



Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

McGorry, PD;Ratheesh, A;Berk, M;Conus, P

Title:

'Is "early intervention" in bipolar disorder what it claims to be?' Malhi et al

Date:

2018-05-01

Citation:

McGorry, P. D., Ratheesh, A., Berk, M. & Conus, P. (2018). 'Is "early intervention" in bipolar disorder what it claims to be?' Malhi et al. *Bipolar Disorders*, 20 (3), pp.181-183. <https://doi.org/10.1111/bdi.12641>.

Persistent Link:

<https://hdl.handle.net/11343/283935>

PROF. PATRICK D MCGORRY (Orcid ID : 0000-0002-3789-6168)

DR. MICHAEL BERK (Orcid ID : 0000-0002-5554-6946)

PROF. PHILIPPE CONUS (Orcid ID : 0000-0002-5832-1910)

Article type : Debate

“Is “early intervention” in bipolar disorder what it claims to be?”

Malhi et al.

**Patrick D. McGorry,^{1,2} Aswin Ratheesh,^{1,2} Michael Berk,¹⁻⁵ Philippe
Conus⁶**

1. Orygen, The National Centre of Excellence in Youth Mental Health, Parkville, Australia
2. Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia
3. Department of Psychiatry, University of Melbourne, Melbourne, Australia
4. IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, Australia
5. Florey Institute for Neuroscience and Mental Health, Melbourne, Australia

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/bdi.12641](https://doi.org/10.1111/bdi.12641)

This article is protected by copyright. All rights reserved

6. Treatment and Early Intervention in Psychosis Program (TIPP), Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital (CHUV), Lausanne, Switzerland

Correspondence: Patrick McGorry, Orygen, The National Centre of Excellence in Youth Mental Health, 35 Poplar Road, Parkville, VIC 3052, Australia.

Email: pat.mcgorry@orygen.org.au.

Word count: 1279

One of the drivers of Malhi et al's¹ pessimistic perspective on early intervention for those meeting criteria for bipolar disorder (BD) is the Hippocratic principle of "first do no harm". Paradoxically, if their overly cautious prescription were followed, then more harm would likely occur through continuing neglect of young people with a substantial, immediate need for care.² Their conclusions derive from two familiar misunderstandings of the clinical staging model. Firstly, they have restricted their gaze within the silo of BD in considering how early intervention could be offered. Clinical staging in psychiatry uses a transdiagnostic framework, acknowledging the heterogeneity and overlap of early clinical phenotypes. Secondly, they misrepresent staging as requiring inevitable progression, rather than each stage connoting only a risk for progression with remission possible at any stage.

The authors observe that the early and late stage bipolar phenotype has become blurred, and that there is a dimensional or porous aspect to the silo, a truth with a wider significance. Mental disorders are not static, sharply defined illnesses with separate aetiologies and courses, but rather overlapping syndromes that develop in

stages, with common risk factors and mechanisms. The latter explains why most psychological interventions are transdiagnostic, and why clinicians often use medications “off-label”, challenging fictional discrete diseases reinforced by the DSM, FDA and pharmaceutical industry. Development of new diagnostic concepts, an important target of early intervention, will define new ways to inform treatment selection. Daily human experience involves periodic and sometimes intense, mercurial changes in mood, perception, salience and behaviour. Where prominent and sustained, they can be discerned as subclinical “microphenotypes”, which wax and wane, interact sequentially or become confluent, and may mature or stabilise towards pure or hybrid “macrophenotypes.” The manic syndrome is just one of these microphenotypes. Unlike current psychiatric diagnoses, staging recognises that single or multiple persistent microphenotypes can justify a need for care on their immediate merits as well as the risk for progression to more familiar macrophenotypes. Such models ensure that interventions are proportional to both current need *and* the risk of future extension of the clinical phenotype and its consequences, while balancing risks of treatment according to the principle “first do no harm”.

The heterogeneity of BD is advanced by the authors as an argument that staging is unlikely to apply, but, seen in a transdiagnostic context, the opposite is the case. Staging acknowledges such phenotypic heterogeneity. The authors search for an elusive specificity too early. From a transdiagnostic perspective, early intervention addressing factors such as substance abuse, lifestyle and stress management is already feasible as Duffy³ acknowledges, despite paradoxically agreeing with the authors’ cautionary stance. Within the silo the authors inhabit, much of their review might appear to make sense and even lend weight to their conclusions. But it represents a map of the old diagnostic world. There is a new world to explore and embrace.

Fluid early microphenotypes represent a potentially pluripotential gateway to a range of later single and comorbid macrophenotypes. The fact that we cannot precisely predict the ultimate destination is no argument for withholding

interventions, which are immediately useful and potentially pre-emptive. The authors' caution is largely based on this argument. Yet they concede that such early intervention involving transdiagnostic psychosocial treatment *is* acceptable, though strangely attempt to use its relative scarcity as an opposing argument. Duffy³ supports their caution, yet offers a sensible staged/stepped care map for early intervention involving early transdiagnostic psychosocial intervention, and later proportional use of medications.

