Conference Report:
Research Priorities for Bipolar Disorder

9th & 10th November 2015
The Royal Society
6-9 Carlton Terrace, London, SW1Y 5AG

Executive Summary

• Research issues, opportunities and challenges concerning Bipolar Disorder were discussed during a two-day meeting of international experts and research funders. The goal of the meeting was to develop consensus recommendations on research priorities for Bipolar Disorder.

• Common themes emerged across discussions throughout the conference:
  ▪ The need to make better use of evidence and treatment options so as to improve care and outcomes.
  ▪ The need to exploit comprehensive data collection and use of datasets and technologies to help gain a better understanding of the disorder and how to best define, diagnose and manage it.
  ▪ The need for more research with high-risk populations, co-morbid conditions and children and young people.
  ▪ A greater focus on international collaborative efforts is required to make more efficient use of scarce resources and help accelerate progress.

• Arising from these themes and discussions, the group made the following recommendations:
  1. Develop an international bipolar data science collaborative to inform research and practice
  2. Invest in research targeting children, young people and other specific populations at risk of Bipolar Disorder
  3. Support the practical application of research toward strategies that will improve care for Bipolar Disorder in the near-term
Background

Bipolar disorder represents a major unmet health need. With a lifetime prevalence of between 1 - 2%, the condition is relatively common and has high visibility in popular culture. Yet, there is a lack of clarity about the development and course of the disorder or how to best treat it. Some of this may be due to overlapping symptomology with unipolar depression and psychosis. Another factor has been our inability to find a treatment that is better than lithium, a drug that has been in use for over 50 years but is not favoured by many patients. The lack of effective and acceptable treatment options has important consequences: it is not a coincidence that people with bipolar disorder are among those of highest risk of suicide.

Bipolar research is underfunded. The recent MQ report on mental health research funding found that bipolar disorder research received only 1.5% of the total UK mental health research expenditure, which is already low by any standards. The paucity of bipolar research is mirrored in other countries, and suggests a need for development of a comprehensive strategy to address this major global unmet need.

To better understand and evaluate research opportunities for bipolar disorder, MQ convened experts from a variety of research disciplines to discuss questions that could lead to the development of research strategies by funders. The meeting was co-hosted by the UK Medical Research Council (MRC), the National Institute of Health Research (NIHR) and the Wellcome Trust. We believe this to be the first such meeting on bipolar disorder for nearly two decades.

This note provides a summary of conference discussions and findings. The agenda and a list of attendees can be found in Appendix 1. For more information about how this conference relates to the MQ research programme, please visit the MQ website at https://www.mqmentalhealth.org/.

Introduction to Sessions and Discussions

The conference was organised around seven topics deemed most relevant to research that will benefit patients and families:

1. What do we mean by “bipolar disorder?”
2. Early identification
3. Risk factors and opportunities for secondary prevention
4. Genetics and other biomarkers
5. Patient, family and carer priorities
6. Better treatments and interventions
7. Improving health outcomes

The format included brief presentations by investigators working in each area, followed by discussion amongst the group. In each case, the dialogue that ensued was enriched with the individual and collective experience in the room. And while there were differences in opinion between investigators, they were most often attributable to the differing cultures and/or healthcare systems of the investigator.
Encouragingly, there was general agreement on the major issues discussed by the group, and a set of common and overarching research themes emerged from the meeting.

The three common themes were:

1. **The need to make better use of evidence and treatment options so as to improve care and outcomes.**
2. **The need to exploit comprehensive data collection and use of datasets and technologies to help gain a better understanding of the disorder and how to best define, diagnose and manage it.**
3. **The need for more research with high-risk populations, co-morbid conditions and children and young people.**

In addition, there was universal support for more international collaboration across research questions, a consistent theme that cuts across all mental health diagnoses.

A discussion of the common themes that emerged during the seven topic sessions is provided below.

