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Stepwise treatment of acute bipolar depression

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Key Message:

Those with a bipolar disorder can experience psychotic, melancholic or non-melancholic depressive episodes, arguing against positioning *'bipolar depression'* as an entity and thus for condition-specific management. While the use of antidepressant drugs has long been controversial, we argue for their need and judicious use.

1 INTRODUCTION

One of the most controversial mood disorder management topics is how to manage bipolar depression, as evidenced by varying guidelines and, in particular, whether antidepressants should be prescribed. In relation to the latter, the first issue is that of efficacy while the second issue is their potential 'cost' in that they may induce switching (into a hypo/manic state) or the induction of a mixed state and/or also worsen the long-term pattern of the disorder. Both issues are worthy of consideration before generating a framework of recommended treatment model.

2 GUIDELINE RECOMMENDATIONS CONSIDERING EFFICACY OF AND CONCERNS ABOUT ANTIDEPRESSANTS IN MANAGEMENT

We recently published an analysis of evidence-based guidelines auspiced by nine professional organizations, addressing the management of bipolar depression and published over the 2002-2015 period.[1] The guidelines were published by the Royal Australian and New Zealand College of Psychiatrists (hereafter referenced as RANZCP), the American Psychiatric Association (APA, 2002 and 2005), the Department of Veterans Affairs and Department of Defence Management (VA/DoD), World Health Organization (WHO), British Association for Psychopharmacology (BAP), the National Institute for Health and Care Excellence (NICE), Canadian Network for Mood and Anxiety Treatments (CANMAT), Japanese Society for Mood Disorders (JSMD) and the World Federation of Societies of Biological Psychiatry (WFSBP) bipolar depression guidelines.

(Table 1 about here)

Table 1 provides a summary of their recommendations for managing specifically bipolar depression. Recommendations range from minimalistic (e.g. WHO simply recommending an antidepressant plus lithium or valproate) to extensive (e.g. CANMAT), and reflect differing models (e.g. severity, stepped or sequencing) and strategies (e.g.

monotherapies versus combination, and primary versus augmentation). There is a weighting towards offering a 'mood stabiliser' (most commonly lithium) and/or an atypical antipsychotic (most commonly quetiapine and olanzapine).

In regards to prescribing an antidepressant, WFSBP includes fluoxetine as a first-line strategy, BAP recommends certain antidepressant classes if the depression is of moderate severity, APA (2002) nominates an antidepressant in conjunction with lithium, JSMD includes an antidepressant as a combination strategy, VA/DoD recommends an antidepressant only if augmentation of base therapies fail, while RANZCP recommends an antidepressant as a later strategy and for antidepressant monotherapy to be avoided in the treatment of bipolar I depression. CANMAT lists antidepressants as a possible third-line strategy, however a 2018 update to these guidelines suggests that SSRIs may be used as adjunctive second-line treatments.[2]

Only three organizations consider bipolar II disorder (BP II) in addition to managing 'bipolar depression' generally. In such considerations, APA (2005) favoured quetiapine monotherapy as a first-line therapy while BAP states that lamotrigine is "more feasible." The 2018 CANMAT update[2] recommended quetiapine as the first-line medication for bipolar II depression, and lithium, lamotrigine, sertraline and venlafaxine as well as adjunctive bupropion, as second-line treatments. WFSBP judged that there was greatest evidence for quetiapine monotherapy and pramipexole plus lithium or valproate as a first-line strategy and, as second-line options, there to be less "rigorous" evidence for valproate, venlafaxine, citalopram and antidepressant monotherapies.

There is some consistency across the guidelines (in prioritising putative mood stabilisers and atypical antipsychotic medications above antidepressants in terms of relative efficacy), but the wide inclusion of antidepressants argues for this class of drugs as being efficacious and hence clinically salient. Inconsistencies across the guidelines limits any generation of a 'meta-consensus' model for managing bipolar depression and its bipolar I and II sub-types.

The WFSBP guidelines note several limitations to guidelines addressing the management of bipolar depression, including the controversial status of antidepressants in managing such states, that most of the pertinent trials of lithium were *"methodologically questionable"* (p. 93), and that *"…there is no choice of first step in treating bipolar depression that produces unequivocal results"* (p 88).