The authors raise the spectre of premature medication use to support their case.¹ One can agree that more research is needed to guide such treatment, especially medication timing and sequence. However they fail to offer a balanced discussion of the risks of antidepressant treatment versus withholding it in young people, especially in those with more severe, persistent depressive syndromes, unresponsive to psychosocial interventions. The central issue for BD is the potential for antidepressants to unmask a latent vulnerability to hypomania, mania or initiate cycling. The principle "first do no harm" dictates that it would be harmful to recommend withholding antidepressants from young people with severe depression lest they might be one of the 25% possessing this vulnerability. Further research can help identify those presenting with depression at greater risk of transition to mania. Meanwhile, covering all such cases with mood stabilizers, would clearly involve unnecessary polypharmacy.

Duffy's³ approach of careful monitoring for activation in young people treated for severe depression with antidepressants seems logical, though better prediction of switching is the ultimate goal, an area where progress has been made.⁴ Some studies have also sought to test the extension into earlier stages of mood stabilisers, which have proven utility in later ones. Evidence so far is too preliminary to support this, and it may prove to be an overreach of treatment specificity. Mechanisms, as reflected in biomarkers, may differ and evolve through illness stages and biotherapies may also be differentially effective or harmful at different stages. These are testable hypotheses, data from which will sharpen clinical decision-making. This uncertainty is used as a straw man by the authors, but it is by no means a fatal flaw

as Duffy³ acknowledges. The authors channel staging when they state that “research involving pharmacotherapies should be refined to focus on perhaps more novel agents that target the potentially unfolding pathophysiology, rather than encouraging the earlier commencement and administration of potent medications designed to treat more chronic and severe phases of illness.”^{1(p632)}

Furthermore, it is not a fair criticism of early intervention to invoke the current behavior of many primary care physicians and some psychiatrists who may use certain medications prematurely. More effective implementation of early intervention and staging guidelines, and developing a stronger evidence base will limit such clinician behaviours, which in no way justify abandonment of early intervention efforts. Similarly, if some clinicians were overly aggressive in early stage cancer patients, the value of early diagnosis and staged care would not be undermined.

Lastly, denying treatment to people with early stage illness will miss the critical window for preventing the neuroprogressive cascade that occurs in a subset of people. Many people begin their trajectory with normal or even superior cognition and normal neuroimaging. As with other macrophenotypes like schizophrenia, there is abundant evidence that with repeated episodes, cognitive and neuroimaging changes emerge, and that the period of greatest risk is in the immediate vicinity of the first episode.⁵ Optimal therapy during this window may prevent neuroimaging, cognitive and functional changes. The maxim “first do no harm” therefore needs to incorporate the clear risk of harm from inactivity during this critical period.

In the end, the authors do not seem fully convinced by their own arguments. There are enough pointers to the current feasibility of early intervention in the authors’ recommendations that, had they not imprisoned themselves within the bipolar straightjacket, they actually might endorse a transdiagnostic approach to early intervention that could include the bipolar target. Duffy³ makes this even clearer. In casting doubt on a constrained version of early intervention and putting the brakes on, they have not considered the risks of consigning the large proportion of

untreated and undertreated cases of emerging mental disorders to continued neglect, largely driven by poor resourcing and design of mental health care. However, if we provide timely access and expert care to all young people with mental ill-health on the basis of their needs but with an eye on the future, this will mean that the minority who later fit the bipolar macrophenotype will be in better shape. This is early intervention within a staging and stepped care model. Further research could move us to truly pre-emptive care, based on a greater transdiagnostic predictive capacity linked to mechanisms and biotherapies.

Acknowledgements

PDM is supported by a NHMRC Senior Principal Research Fellowship (1060996). MB is supported by a NHMRC Senior Principal Research Fellowship (1059660).

References

1. Malhi GS, Morris G, Hamilton A, Outhred T, Mannie Z. Is “early intervention” in bipolar disorder what it claims to be? *Bipolar Disord*. 2017;19:627-636.
2. Vieta E, Salagre E, Grande I, et al. Early intervention in bipolar disorder. *Am J Psychiatry*. 2018; in press doi: 10.1176/appi.ajp.2017.17090972.
3. Duffy A. Early intervention in bipolar disorders: where we are now and need to go next. *Bipolar Disord*. 2018; in press doi:10.1111/bdi.12599.
4. Ratheesh A, Cotton SM, Davey CG, et al. Pre-onset risk characteristics for mania among young people at clinical high risk for psychosis. *Schizophr Res*. 2017; in press doi:10.1016/j.schres.2017.04.036.
5. Berk M, Post R, Ratheesh A, et al. Staging in bipolar disorder: from theoretical framework to clinical utility. *World Psychiatry*. 2017;16:236-244.