



Clinical Recommendations for Treatment of Bipolar Disorder for Hong Kong

(Version: May, 2009)

Objectives of Treatment

- Rapid control of symptoms especially agitation, impulsivity, aggression, suicidality and psychotic features
- Regain pre-morbid functioning
- Establish maintenance regime and prevention of relapse or switch

NB: The following recommendations are mainly based on the most updated Canadian guidelines, with valuable comments from advisors of SABAD & fellow psychiatrists, though other sources are sometimes referred

Specific Issues for Hong Kong

- When there are a lot of choices for 1st-line treatment, 2nd-line or 3rd-line recommendations will usually be omitted
- These recommendations are tailored for specialists and also primary care doctors with special interests in management of bipolar patients
- Thus there is a word of caution in the use of some medications with toxic side-effects, especially by non-specialists
- The rational choice of medication should also be based also on tolerability, symptomatology, comorbidities & other relevant factors

Limitations of Guidelines

- Not absolute, especially those arrived by consensus
- May not be applicable in some clinical situations (e.g. with atypical & complicated cases)
- Individual differences in response
- May restrict or discourage innovations
- Conflicts exist between different guidelines
- Cultural variations e.g. dosage, economic restrictions, etc. should be considered

Levels of Evidence

- Levels of evidence:
 - Level 1: meta-analysis or replicated Double-Blind Randomised Controlled Trial that includes a placebo
 - Level 2: at least 1 DB-RCT with placebo or active comparison
 - Level 3: prospective uncontrolled trial with 10 or more subjects
 - Level 4: anecdotal reports or expert opinion
- First line Rx: level 1 & level 2 evidence plus clinical support for efficacy & safety
- Second line Rx: level 3 evidence or higher plus clinical support for efficacy & safety Ref: CANMAT 2007

Baseline Assessment

- History:
 - personal history (s/- of hypomania, substance abuse);
 - family history (bipolar disorders, CVD, DM)
- Physical exam: body weight, blood pressure, waist circumference, BMI
- Laboratory tests:
 - CBC, RFT, metabolic screening (fasting glucose & fasting lipid profile);
 - pregnancy test if doubtful

I. Acute Mania

- Criteria for manic episode: 1 week elevated or irritable mood (with marked impairment of functioning); with or without psychotic features
- Criteria for hypomania: at least 4 days of elevated, expansive or irritable mood (not severe enough to cause marked impairment of functioning)
- 3 or more manic symptoms
- Mixed states
- Rapid cycling

Acute Manic or Mixed Episode

- **1st line Rx**
- Lithium*, divalproate, *chlorpromazine**, olanzapine, risperidone, quetiapine (XR), aripiprazole or ziprasidone
- Lithium* or divalproate + risperidone, quetiapine, olanzapine or aripiprazole
- Switch to another or combination of two 1st-line agent
- Parental injections of atypical antipsychotics can be used for very severe mania or agitation*

NB: Monotherapy with gabapentin, topiramate, lamotrigine, verapamil, tiagabine, OR risperidone or olanzapine + carbamazepine not recommended

* *To be used with caution, especially by non-specialists*

II. Acute Bipolar Depression

- More disabling than mania
- Misdiagnosis as unipolar depression
- Two types: bipolar I & II depression

Acute Bipolar I Depression

- **1st-line Rx**
- Lithium*, OR
- Lamotrigine; OR
- Quetiapine (XR); OR
- Lithium* or Divalproate + SSRI; OR
- Olanzapine + SSRI; OR
- Lithium* + divalproate; OR
- Lithium* or divalproate + bupropion
- Switch to another choice in 1st-line

NB: Gabapentin or aripiprazole monotherapy not recommended

** To be used with caution, especially by non-specialists*

Acute Bipolar II Depression

- **1st-line:**
- Quetiapine
- **2nd-line:**
- lithium*; OR lamotrigine; OR Divalproate; OR
- lithium* or divalproate + antidepressants; OR
- lithium* + divalproate; OR
- atypical antipsychotics + antidepressants**;

** To be used with caution, especially by non-specialists*

*** Careful longitudinal history taken before antidepressant monotherapy*

III. Maintenance Treatment

- At least 2 episodes of mania or depression (including current episode) within 2 years (Grof & Angst)
- 2 major episodes of mania &/or depression, irrespective of frequency (Goodwin & Jamison)
- Single manic episode or both hypomanic and depressive episode. Also consider past suicidal attempts, psychotic episodes and functional disability associated with episodes (NIMH consensus development panel guidelines)
Adopted from Australian & New Zealand Clinical Practice Guideline (2004)

NB: There is currently a trend to provide maintenance therapy after one single **severe** episode.

Maintenance Therapy for BP I

- Lithium*; OR
- Lamotrigine (limited efficacy for preventing manias); OR
- Divlaproex; OR Olanzapine; OR Quetiapine; OR
- Quetiapine + lithium/valproate; OR
- Risperidone long-acting injection
- Adjunctive Risperidone long-acting injection (prevent mania); OR
- Adjunctive aripiprazole

NB: Monotherapy with gabapentin, topiramate, antidepressants not recommended

**To be used with caution, especially by non-specialists*

Maintenance Treatment for BP II

- **1st-line:**
- Lithium*; OR lamotrigine
- **2nd-line:**
- Divalproate; OR
- Lithium* or divalproate or atypical antipsychotic + antidepressant; OR
- Combination of 2 of following: Lithium*, lamotrigine, divalproate or atypical antipsychotic