**A Closer Look at Common Themes**

1. **The need to make better use of evidence and treatment options so as to improve care and outcomes**

   **Current treatments**

   It is well documented that lithium is one of the most successful medications for treating bipolar disorder (BD), due to its effect in mood stabilisation and preventing depressive episodes and suicide. Despite its efficacy, there is a marked difference in use across regions and only 10%-40% of patients who would benefit receive treatment. This is partly due to concerns about adverse events, but also reflects a lack of understanding of the risks and benefits of the drug amongst the professional community. There is a clear case for advocacy and education about its benefits. There is also a need for further research into reducing known side effects, and investigating which groups are most responsive to the drug. The International Group for the Study of Lithium Treated patients (IGSLI) is seeking more resources to resolve these questions.

   To date, there has been a notable lack of success in development of new drugs for BD; there was a general view that this is more due to gaps in our understanding which lead in turn to development failures, rather than new medicines failing due to a lack of effect. In the longer-term, basic research into genes, risk factors and comorbidity is needed to develop new treatment targets. In the mid-term, tractable targets such as sleep, daily energy rhythms, fatigue and cognition should be more fully explored. And in the near-term, it is possible that existing drugs may be “re-purposed” toward bipolar disorder and there are several teams working in this direction, also in need of resourcing.

   The evidence-base for psychological treatments is not that much more encouraging. NICE recommends use of talking therapies for depressive symptoms and also family-
focused care, but the evidence for other therapeutic approaches is weak. There is an apparent need for further research in this area.

Therapies tailored to the individual and to the ‘stage’ of disorder are required, as is more evidence on combination therapy (using both drug and psychological treatments) and on new ways to deliver interventions – such as mobile technology. Much more work is needed on functional outcomes of treatment, a primary concern of patients and families.

**Issues in health care delivery**

The group flagged many issues in health care provision that exist within and across nations and health systems. There was agreement that addressing these issues will not only improve care and support for patients, but also facilitate better research. These include:

- Need to acknowledge uncertainty regarding diagnosis, diagnostic criteria, and the definition of the illness
  - Uncertainty leads to a propensity for patients to receive many different diagnoses prior to being eventually diagnosed and successfully treated for BD
  - The diagnostic odyssey in turn undermines trust in treatments and in Health Care Providers (HCPs).
- Lack of knowledge amongst front-line HCPs – both in primary care and psychiatry.
- Challenges in gathering high quality, real world, primary and secondary care data, collected over a long period of time (known as longitudinal data)
- Need for quality data to support research efforts to:
  - Develop predictive biomarkers
  - Define what works for whom and when
- Lack of continuity of care, as exemplified by:
  - Patient and family frustration at having to repeat the history of their illness as they move through the system or geographically
  - Difficulty transitioning from primary to secondary services
  - ‘Losing’ patients in transition from child to adult services
- Need to restructure care models to support:
  - Access to and delivery of personalised care
  - Addressing physical health issues
  - Preventing suicide or early mortality
- Need for early uptake and adoption of evidence-based innovations

The group acknowledged that many of the issues identified by the bipolar community are symptomatic of larger and more systemic problems of our current health care models. However, there are a number of areas where substantial improvement in outcomes and satisfaction could be realised through engagement of health care providers, development of resources for a more systematic approach to care and elevating the importance of BD amongst clinical and translational researchers to address the issues outlined above.
2. The need to exploit comprehensive data collection and use of datasets and technologies to help gain a better understanding of the disorder and how to best define, diagnose and manage it.

**Importance of data – old and new**

Researchers agreed that the advent of new data technologies and low computing costs represent a great opportunity to generate new insights into BD. Harnessing the power of such ‘big data’ has the potential to inform virtually all areas of the disorder: the definition, diagnosis, early detection and treatment, understanding symptoms, cycles and different types of BD and its causes. Population data can help improve care; data collected from patients over a long period of time were highlighted as particularly valuable, especially when investigating early signs, comorbidity and the impact of services/interventions.

