Institution: University of Oxford		
Unit of Assessment: 4 - Psychology Psychiatry and Neuroscience		
Title of case study: Improved outcomes and suicide prevention from changes to prescribing practice in treating depression, bipolar disorder and schizophrenia		
Period when the underpinning research was undertaken: 2009-2018		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Andrea Cipriani	Professor of Psychiatry	2013 – present
John R Geddes	Head of Department of Psychiatry	1995 – present
Keith Hawton	Professor of Psychiatry	1995 – 2017
Period when the claimed impact occurred: August 2013 to December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Researchers at the University of Oxford have developed novel approaches in evidence synthesis and applied clinical research to implement evidence-based research findings into routine mental health care. For the first time they ranked evidence-based interventions using comparative effectiveness research to guide clinicians to choose the best pharmacological treatment for each patient. With a specific focus on depression, bipolar disorder, schizophrenia and suicide prevention, interventions recommended by this research are now first-line treatments in current international clinical guidelines in the UK, Australia, Canada, China, Italy, Japan, the Netherlands, Singapore and the US, leading to change in prescription patterns of psychotropic drugs. For instance, six years after their recommendation of sertraline as a first-line treatment for depression, this drug became the most commonly prescribed antidepressant in the US. The research has also reduced the negative attitudes and discrimination against people with mental health issues. A spontaneous user-originated hashtag on social media, #MedsWorkedForMe, was used by 2,669 people within 4 days of publication of a 2018 research article, to share positive stories to combat stigma associated with using antidepressants.

2. Underpinning research

Psychiatric disorders account for nearly 13% of the global burden of disease. When several treatment options are available, standard meta-analyses provide only partial information because they can only answer questions about pairs of treatments. Geddes and Cipriani were the first mental health researchers to use network meta-analysis, an innovative technique that allows the estimation of the relative effect of many treatments, one against the other, and produces ranked treatment options, even when the options are not directly compared against each other by an experimental study. Geddes collaborated with Cipriani and others to design and conduct the first full network meta-analysis conducted in the field of psychiatry. This analysis compared 12 second-generation antidepressants for major depression and found that sertraline gave the best outcomes [1].

Geddes and Goodwin at Oxford, with Cipriani and Barbui at the University of Verona, designed a subsequent network meta-analysis to investigate the effects of pharmacological interventions for acute mania in patients with bipolar disorder. Geddes contributed to the design, analysis and interpretation, and Geddes and Cipriani drafted the manuscript. Many drugs from different classes are licensed with this indication and, at that time, clinical guidelines suggested that these treatments were equally effective. Their analysis showed that this widespread notion was not true and demonstrated for the first time that two individual antipsychotics (namely, risperidone and olanzapine) were significantly more effective than all other commonly prescribed drugs for adults with acute mania [2].

Hawton and Geddes then worked in Oxford with Cipriani to design a review together that could investigate a ‘new’ effect of an ‘old’ drug, lithium, for suicide prevention. Hawton and Geddes both contributed further to acquisition of suitable data and metadata, interpretation and critical

review. During this time, Cipriani took up a post at the University of Oxford (2013). Their systematic review and meta-analysis was published in 2015 and showed for the first time that lithium is highly effective in reducing suicide risk, not only in patients with bipolar disorder, but also in those with unipolar depression, by more than 80% [3]. The University of Oxford team found that lithium may exert its specific antisuicidal effects by decreasing aggression and impulsivity. These results showed that lithium is also the best pharmacological treatment for bipolar disorder, consistent with other research carried out by Cipriani concerning the long-term effects of lithium.

Once in post at Oxford, Cipriani planned, coordinated and wrote the first network meta-analysis in child and adolescent psychiatry, published in 2016 [4]. After 5,794 citations were identified and 165 potentially eligible articles were screened, 5,260 participants were included in the analysis, who were taking one of 14 different antidepressant treatments. This study found that only one drug, fluoxetine, was effective for the acute treatment of major depressive disorder in young people [4]. All other drugs offered no clear advantage for children and adolescents and therefore were not considered suitable as routine treatment options.

Cipriani and Geddes went on to bring their expertise to the largest and most comprehensive pairwise meta-analysis of all acute-phase, placebo-controlled antipsychotic drug trials in schizophrenia, since the introduction of chlorpromazine [5]. The analysis included 167 double-blind randomised trials with 28,102 mainly chronic participants. This research, published in 2017, showed that clinicians can expect that approximately two times more patients improve when treated with antipsychotics compared with placebo. The analysis demonstrated that antipsychotics not only suppress positive symptoms but they also help social reintegration, reflected by improvements in social functioning and quality of life.