NB: Gabapentin not recommended

** To be used with caution, especially by non-specialists*

Maintenance of Rapid Cyclers

- **1st-line:**
- Lithium*; OR
- Divalproate**
- **2nd line:**
- Lithium* + divalproate; OR
- Lithium* + carbamazepine; OR
- Lithium* or divalproate + lamotrigine; OR
- Olanzapine

NB: Antidepressants not recommended

* *To be used with caution, especially by non-specialists*

** *Not fully confirmed to-date*

IV. Special Patient Population (1)

- Pregnant women
 - No evidence of risk: clozapine
 - Risk cannot be ruled out: gabapentin, topiramate, olanzapine, risperidone, quetiapine, ziprasidone
 - Positive evidence of risk: lithium, divalproate, carbamazepine, lamotrigine
 - Electro-convulsive therapy may be considered

NB: Omit medications if possible in first trimester because of teratogenic risk

Special Patient Population (2)

- Breast feeding women
 - With caution: lithium (with monitoring for complete blood picture or CBP, hypotonia, psoriasis, lethargy & cyanosis in infants)
 - Possible: divalproate, carbamazepine (monitoring for hepatotoxicity & haematological toxicity especially in infants)
 - Unknown: benzodiazepine, SSRI, antipsychotics, lamotrigine

Special Population (3)

- Paediatric patients
 - Lithium; OR
 - Divalproex; OR
 - Olanzapine, quetiapine, ziprasidone, risperidone*, aripiprazole
 - Quetiapine + divalproex
 - *FDA for aged 10 or above
 - Oxycarbazepine not effective

NB: Evidence based on at least 1 double-blind RCT with placebo or active comparator

V. Rx of Psychiatric Comorbidities

- Panic disorder: Selective Serotonin Reuptake Inhibitors (SSRIs) better than tricyclic antidepressants (TCAs)
- Obsessive-compulsive disorder (lower prevalence than Major depressive disorder): SSRIs better than clomipramine
- Body dysmorphic disorder: SSRIs + atypical antipsychotics
- Substance abuse (poor compliance): Serotonin Reuptake Inhibitors (SRIs +/- atypical antipsychotics)

Rx of Physical Comorbidities

- Obesity, metabolic syndrome & diabetes mellitus: avoid those medications which greatly increase body weight
- Hypertension & cardiac disorder: not contraindicated except for Lithium given diuretics
- Migraine: may be aggravated by SRIs

NB: Beware of drug-drug interactions between psychotropics & medications prescribed for medical diseases

Drugs That Do Not Work (So Far)

- **Bipolar mania**
- Level 1 evidence: lamotrigine, topiramate
- Level 2 evidence: gabapentin, verapamil, Lithium or divalproate + ziprasidone; adjunctive lamotrigine
- **Bipolar depression**
- Level 2 evidence: gabapentin

Psychosocial Therapies

- Often as adjunct to pharmacotherapy
- Psychoeducation
- Cognitive behaviour therapy (CBT)
- Interpersonal psychotherapy (IPT)
- Interpersonal & Social Rhythm Therapy (ISRT)

NB: Beware of burden of care on caregivers

Electro-Convulsive Therapy

- 2nd line for acute mania
- Otherwise last resort
- especially for psychotic depression, acute mania with delirium, catatonia or stuporose
- Fast effect if strong suicidal risk
- Medications still needed most of the time
- Pregnancy, when medications are not suitable or contra-indicated

Importance of Monitoring of AED

- Carbamazepine: serum level q3 months (17-50umol/l); liver function test q3-6 months; complete blood picture q3-6 months; sodium & electrolytes q3-6 months
- Valproate: serum level q3 months (300-700umol/l); liver function test q3-6 months; complete blood picture q3-6 months
- Lithium: serum level on day 5 & every dose change until 2 within therapeutic range; then q3 months (**NICE**: ≥ 0.8 mmol/l, less efficacy for 0.6-0.8); calcium level, thyroid stimulating hormone & electrolytes, renal function test q6-12 months

Discontinuation of Long Term Rx

- Following discontinuation of medicines, the risk of relapse remains, **even after years of sustained remission.**
- Discontinuation of any medicine should normally be tapered over at least 2 weeks and preferably longer
- Relapse to mania is an early risk of abrupt lithium discontinuation.

NB: Discontinuation of medicines should not be equated with withdrawal of services.

Consult or Refer

- Consult or refer to senior colleague or specialist when there is
 - No clinical improvement, frequent relapses, or worsening of mental condition after adequate trial of 1 (or at most 2) 1st-line medications: adequate dosage for an adequate period of time (4 to 8 weeks)
 - Danger to self or to others (include offences)
 - Complicated by substance abuse, personality disorders, eating disorders, etc.
 - Unmanageable physical comorbidity

Conclusion

- The above recommendations are for guidance only
- Clinical judgment (with reasons) remains the key element in management
- Not to be distributed without prior approval from SABAD
- The present version would be updated from time to time & is available at the SABAD's website:
<http://www.sabad.org.hk>
- Feedback from users of these clinical guidelines are welcome

Highlights of UK NICE Guidelines (2006)

- Caution in diagnosis of mania in prepubertal children
- Concerns about use of valproate in women of reproductive potential (risk of polycystic ovary)
- Highlights diabetes/metabolic problems with olanzapine
- But recommends lithium, olanzapine & valproate for maintenance
- Ref: www.nice.org.uk

Key References

- Yatham LN, Kennedy SH, Schaffer A et al (2009) Canadian Network for Mood & Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009, *Bipolar Disorders*, 11, 225-255
- Royal Australian & New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Bipolar Disorder. *Australian & New Zealand Journal Psychiatry*, 2004, 38, 280-305