It was noted that there is a plethora of existing data arising from clinical practice and prior research that can be utilised from several different countries, the UK and Denmark in particular, as they have invested in the resources needed to analyse the health records of individual patients over time. Many datasets exist in isolation: there is value in grouping these data for larger studies and/or linking individual data for richer in-depth analyses. This is not without challenges, due to issues concerning patient consent, data quality and compatibility of data. However, it was unanimously agreed that it would be worth the effort.

The need for collection of new data was also emphasised. There are common and persistent barriers to this, including professionals' ability to accurately identify BD and its symptoms, data capture, capacity limitations, politics and human error.

Despite these challenges, there was agreement that there is a need for a major push in this area. Resolving the issues around 'big data', best practices in data collection and political barriers will require expert voices such as those who attended the conference.

**Opportunities through technology**

Momentary or time-stamped data collection via devices or wearable digital technology is an exciting new avenue of research that can help answer the mathematical need for more real-world data to understand BD. Devices such as smart watches and phones can monitor self-reported mood and symptoms, and can even transfer the data directly to researchers and health care providers.

Several ongoing projects are exploring and piloting this technology, such as the Conbrio studies at Oxford University and the ClinTouch Project at the University of Manchester. Preliminary findings at this stage suggest that this type of data is providing new insights into BD on sleep and energy patterns (biological factors), mood patterns (psychological factors) and social or environmental factors involved in the development and maintenance of BD. More research and development is needed in order to assess its potential and benefits.

**Importance of self-monitoring and patient buy-in**

Self-monitoring and understanding was also highlighted as a key area of data collection, notably during the presentation by a patient representative and trustee for
Bipolar UK. This perspective reinforced many of the topics discussed over the two days, including the significance of patients building an understanding and acceptance of their condition and playing an active role in managing their symptoms. Sleep, daily routine, family support, and medication management were identified as critical self-management opportunities that can be further validated by longitudinal (self) monitoring. The need for recognition of the lifetime course of BD was highlighted: symptoms and episodes change and evolve throughout a patient’s lifetime, and may be further impacted by life circumstances.

**Development of a data science research platform**

The group expressed strong interest in developing an international data science platform to support in-depth study of BD. A key factor in this recommendation is the growing recognition that there are insufficient study populations in any one research group or country capable of delivering meaningful insight into complex problems like BD.

A comprehensive research platform would be an invaluable resource to fully characterise BD. Retrospective and prospective analysis of biological, physiological, clinical, social, imaging, genetic and behavioural data is greatly needed to inform both research and practice.

A model for such a platform already exists in the form of the Dementia Platform UK (DPUK), a collaborative group of researchers and funders seeking to inform drug development for dementia. While still in its formative stages, the DPUK aims to use administrative, cohort and research data to help accelerate findings. The Psychiatric Genomics Consortium (PGC) is an excellent example of a successful international data collaboration. The PGC is in search of well-characterised patients to support future work – a BD data platform would be an important resource for such studies.

**3. The need for more research with high-risk populations, co-morbid conditions and children and young people.**

**Children and young people**

It is clear that for most people with BD, symptoms emerge in adolescence (before age 25) and there is an urgent need to learn more about how the disorder develops so that we can plan earlier and more effective interventions.

While BD is twice as common as autism or schizophrenia, our understanding of the emergence and development of the disorder is limited. BD is highly heritable, yet genetic risk factors are not specific enough to serve as biomarkers. The interaction of environmental factors should be studied as significant life-events may aggravate symptoms and potentially advance the condition. Important family information and clinical data about the course of symptom development is all too often lost during the transition from child to adult services.

Importantly, not all risk or signature behaviours lead to BD – for example, less than half of children with mood disorder symptoms go on to develop it. There are specific challenges to understanding the disorder in children, as not enough is known about
mania (which occurs rarely in children) or how more commonly seen conduct disorders factor into the development of BD.