In 2018, Cipriani and Geddes designed, led and published an updated network meta-analysis on antidepressants [6] including 522 double-blind trials with overall 116,572 patients. This was the largest network meta-analysis ever carried out in medicine and it conclusively established that antidepressants are more effective than placebos. The study shows that antidepressants are more efficacious than placebo in adults with major depressive disorder and represents the final answer to a long-standing controversy about whether antidepressants work for depression. The network meta-analysis also identified significant differences between antidepressants, which are relevant to health-care economists and policy makers, clinicians, and patients. The clinical relevance of this study was maximised by focusing not only on modern antidepressants but also including the essential antidepressants then recommended by the WHO.

3. References to the research

Highlighted are Oxford researchers.

1. Cipriani A, Furukawa TA, Salanti G, **Geddes JR**, Higgins JP, Churchill R, Watanabe N, Nakagawa A, Omori IM, McGuire H, Tansella M, Barbui C. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009;373:746-58. DOI: 10.1016/S0140-6736(09)60046-5
2. Cipriani A, Barbui C, Salanti G, **Rendell J, Brown R, Stockton S**, Purgato M, Spineli LM, **Goodwin GM, Geddes JR**. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet* 2011;378:1306-15. DOI: 10.1016/S0140-6736(11)60873-8
3. Cipriani A**, Hawton K, Stockton S, Geddes JR**. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ* 2013;346:f3646. DOI: 10.1136/bmj.f3646
4. **Cipriani A,** Zhou X, Del Giovane C, Hetrick SE, Qin B, Whittington C, Coghill D, Zhang Y, Hazell P, Leucht S, Cuijpers P, Pu J, Cohen D, Ravindran AV, Liu Y, Michael KD, Yang L, Liu L, Xie P. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet* 2016;388:881-90. 10.1016/S0140-6736(16)30385-3
5. Leucht S, Leucht C, Huhn M, Chaimani A, Mavridis D, Helfer B, Samara M, Rabaioli M, Bächer S, **Cipriani A, Geddes JR**, Salanti G, Davis JM. Sixty years of placebo-controlled

antipsychotic drug trials in acute schizophrenia: systematic review, Bayesian meta-analysis and meta-regression of efficacy predictors. *Am J Psychiatry* 2017;174:927-42. 10.1176/appi.ajp.2017.16121358

6. **Cipriani A**, Furukawa TA, Salanti G, Chaimani A, **Atkinson LZ**, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, **Geddes JR**. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 2018;39:1357-1366. https://doi.org/10.1016/s0140-6736(17)32802-7

4. Details of the impact

Change in drug prescribing patterns and improvement of patients' clinical outcome

The results for the network meta-analyses and systematic reviews for depression, bipolar disorder and schizophrenia that Cipriani and Geddes with their collaborators developed in Oxford between 2009 and 2018 have had a significant impact on the treatment of these conditions in the NHS and overseas. The team's 2009 Lancet publication [1] recommended sertraline as first-line treatment for depression, and in 2015 sertraline became the most commonly prescribed antidepressant in the US, with a 22.6% increase in prescriptions, the largest increase in prescribing among all antidepressants (from less than 2,100,000 to more than 2,700,000 prescriptions/year) [A]. It has also been described as the most prescribed antidepressant in Japan [B(ii)].

In China, by 2019 more than 30,000 psychiatrists had followed recommendations for treatment of bipolar disorder [C(i)] and schizophrenia [C(ii)] that were based on findings from the University of Oxford research, directly influencing the treatment of nearly a hundred million patients in China. The Vice-Chairman of the Chinese Neurology Society wrote citing [2, 3, 4], amongst others, and confirmed that the University of Oxford reviews

> *"... have had a great impact on clinical practice in China: they have changed the prescription patterns of psychotropic drugs in our country and have improved the clinical outcome of our patients, reducing significantly the number of hospital admissions for patient with schizophrenia and reducing the length of stay for inpatients and the number of suicides and deliberate self harm for patients with bipolar disorder."* [B(iii)]

The Professor of Medicine, of Health Research and Policy, and Director, Meta-Research Innovation Center at Stanford University, cited papers including [2,3,4,6] in summarising the influence of this body of work:

> *" This powerful work has had tremendous implications for setting the guidelines of clinical practice... it has been extremely valuable also for offering tangible information on crucial questions to tens of millions of patients worldwide."* [B(i)]

Changes to guidance to treat depression, bipolar disorder and mania

The University of Oxford work in evidence synthesis [1, 2] allowed for the first time the evidence-based ranking, in order of effectiveness, of all most commonly prescribed pharmacological treatments for depression and bipolar disorder. By including in the analysis drugs that are in the WHO Model List of Essential Medicines, these rankings have greatly facilitated the real-world decision making between clinicians and patients in both primary and secondary care across the globe, and also in low and middle income countries. The Dean of Medical School, University of Toronto, wrote that [1] was *"the single most influential paper in shaping treatment guidelines and practice"* and went on to explain that, *"The more recent network meta-analyses* [on depression and bipolar disorder] *are another game-changer, as they allow extrapolation from randomized clinical trials to real world clinical settings which are compelling for many clinicians including those outside of academic settings".* [B(iv)]

The team's research-based recommendations have been included in official clinical guidelines in a number of countries, including:

- **Canada -** The Canadian Network for Mood and Anxiety Treatments (CANMAT) offers clinicians clear use recommendations for first, second, and third-line treatments, while considering the robustness of evidence and clinical relevance. The 2018 CANMAT

guidelines recommend lithium as the best treatment for acute mania, bipolar depression and maintenance treatment for bipolar disorder and suicide prevention [D], based on the results from the network meta-analyses, citing papers including [3] and corroborated by letter [B(iv)].

- **United Kingdom**: National Institute for Health and Care Excellence (NICE) guidelines on the optimal treatment of bipolar disorder (NCG 185, first released 2014) state that the network meta-analysis [2] *"... found robust evidence that several pharmacological interventions are efficacious. Furthermore, there was evidence of differential effectiveness among medications, which is a unique strength of network meta-analysis"* [E, section 6.2.4]. The results were then used as the evidence base to support specific recommendations also for the cost-effectiveness analysis: *"The interventions assessed in this economic analysis were determined by the availability of data reported in the network meta-analysis by Cipriani and colleagues, 2011"* [E, section 6.25, p125].
- **United Kingdom:** The British Association for Psychopharmacology, the largest such association in Europe, issues guidelines based on the best available evidence to aid clinical decision-making and provide information for patients and carers. Its 2016 guidelines on bipolar disorder draw on the network meta-analysis [2] in the recommendations for treating mania: *"The network was highly coherent, and so strongly supports the validity of the overall recommendation to use dopamine antagonist/partial agonists in mania"* [F, p523].
- **Australia and New Zealand**: The Royal Australian and New Zealand College of Psychiatrists Mood Disorders Clinical Practice Guidelines for treating bipolar disorder first drew on Cipriani and Geddes' work [2] in 2015, stating that, *"The choice of medications is determined by the availability of medications, the required speed of onset of action and the proposed future choice of medications (Cipriani et al., 2011)"* [G(i), p67]. Their update in 2020 cited [1,2,4,6] both in recommending 'Choice' antidepressants [G(ii), section 7.2] and those to discontinue for children and adolescents [I, box 18]. While the 2020 guidelines were in preparation, the Chair of the working group for these guidelines highlighted the role of the most recent work [4,6]:

  "Presently, the 2015 guidelines are being updated and will be published in 2020, and once again Cipriani's articles feature strongly.... In particular his most recent network meta-analyses comparing the efficacy and tolerability of antidepressants for major depression in children and adolescents and the acceptability of 21 antidepressant drugs for the acute treatment of depression in adults (2016 and 2018)." [B(v)]

Changes to guidance to treat schizophrenia

The 2017 meta-analysis [5] has been used to accurately quantify, for the first time, the magnitude of the effect of antipsychotics versus placebo in the acute treatment of schizophrenia, informing guidelines in the USA and UK.

