Clinical Recommendations for Treatment of Bipolar Disorder for Hong Kong 2013

Version: March 2013
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 or 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 (CR or ER), olanzapine, risperidone, quetiapine (IR or XR), aripiprazole, ziprasidone, asenapine, paliperidone ER
- Lithium* or sodium valproate + risperidone, quetiapine, olanzapine, aripiprazole, asenapine
- switch to another or combination of two 1st-line agent
- Parental injections of atypical antipsychotics can be used for very severe mania or agitation*

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

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

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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 (IR or 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, aripiprazole, ziprasidone monotherapy; adjunctive ziprasidone or levetiracetam not recommended

* to be used with caution, especially by non-specialists
Acute Bipolar II Depression

1st-line:
• Quetiapine (IR or XR)

2nd-line:
• lithium*; OR lamotrigine; OR sodium valproate;
• lithium* or sodium valproate + antidepressants; OR
• lithium* + sodium valproate; 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)


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
- Valproate; OR
- Olanzapine; OR
- Risperidone long-acting injection; OR
- Aripiprazole

Adjunctive lithium or valproate, quetiapine, risperidone long-acting injection (prevent mania), ziprasidone, aripiprazole

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

NB: Monotherapy with gabapentin, topiramate, antidepressants not recommended
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

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

• Olanzapine OR
• Ziprasidone; OR
• Adjunctive risperidone
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

- 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
  - Valproate; OR
  - Olanzapine, quetiapine, ziprasidone, risperidone*, aripiprazole
  - Quetiapine + divalproex
  - Oxycarbazepine not effective

*FDA for aged 10 or above

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 tricyclics 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

• 2\textsuperscript{nd} 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

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 q3-6 months (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 q3 months 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**

* 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

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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: 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
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