valproate or ziprasidone are not recommended.
- If a full blown mixed episode according to DSM-IV criteria is present, then lithium or quetiapine monotherapy and haloperidol, risperidone or celecoxib plus a mood stabilizer and the combination of olanzapine plus lithium are not recommended
- Valproate is not suitable for women of child bearing age.

Note:

* no wide clinical experience

Recommendation of not to use a treatment option is based on the efficacy and safety of this specific treatment option on the clinical characteristics of acute mania. However, an agent or treatment modality which is otherwise not recommended during the acute phase could be added if a specific reason is at place (e.g. starting with lamotrigine early because of a depressive predominant polarity in order to prevent future depressive episodes or topiramate for weight reduction etc.)

2. Treatment of acute bipolar depression

First step:

- Start with quetiapine or lurasidone
- Consider CBT as add-on to medication and according to the patient preference and to availability. Never consider CBT as monotherapy

Second step

- Olanzapine monotherapy or OFC
- Combine a mood stabilizer with lurasidone, modafinil or pramipexole

- Lithium plus lamotrigine, or pioglitazone*
- If rapid cycling is present in BD-I start with valproate, in BD-II with lithium
- If not rapid cycling and BD-II start with escitalopram or fluoxetine monotherapy
- For the treatment of comorbid anxiety add paroxetine, quetiapine, valproate or lurasidone, and consider Mindfulness based interventions as add-on to these agents

Third step

- Valproate, aripiprazole, imipramine, phenelzin or lamotrigine monotherapy
- Lithium plus L-sulpiride

Fourth step

- Start with tranylcypromine or lithium monotherapy
- Venlafaxine preferably in combination with an antimanic agent
- Armodafinil or ketamine in combination with a mood stabilizer
- Lithium plus fluoxetine or lamotrigine
- Carbamazepine plus Free and Easy Wanderer Plus (FEWP)
- Levothyroxine (L-T4) plus a mood stabilizer
- Lithium plus oxcarbazepine

Fifth step:

- ECT
- Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist

Not recommended:

- Monotherapy with donepezil, paroxetine (except for comorbid anxiety), ziprasidone, gabapentin and TMS
- Combination of any mood stabilizer with agomelatine, paroxetine, ziprasidone, bupropion, celecoxib, levetiracetam, lisdexamfetamine, risperidone or pregnenolone
- Memantine plus lamotrigine
- Lithium plus aripiprazole, donepezil, or imipramine
- Risperidone or ziprasidone for concomitant anxiety

Note:

* no wide clinical experience

Some agents may put the patient at a higher risk to switch (e.g. antidepressants or stimulants). In spite of the 'monotherapy' recommendation it is at the therapist's discretion to add an antimanic agent as a prophylactic measure since, for most of these agents and contrary to common believes, the data are negative or equivocal for switching.

3. Treatment during the maintenance phase

First step:

- If predominant polarity is manic start with lithium, aripiprazole, olanzapine, paliperidone, quetiapine or risperidone (including RLAI) monotherapy
- If predominant polarity is depressive or no predominant polarity can be assumed, start with quetiapine or olanzapine monotherapy
- If mixed episodes are frequent, start with olanzapine or aripiprazole plus a mood stabilizer
- In rapid cycling patients start with lithium monotherapy
- For all cases consider CBT or psychoeducation as add-on to medication on the basis of clinical judgement of the therapist and according to the patient preference and to availability. Never consider CBT or psychoeducation as monotherapy

Second step:

- Add lithium on the first step option
- Lithium plus carbamazepine
- Quetiapine plus lithium or valproate
- If depressive polarity is present add fluoxetine or lamotrigine

Third step:

- Add valproate or carbamazepine on second step treatment
- If not in place, add risperidone LAI on current treatment if manic episodes keep emerging
- Add N-acetylcysteine

Fourth step:

- If manic episodes keep emerging add an agent which has proven efficacy against acute mania no matter whether it has proven maintenance efficacy. Consider haloperidol.
- Consider lithium plus lamotrigine.
- If depressive episodes keep emerging add an agent with proven efficacy against acute bipolar depression no matter whether it has proven maintenance efficacy. Consider adding venlafaxine

Fifth step:

- Consider any combinations from steps 1-4 which have not been tried
- Consider maintenance ECT
- Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist
- Consider IPSRT as add-on to medication on the basis of clinical judgement of the therapist and according to the patient preference and to availability. Never consider IPSRT or psychoeducation as monotherapy

Not recommended:

- Adding memantine or perphenazine on a mood stabilizer
- Aripiprazole plus lamotrigine or valproate
- Lamotrigive plus valproate

- Lithium plus lamotrigine, imipramine or oxcarbazepine.