Varying recommendations in relation to the use of antidepressants are evident, including not being listed at all (e.g. NICE), being first-line options (e.g. WFSBP), an augmentation strategy (e.g. VA/DoD), a combination strategy (CANMAT) and a second-line combination strategy (e.g. RANZCP). In terms of antidepressant class, SSRIs are the most common class recommended. While a tricyclic option is listed by WFSBP (step 2) and CANMAT (third-line), others (i.e. BAP, JSMD, VA/DoD) specifically state that a tricyclic should *not* be used, and several (i.e. BAP, RANZCP) also state that an SNRI should *not* be used if possible, or used with caution where necessary (RANZCP). Fluoxetine (in combination with olanzapine) is listed by several (i.e. WFSBP, NICE, APA 2005).

A key concern about the use of antidepressants is their risk of inducing switching (see Pacchiarotti et al.[3] for a detailed overview). A series of meta-analyses have quantified low switch rates in the order of 5-10% in those with bipolar depression, while the risk has been shown to be distinctly less likely in those with a bipolar II compared to a bipolar I condition.

This does not, however, reject the possibility that varying antidepressant drug classes may have differing propensities for inducing switching. It may be that the potency of an antidepressant in relieving bipolar depression correlates with the drug's switching potential. In meta-analyses , the switch rate for tricyclics appears higher than for all other antidepressant drugs, while several studies have indicated a higher risk with the serotonergic/noradrenergic agent venlafaxine. Thus, true antidepressant-induced switching may be relatively uncommon and be somewhat dependent on the antidepressant drug class, but in practice be an acceptable risk subject to patients being warned about the possibility.

3 CONSIDERATIONS INFLUENCING OUR RECOMMENDATIONS

Before offering management suggestions it is reasonable to first ask "what is bipolar depression?" and here we argue against it being considered as a homogeneous entity. A percentage of bipolar I patients experience psychotic depressive episodes. Multiple studies of bipolar I and II patients (see review[4]) indicate that, for those with non-psychotic episodes, their depressive clinical features correspond more closely to melancholic depression than to non-melancholic depression. Melancholia has been variably positioned as a more 'severe' depression or as a categorical 'type'. We favour the latter model[5] and with over-represented features including an anhedonic and non-reactive depressed mood, anergia, mood and energy being worse in the morning and impaired concentration, and with episodes often autonomous and, if not, disproportionately severe in relation to any stressors. It is, however, also important to note that those with a bipolar disorder are as likely – or even more likely – as

those in the general community to experience episodes of reactive (non-melancholic) depression as a consequence of environmental stressors. Thus, rather than consider the treatment of 'bipolar depression' per se, our treatment recommendations offer condition-specific recommendations rather than providing a 'one size fits all' management model.

Several general principles guide our management recommendations. First, most patients presenting with an episode of bipolar depression are experiencing severe distress and may be at risk of suicide or self-harm. Not to prescribe an antidepressant and/or an antipsychotic and simply wait for the current or any newly prescribed mood stabiliser monotherapy medication to take effect may extend that risk. Thus, we are not positioning antidepressants as a monotherapy but as a first-line strategy prescribed in conjunction with a mood stabiliser. Second, there appears to be a gradient of effectiveness across differing antidepressant drug classes for managing unipolar melancholia. In relation to the principal medication classes, based on our clinical experience the TCAs appear more effective than the SSRIs, while the SNRIs appear intermediate between those two classes. It is therefore not unreasonable to assume such a gradient in managing bipolar patients with a melancholic depressive episode. Third, even if there is a higher risk of switching with the use of broader-action antidepressants, we suggest that this risk may be adequately handled by so warning the patient and reviewing progress at regular intervals to observe for any switching or mixed states. Fourth, we are persuaded that use of an antidepressant with an atypical antipsychotic (AAP) drug (especially one with strong dopaminergic propensities) is beneficial and supported by most treatment guidelines. However, rather than maintain the AAP once the patient's depression has remitted, we recommend trying to cease the AAP, viewing it best as having provided a "jump lead to a battery" type of response, and only in a minority of cases requiring continuation. In other words akin to the role of ECT in the treatment of melancholic or psychotic depression.

4 OUR RECOMMENDATIONS

In table 2 we offer recommendations in relation to bipolar disorder, and in practice weight lithium for bipolar I disorder and lamotrigine where mania is less common as the ongoing mood stabiliser, judging the possible need for hospitalization and ECT being highest for those with psychotic depressive episodes, and recommending broad-action antidepressant classes for all scenarios apart from episodes of situational non-melancholic depression.

(Table 2 about here)

5 CONCLUSION

We detail the limited consistency in evidence-based guidelines auspiced by several professional organizations in managing bipolar depression. In putting forward management recommendations, rather than consider 'bipolar depression' as an entity,we structure recommendations in relation to its differing presentations.