Children and young people (through age 25) are now one of the highest priority demographics for research in BD and other mental health conditions. It is important to know more about how symptoms begin to present and how they diverge into specific conditions. More needs to be learned about how early interventions (e.g. psycho-social therapies) work, whom to target for such interventions and when.

**High-risk populations**

Other patient subtypes were identified as priorities for investigation, including individuals who are children of parents with BD, or individuals who are:

- Suicidal
- Have concomitant drug and alcohol use
- Have comorbidity with other physiological and/or mental health conditions
- Are at risk for illness post-childbirth

People with co-occurring disorders are frequently excluded from research studies due to perceived sensitivities or the complexities of their illnesses. As co-morbidities are common in BD, it is crucial that these individuals are not excluded from research going forward. Indeed, many previous studies could be rerun with these populations and ways of systematically including them in future studies need to be developed.

In summary, research in these unique patient populations will not only be critical to advancing our understanding of the disease, but also to our ability to plan and conduct well-designed trials that will improve patient outcomes in the real world.
Summary of Meeting Priorities

We are grateful to conference participants for their enthusiastic participation in discussions and generation of questions for the priority-setting exercise. The list of questions considered by the group is provided as Appendix 2. It offers a more detailed look at the nature and direction of the questions raised during individual session. We recommend it to funders considering investment in bipolar research.

The goal of this conference was to develop a set of priorities for bipolar disorder research for use by researchers, funders and the public advocates. The priorities agreed to by conference participants are clear, concise and actionable. They are:

1. **Develop an international bipolar data science collaborative to inform research and practice.** This will aid in:
   - Deepening our understanding of Bipolar Disorder and how it relates to other mental health conditions
   - Development of better definitions and diagnostic criteria
   - Development of biomarkers
   - Targeting and stratifying patients for treatment studies

2. **Invest in research targeting children, young people and other specific populations at risk for bipolar disorder.** This will help us learn:
   - How mental health conditions emerge in childhood and adolescence and differentiate into distinct conditions like bipolar disorder
   - If early intervention can delay onset of bipolar symptoms and/or prevent progression and severity
   - What treatments work best for whom and when should they be used

3. **Support the practical application of research toward strategies that will improve care for bipolar disorder in the near-term.** This will help us:
   - Make better use of current treatment strategies
   - Clarify treatment recommendations for health care providers
   - Work with front line health care providers to ensure uptake and adoption of best practices in bipolar management

Next Steps

It was agreed that “deliverables” of the Conference should include efforts to share the discussion more broadly with researchers and research funders. There was interest in following up with a paper for publication – MQ’s Director of Research, Sophie Dix is currently preparing a manuscript with the conference co-chairs. There was also strong support for more engagement with the patients, carers and healthcare systems (e.g. the NHS) on research needs.

In follow-up to this discussion, MQ will:
- Circulate this report to conference participants
- Post the report on the charity website, at which time recommendations will be shared with other research funders
- Circulate the report to UK and International Mental Health Research Funders Alliance
- Ask other research funders to aid in the dissemination effort
The conference priorities will be revisited again in summer 2016 by the MQ research team and others when the results of the Bipolar Priority Setting Project (Bipolar PSP, a James Lind Alliance project) on patient and carer priorities for research will be reported. As co-supporters of this project, MQ, NIHR, the Oxford Biomedical Research Centre, and the Leeds and York Partnership Foundation Trust are committed to disseminating findings broadly. In this vein, MQ is pursuing discussions with research groups worldwide around the establishment of global collaboratives though the International Alliance of Mental Health Research Funders.

Finally, MQ can confirm that the findings of this conference will inform development of future research programmes of the charity. Indeed, funding streams already in development on Data Science and Young People’s Mental Health were clearly identified as topics of high importance by delegates. The organisation has already begun incorporating bipolar recommendations into these programmes as well as its established initiatives: PsylImpact and Research Leadership.