- **USA**: The American Psychiatric Association guidelines recommend that "*patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects."* [H(i), Statement 4]. They cite [5] as one of two *"high-quality meta-analyses that examined findings from RCTs of antipsychotic medications in schizophrenia"* and conclude that *"the strength of the research evidence is rated as high in demonstrating that the benefits of treatment with an antipsychotic medication outweigh the harms..."* [H(ii) pp210-11].
- **United Kingdom**: The same meta-analysis [5] was used to inform the updated British Association of Psychopharmacology guidelines recommending pharmacological treatment of schizophrenia: *"A meta-analysis of placebo-controlled acute treatment studies in established schizophrenia found that just over 50% of participants responded to antipsychotic treatment, compared with a figure of 30% for those receiving placebo. The respective proportions for ... 'much improved' were 23% and 13%".* [I, p11]

Combating stigma about using drug treatment to manage mental health

The extensive press coverage of the 2018 Cipriani et al. study [6] led to the spontaneous #MedsWorkedForMe hashtag, used to share personal stories about how antidepressants helped them manage their mental health. In just a few hours, the 5 posts in the initial thread were retweeted 335 times, liked 1,448 times, and generated 156 replies and then retweeted 730 times. This social media activity is reflected in the study having the highest ever Altmetric score

of any psychiatry paper (4,543), and in the top 5% of all research outputs. The hashtag was a 'UK Trending Topic' in February 2018 [J(i)], and the hashtag originator went on to be interviewed by the British Medical Journal [J(ii)]. Patients sharing their positive stories were prominently featured in the extensive media coverage [K]. Example tweets in response include:

> *"I think seeing people you look up to publicly admitting to their depression helps you realise you're not alone and sharing real advice on what works for them - drugs, … - is probably one of the most powerful things someone can do."*
>
> *"The stigma which surrounds taking medication for mental illness needs to end. Mental illnesses are valid illnesses. No one should ever be made to feel shamed for taking medication."*
>
> *"Mental illnesses must be the only life threatening illnesses that medication is seen as a luxury and not a need. Antidepressants aren't 'happy pills'; they don't cure you, they just make it a bit easier to function. Stop stigmatising, these drugs can save lives."*

5. Sources to corroborate the impact

A. Luo Y et al. National Prescription Patterns of Antidepressants in the Treatment of Adults With Major Depression in the US Between 1996 and 2015: A Population Representative Survey Based Analysis. *Front. Psychiatry.* 2020;11:35. DOI:10.3389/fpsyt.2020.00035

B. Letters from (i) Professor of Medicine, Stanford University School of Medicine; (ii) Project Leader, Addictive Substance Project, Chair, Department of Psychiatry and Behavioral Sciences, Tokyo Metropolitan Institute of Medical Science; (iii) Vice-chairman of the Chinese Neurology Society & Director, Institute of Neuroscience, Chongqing Medical University; (iv) Dean of the Faculty of Medicine, University of Toronto; (v) Head of Department of Psychiatry, Royal North Shore Hospital.

C. Chinese Medical Association. (i) Guidelines for bipolar disorder in China (second edition). (ii) Guidelines for schizophrenia in China (second edition).

D. Yatham 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 disorders* 2018;20:97-170. DOI: 10.1111/bdi.12609

E. NICE Guidance CG185 (2014, updated 2018 and 2020). Full guideline, available at https://www.nice.org.uk/guidance/cg185/evidence/full-guideline-pdf-4840895629

F. Goodwin GM et al. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2016;30:495–553. DOI: 10.1177/0269881116636545

G. Malhi GS et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. (i) 2015 guidelines: *Aust N Z J Psychiatry*. 2015;49(12):1087-1206. DOI: 10.1177/0004867415617657, (ii) 2020 guidelines (first published 22 December 2020): *Aust N Z J Psychiatry*. 2021:55(1)7-117. DOI: 10.1177/0004867420979353

H. The American Psychiatric Association Practice guidelines for the treatment of patients with schizophrenia (2020), (i) summary *Am J Psychiatry* 177:9, September 2020 and (ii) Full guidelines, Appendix C: Review of Research Evidence, Pharmcotherapy, available from https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

I. Barnes TR et al. Evidence-based guidelines for the pharmacological treatment of schizophrenia: Updated recommendations from British Association for Psychopharmacology. *J Psychopharmacol* 2020;34:3-78. doi:10.1177/0269881119889296

J. (i) Twitter record of #MedsWorkedForMe as a UK trending topic, 22 Feb 2018. https://twitter.com/holly/status/966721330757414912
(ii) BMJ Blog interview with the hashtag's originator https://blogs.bmj.com/ebmh/2018/05/04/medsworkedforme-in-conversation-with-holly-brockwell/

K. BBC TV News feature and interviews 23 Feb 2019 https://youtu0oH3Pu_6oEg.be/