Clearly, the most controversial component is the recommendation of broad-action antidepressants such as SNRIs and TCAs when these are usually rejected in guidelines reflecting concerns about switching and the induction of mixed states. As noted, however, we judge them as more effective than SSRIs and believe that concerns about their use should be respected by warning the patient of their risks and reviewing progress at frequent intervals. We do not recommend such classes if the patient had previously – or is currently experiencing - a distinctive mixed state. We recommend that, if an antipsychotic drug is used in the acute phase, attempts to taper it should be made once the patient is euthymic but respect the reality that a percentage require a maintenance antipsychotic agent (in addition to other medications) to maintain euthymia. Thus, the choice of any ongoing antipsychotic drug should take into account medium and long-term side-effects.

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GP has spoken at meetings or been on advisory boards for the following companies: Servier, Lundbeck and Otsuka. GSM has received grant or research support from AstraZeneca, Eli Lilly, Organon, Pfizer, Servier and Wyeth; has been a speaker for AstraZeneca, Eli Lilly, Janessen-Cilag, Lundbeck, Pfizer, Ranbaxy, Servier and Wyeth; and has been a consultant for AstraZeneca, EliLilly, Janssen-Cilag, Lundbeck and Servier. PB has received consultation fees, sponsorship and speaker fees from Servier; is a member of the advisory board for

Lundbeck, Eli Lilly, AstraZeneca and Janssen; has received speaker fees from Lundbeck, AstraZeneca and Janssen; and has received funding for a clinical trial from Brain Resource Company and Ferring Pharmaceuticals. MH has received grants and personal fees from Servier; personal fees from Janssen-Cilag, Lundbeck, Eli Lilly, Hahn, Sequiris, Bionomics and Mundipharma. RJP uses software for research at no cost from Scientific Brain Training Pro. AS has been a speaker for Servier, Lundbeck and Otsuka; has equity in CNSDose LLC and ABC Life Pty Ltd.

REFERENCES

1. Parker GB, Graham R, Tavella G. Is there consensus across international evidence-based guidelines for the management of bipolar disorder? *Acta Psychiatr Scand.* 2017;135:515-26.
2. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord.* 2018;20:97–170.
3. Pacchiarotti I, Bond SJ, Baldessarini. RJ et al. The ISBD Task force report on antidepressant use in bipolar disorders *Am J Psychiatry*, 170, 1249-1262.
4. Parker G. The clinical diagnosis of bipolar depression, in Zarate JR CA, Manji HK (eds). Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis, and Pharmacotherapy. Switzerland: Springer; 2016.
5. Parker G, Bassett D, Outhred T, et al.. Defining melancholia: A core mood disorder. *Bipolar Disord.* 2017;19:235-7.

TABLE 1 Guidelines for managing bipolar depression as prepared by nine organizations and with references to antidepressant drugs highlighted in red text. (See Parker et al. 2017).

World Federations of Societies of Biological Psychiatry (WFSBP)	**Canadian Network for Mood and Anxiety Treatments (CANMAT)**
Step 1: Quetiapine, **fluoxetine**, lamotrigine, olanzapine, valproate, carbamazepine, lithium. **Step 2**: After 4 weeks, if partial response, change dose and consider psychotherapy; if no response, switch to another monotherapy or consider a combination therapy (olanzapine-fluoxetine; lamotrigine + lithium; modafanil + base	**First-line**: Monotherapy: Lithium, lamotrigine, quetiapine, quetiapine XR Combination therapy: Lithium or valproate or olanzapine + **SSRI** **Second-line**: Monotherapy: Valproate or lurasidone Combination therapy: Quetiapine + **SSRI**;