**In Closing**

The MQ Conference on Research Priorities for Bipolar Disorder represents a ground-breaking step forward in efforts to identify gaps and promote research in the field. When taken together with patient, family and carer input from the Bipolar PSP project, there is new voice – and momentum – in the bipolar research community. Should additional funding be secured, these will surely galvanise efforts to address questions and foster innovation in bipolar disorder research around the world.

We are grateful to the delegates for their commitment to ensuring vibrant and productive discussion throughout the two-day course of events. And we want to especially recognise the planning committee – Allan Young, John Geddes, Ian Goodyer, David Micklowitz, Jemma Kwint, Jo Jenkinson, Raliza Stoyanova and Sophie Dix - for their leadership and generosity in making the event a success.

*With many thanks to the Bernard Lewis Family Charitable Trust for their invaluable support in making this conference possible.*
APPENDIX 1 – Conference Agenda

Conference on Research Priorities for Bipolar Disorder
9th & 10th November 2015
Wolfson Suite, The Royal Society
6-9 Carlton Terrace, London, SW1Y 5AG

Agenda

DAY 1 - Monday, 9th November

Toward a Better Description and Definition of Bipolar Disorder

9:00 Registration and continental breakfast

9:30 Welcome and introductions
Sophie Dix – MQ: Transforming Mental Health

9:45 Session 1 – What do we mean by “bipolar disorder”? 
Chair – Ian Goodyer, University of Cambridge

9:55 Overview of diagnostic criteria – Patricia Suppes, Stanford University
10:05 Longitudinal, multidimensional assessment of mood instability – John Geddes, University of Oxford
10:15 What can population data tell us? – Argyris Stringaris, King’s College London
10:25 Discussion

10:55 BREAK

11:15 Session 2 – Early identification of bipolar disorder
Chair – Ian Goodyer, University of Cambridge

11:25 Children & adolescents – Eric Youngstrom, University of North Carolina
11:40 Bipolar in the perinatal period – Ian Jones, Cardiff University
11:50 Discussion

12:20 LUNCH
13:20  **Session 3 – Risk factors & opportunities for secondary prevention**  
Chair – John Geddes, University of Oxford

13:30  Building resilience in the family context – David Miklowitz, University of California, Los Angeles
13:40  Sleep and circadian rhythms – Ellen Frank, University of Pittsburgh
13:50  Co-morbidity and substance abuse – Anne Lingford-Hughes, Imperial College London

14:00  Discussion

14:30  **BREAK**

14:50  **Session 4 - Genetics and other (bio)markers**  
Chair - Allan Young, King’s College London

15:00  Genes and epigenetics of Bipolar Disorder – Gerome Breen, King’s College London
15:10  Biomarker development for mood disorders – Sidney Kennedy, University of Toronto
15:20  Cognitive factors in bipolar disorder – Guy Goodwin, University of Oxford

15:30  Discussion

16:00  **Session 5 – Patient, family and carer priorities**  
Chair – Sophie Dix, MQ: Transforming Mental Health

16:10  The James Lind Alliance bipolar research priority setting partnership – Tom Hughes, Leeds and York NHS Foundation Trust
16:20  Lived experience perspectives – Jeremy Clark, Bipolar UK

16:30  Discussion

17:00  **Summary of the day**  
Cynthia Joyce, MQ: Transforming Mental Health

17:15  **Close Day 1**

18:30  **Drinks reception followed by dinner**  
The Terrace Grill and Bar at Le Meridien Hotel  
21 Piccadilly, London W1J 0BH

19:30 – Dinner is served
DAY 2 - Tuesday, 10 November

Interdisciplinary Approach to Interventions for Bipolar Disorder

9:00 Coffee and Tea

9:15 Session 6 - Better treatments & interventions
Co-chairs – Allan Young, King’s College London
David Miklowitz, University of California, Los Angeles

