Clinical Recommendations for Treatment of Bipolar Disorder for Hong Kong

(Version: August, 2010)
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, rapid cycling 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 number 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 or higher evidence 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)
  – Cigarette & alcohol intake
  – Pregnancy & contraception (women of childbearing age)

• Physical exam: blood pressure, body weight, waist circumference, BMI

• Laboratory tests:
  – CBC, electrolytes, RFT, LFT, metabolic screening (fasting glucose & fasting lipid profile) & ECG;
  – TFT & pregnancy test if clinically indicated
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 is monotherapy with:
• Lithium*, sodium valproate, *chlorpromazine*, olanzapine, risperidone, quetiapine (XR), aripiprazole or ziprasidone
• Lithium* or sodium valproate + 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 sodium valproate + SSRI; OR
- Olanzapine + SSRI (especially fluoxetine); OR
- Lithium* + sodium valproate; OR
- Lithium* or sodium valproate + 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 sodium valproate; OR
• Lithium* or sodium valproate + antidepressants; OR
• Lithium* + sodium valproate; OR
• Atypical antipsychotics + antidepressants**;

NB:
*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)


NB:
There is currently a trend to provide maintenance therapy after one single severe episode.
Maintenance Therapy for BP I

• Lithium*; OR
• Quetiapine; OR
• Lamotrigine (limited efficacy for preventing manias); OR
• Divlaproex; OR Olanzapine; 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:
• Sodium valproate; OR
• Lithium* or sodium valproate or atypical antipsychotic + antidepressant; OR
• Combination of 2 of following: Lithium*, lamotrigine, sodium valproate or atypical antipsychotic

NB:
Gabapentin not recommended
*to be used with caution, especially by non-specialists
Maintenance of Rapid Cyclers

1st-line:
• Lithium*; OR
• Sodium valproate**

2nd line:
• Lithium* + sodium valproate; OR
• Lithium* + carbamazepine; OR
• Lithium* or sodium valproate + 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, sodium valproate, carbamazepine, lamotrigine
  – Electro-convulsive therapy may be considered

NB:
Omit medications if possible in first trimester because of teratogenic risk; abrupt withdrawal runs the risk of relapse
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: sodium valproate, carbamazepine (monitoring for hepatotoxicity & haematological toxicity especially in infants)
  – Unknown: benzodiazepine, SSRI, antipsychotics, lamotrigine

**NB:**
Minimum effective dose is needed, avoid polypharmacy, and breastfeed before taking medications
Medications During Breastfeeding

- Valproate & carbamazepine are usually considered safe (though side-effects in infants have been reported)
- Lithium should not be prescribed
- Other anticonvulsants not recommended because of insufficient data
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 sodium valproate + 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 contraindicated

NB:
Preferably done in hospital, with assistance from an anesthesiologist
Monitoring AED (1)

• Carbamazepine: serum level q3 months (17-50umol/l); liver & renal function tests q3-6 months; complete blood picture q3-6months (then annually); review oral contraceptive efficacy

• Valproate: serum level q3 months (300-700umol/l); liver function test q3-6 months; complete blood picture q3-6 months; enquire menstrual changes for women of reproductive age q3months for 1st year (then annually)

NB:
2 levels to establish therapeutic dose (separated by 4 weeks for CPZ)
Monitoring AED (2)

- Lithium: serum level at steady state (>5 days of starting) until 2 within therapeutic range*; at steady state after every dose change; then q3 months & as clinically indicated
- Calcium level, thyroid stimulating hormone & renal function test q6-12 months
- Weight q6-12 months
- *NICE: ≥0.8 mmol/l, less efficacy for 0.6-0.8

NB:
If CPZ + lamotrigine: concern over skin eruptions; if CPZ + valproate: advice on bone health
Serious side-effects of AEDs

- **Boxed warning: Lithium: neurotoxicity**
- **Valproate**: hepatotoxicity, pancreatitis, teratogenicity
- **Carbamazepine**: rash**, blood dyscrasia
- **Lamotrigine**: rash**

**NB:**
- *caution in childbearing women, should provide contraceptive advice*
- **advise to avoid use of new perfumes, detergents or other household chemicals, etc.*
Monitoring Atypical Antipsychotics

• Personal & family history of cardiac & metabolic problems
• Weight, blood pressure q3m
• Fasting glucose & lipid profile q3-12m, then annually
• ECG if indicated (QTc)*
• Prolactin level if indicated

NB:
If on clozapine: check CBP regularly; olanzapine can interact with cigarette smoking
*normal value: <430 (male); <450 (female)
Use of Antidepressants

- Not useful for BP I or psychotic depression
- Maybe useful for BP II depression, perhaps as an adjunct to mood stabilizers
- Risk of rapid cycling
- Risk of hypo/manic switch still controversial
- AD of increasing risk: SSRIs < NDRI < SNRIs & TCAs
- Close monitoring of mood change needed
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

- 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](http://www.nice.org.uk)
Key References


• Ng, F, Mammen, K, Wilting, I et al (2009) the ISBD consensus guidelines for the safety monitoring of bipolar disorder treatments. *Bipolar Disorders*, 11, 559-595