medication; and 9 others (eg N-acetylcysteine + lithium; **tranylcypromine** + base treatment; **venlafaxine** + base treatment; **imipramine** + lithium). **Step 3:** If noimprovement after 4 weeks trial augmentation strategy. **Steps 4 and 5:** Trial varying combinations	adjunctive modafanil; lithium or lamotrigine + valproate or + lurasidone. **Third-line:** Monotherapy: Carbamazapine, olanzapine, ECT Combination therapy: lithium + carbamazapine or pramipexole; lithium + **venlafaxine** or a **MAOI**; lithium or valproate or AAP + **TCA**; lithium or valproate or carbamazapine + **SSRI** or + lamotrigine; quetiapine + lamotrigine
British Association for Psychopharmacology (BAP) **Severe:** Consider ECT. [If psychotic 'consider adding' an antipsychotic]. **Moderate:** Quetiapine or lamotrigine; **SSRI** or **other antidepressant** but not **TCA** or **SNRI**. **Mild:** Quetiapine or lamotrigine **If BP I:** Add anti-manic agent (lithium, valproate or an AP) + evidence-based psychotherapy.	**US Veteran Affairs and Department of Defence (VA/DoD)** **Monotherapy:** First-line: olanzapine, lamotrigine or lithium. Several other second-line treatments. **Combination:** Lithium + lamotrigine **If augmentation required:** Use **SSRI**, **SNRI**, **buproprion** but not a **TCA.**
National Institute for Health and Care Excellence (NICE) Inprimary care (and if mild in secondary care) provide an evidence-based psychotherapy. If moderate to severe in secondary care provide	**Japanese Society of Mood Disorders (JSMD)** **Monotherapy:** Quetiapine, lithium, olanzapine or lamotrigine. **Combination therapy:**

<table>
<tr><td>(i) olanzapine + fluoxetine or quetiapine, or (b) olanzapine or lamotrigine monotherapy.</td><td>Lithium + lamotrigine, or antidepressant drug (not TCA) + ECT</td></tr>
<tr><td>American Psychiatric Association (APA)
Monotherapy:
Lithium or lamotrigine
Combination:
Lithium + an antidepressant + (if severe of psychotic) an antipsychotic.
2005 update:[4]
olanzapine + fluoxetine, quetiapine or lamotrigine.</td><td rowspan="2">Royal Australian and New Zealand College of Psychiatrists (RANZCP)
Psychosocial adjunctive to pharmacotherapy.
Step 1:
A SGA (quetiapine, lurasidone or olanzapine) or a mood stabilizer (lithium, lamotrigine or valproate).
Step 2:
One SGA + one mood stabilizer, or an antidepressant (with caution) added to a SGA or mood stabilizer.
Step 3:
ECT
Step 4:
TMS or an adjunctive (other) medication.
For BP II:
Same but favour quetiapine or lamotrigine and antidepressants may be used with caution (avoid TCAs and SNRIs).</td></tr>
<tr><td>World Health Organization (WHO)
Antidepressant + lithium or valproate</td></tr>
</table>

XR = extended release, ECT = electroconvulsive therapy, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin–norepinephrine reuptake inhibitor, TCA = tricyclic antidepressant, MAOI = monoamine oxidase inhibitors, AP = antipsychotic, SGA = second-generation antipsychotic, TMS = transcranial magnetic stimulation.

When managing psychotic depression

Step 1:

- First consider need for hospitalization.
- Next, commence lithium or, if already on lithium but at a sub-optimal level, adjust dose to aim to approximate a 0.8 mmol/L level. If lithium is unacceptable, consider commencing valproate.
- Simultaneously, commence an antidepressant (SNRI or TCA).
- Simultaneously, commence an antipsychotic with strong dopaminergic profile (e.g. olanzapine).

Step 2:

- If no better consider an alternative antidepressant (e.g. MAOI) or ECT.

Step 3:

- Once euthymic, taper and cease antipsychotic (if unsuccessful, consider lurasidone or another atypical antipsychotic with a low side-effect profile). Maintain the lithium if beneficial and seek to taper and cease the antidepressant. Implement psychosocial interventions.

When managing melancholic depression

Step 1:

- Commence lithium or, if already on lithium but at a sub-optimal level, adjust dose aiming for approximately a 0.8 mmol/L level. Consider valproate if lithium unacceptable.
- Simultaneously, commence an antidepressant (SNRI or TCA).

TABLE 2 Recommendations for managing BPI depression.

Step 2:

- If not improved after a week, commence an antipsychotic with strong dopaminergic profile (e.g. olanzapine).

Step 3:

- If no response consider an alternative antidepressant (e.g. MAOI). Consider ECT.

Step 4:

- Once euthymic, taper and cease antipsychotic (if unsuccessful change to maintenance lurasidone or another atypical antipsychotic with a low side-effect risk). Maintain lithium if beneficial and seek to taper and cease the antidepressant.

When managing non-melancholic depression

Step 1:

- Establish whether due to psychosocial factors and, if so or likely, trial non-drug strategies such as psychotherapy or counselling.

Step 2:

- Review mood stabiliser and consider an antidepressant if psychotherapy and other non-drug strategies fail.