Society for Advancement of Bipolar Affective Disorder
雙 相 情 緒 學 會

Clinical Recommendations for Treatment of Bipolar Disorder for Hong Kong 2013

Version: March 2013

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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 sever 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

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 levetiracetaim 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)

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
- 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*, lamotrgine, 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

- 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

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****

*** 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: 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 (2013) 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 2013, *Bipolar Disorders*, 15, 1-44
- 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
- Royal Australian & New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Bipolar Disorder. *Australian & New Zealand Journal Psychiatry*, 2004, 38, 280-305