9:25 Repurposing compounds – Allan Young, King’s College London
9:35 What can we do to make lithium treatment better? – Michael Bauer, Dresden University of Technology
9:45 Improving psychological treatments – Steve Jones, Lancaster University
9:55 Combining treatments in Bipolar & high risk populations – Matthias Schwannauer, The University of Edinburgh
10:05 New targets for Bipolar Disorder – focus on mood switching – Charles Large, Autifony Therapeutics Ltd
10:15 Discussion

11:00 BREAK

11:20 Session 7 – Improving health outcomes
Chair – Richard Morriss, University of Nottingham

11:30 Care Models for Bipolar Disorder – Mark Bauer, Harvard Medical School
11:40 Impact of comorbidity on treatment outcomes – Richard Morriss, University of Nottingham
11:50 Suicide interventions and targets – Keith Hawton, University of Oxford
12:00 Discussion

12:30 LUNCH

13:30 Session 8 - Summing up & next steps
Chair – Alan Young, King’s College London

13:40 Prioritizing recommendations
14:30 Recommendations to funders
15:15 Next steps

15:45 Thank you and meeting close
Sophie Dix & Cynthia Joyce, MQ: Transforming Mental Health

16:00 Close Day 2
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APPENDIX 2 – Questions for Group Discussion

1. Validating clinical phenotypes of bipolar disorder remains a key task. What is the best way forward for validation studies?

2. How can we as a research community design and conduct studies that will improve understanding of these disorders, aid clinical practise and inform policy toward better services for patients?

3. Is this the time for large-scale prospective and longitudinal investigations of recognized behavioural signatures (may or may not be transdiagnostic)?
   a. Mood instability
   b. Sleep dysregulation/circadian rhythms
   c. Stress
   d. Substance abuse

4. Should there be concerted multi-centre efforts to build databases and conduct data driven research with existing as well as new data sets?

5. Invest in designing pragmatic trials comprising real world data (all comers, balance of evidence) to inform care.

6. Should we invest in large scale investigations of pregnant women and their offspring in prospective designs taking a vertical science approach (from mothers to molecules) within an interpersonal design (the mother infant dyad as a dual study of mood instability and affect regulation)?

7. Should we invest in large-scale longitudinal investigations of bipolar symptoms across childhood & adolescence? Enhance early diagnosis?

8. Should we invest in long-term pragmatic studies of comorbid conditions (both psychological and physical)? If so, what is the most cost-effective way to conduct these studies?

9. Can comorbidity studies inform us about underlying mechanisms in bipolar disorder?

10. Can we prevent or delay the onset of BD in high-risk groups (sleep, substance abuse, family resilience)?

11. How do we target interventions?

12. How can we deliver interventions in community health settings?

13. How can we best apply the new genetics and epigenetics techniques to bipolar disorder?

14. What is the best way we can use biomarkers in bipolar disorders research?

15. How should we further study cognition in bipolar disorder?


17. Ensure consistency of care, such that there are guidelines for diagnosis and
treatment and patients will have continuity of evidence-based care regardless of moving between providers and geographies.

18. How can we improve the use of old and new medicines for bipolar disorder? Drug repositioning; war chest of parked compounds; experimental medicine...

19. How do we run trials that keep in mind the psychosocial context of the illness when looking for biomarkers of testing new drugs?

20. To what extent is the number of prior episodes (more or less than 7) a determinant of whether patients respond to treatment?

21. Our biological markers will be more powerful if they can be linked to behavioural variables with prognostic value, but how do we achieve this? 
   a. How to implement CCMs in clinical practice? 
   b. Policy; funding and or reimbursement 
   c. System reorganization 
   d. Culture change

22. Evidence-based implementation strategies: what are the best trial designs to ensure adequate evaluation of impacts on suicidal behaviour & its prevention in bipolar?