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Title: Falling between the cracks? The case for improved care and provision of treatment for people with first episode mania.

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Summary

The care of people with first episode mania has been overlooked in comparison to people with other non-affective psychoses, despite evidence suggesting targeted treatments may be of benefit for this patient group. In this personal view, we outline the epidemiology of first episode mania in the context of bipolar disorder in general, the natural history of mania (with emphasis on its recurrent nature), current evidence for pharmacological, psychological, service-level interventions and current guidelines for first episode mania. We note the paucity of high quality evidence for interventions in first episode mania, and the lack of agreement amongst treatment guidelines in relation to treatment-especially maintenance treatment. We suggest that, based on high morbidity and clinical need, research evidence to guide guideline development is necessary, and in the interim, clearer guidance should be given, specifically suggesting they should be looked after within first episode psychosis service, where they exist.

Word count;147 words

Research in Context

Evidence before this study

Care for people with first episode mania is not uniform across similar health systems. Very few trials have examined interventions in this patient group, despite evidence which suggests targeted interventions may be of benefit.

We highlight the need for clearer treatment guidance for people with first episode of mania, and need for targeted care for this patient group, identifying gaps in level 1 evidence.

Implications of all the available evidence

Further effort should be made to ensure optimised care of this patient group within existing services and further research is required to establish longer-term effectiveness of specific pharmacological, psychological and service-level interventions.

Search strategy and selection criteria

We searched PubMed for studies published in English from inception until 31st October 2018, using the MeSH headings ((early intervention OR first episode mania) AND bipolar disorder). This yielded 1174 results. Relevant guidelines from the last ten years were identified through manual search and examination by SJ and AR.

Added value of this study

This study highlights the factors that contribute to the health burden of first episode mania and makes suggestions for clearer treatment guidelines and further research regarding pharmacological, psychological and service-level interventions.

Introduction

There is increased awareness that psychiatric disorders may begin, evolve and are modifiable in youth. It should be noted that this increased awareness has only occurred in some centres and parts of the world (see below).

The modifiable nature of intervention is based on research over the last thirty years, examining early detection and early intervention for psychosis/first episode psychosis (FEP) services (1). Motivation for FEP services came from longitudinal studies showing improved outcomes in people with first episode schizophrenia when treatment was initiated earlier (2), either with antipsychotics (3–5), and then psychosocial interventions (6), one hypothesis being that early, and for some, sustained treatment would improve long-term outcome.

Although around 70% of those seen by these services fulfil diagnostic criteria for schizophrenia on follow-up, the criteria for entry were deliberately wide and people with affective psychosis are also included (13% bipolar disorder, 12% depression with psychosis in one cohort study)(7). This subgroup is mainly comprised of people with bipolar disorder (predominantly bipolar 1, who have experienced first-onset mania), which has strong diagnostic stability (8). More importantly, the clinical picture, and response to treatment(s) in these patients can be quite different to that in those with schizophreniform psychosis (please see Table 1).

However, specific advice for this population is often missing from most, but not all, National guidelines, some of the current recommendations being inconsistent with evidence and/or clinical practice. The objective here is to review epidemiology, clinical presentation, natural history and treatment interventions for first episode bipolar disorder, specifically first episode mania– the point of definitive diagnosis. We highlight need for targeted care for this population within existing FEP services,

earlier recognition, and targeted care within Child and Adolescent Mental Health Services (CAMHS) and generically.

Epidemiology and health burden

Prevalence estimates for bipolar disorder (BD) vary, depending on criteria and country, the WHO World Mental Health Survey estimating 0.6% for Bipolar I, 0.4% for Bipolar II, and 2.4% for bipolar spectrum disorder (9). It is worth noting that the terminology for bipolar disorder has changed in ICD 11 and DSM-5, significant points being incorporation of bipolar II in ICD 11 and the additional requirement of increased activity (to mood elation or irritability) in both classification systems (10). Incidence rates of BD also vary, from 2.2/ 100 000 person years (PYs) in rural Ireland to 12.3/100 000 PYs in Finland, probably due to methodological factors (diagnostic threshold, availability of inpatient beds, and sampling methods) (11). Given that a significant number of people with first episode mania will develop psychosis, it is also worth examining the psychosis literature. A systematic review of UK studies in psychoses identified incidence of bipolar psychosis of 3.7/100 000 PYs, with significant heterogeneity (12). An older registry-based sample from Camberwell, London, from 1965 to 1999, identified incidence of first episode mania of 16.8/100,000 PYs in those aged 21 to 25 years (using 5-year age bands). This declined thereafter, with a small peak in later life (40-55 years) (13) (see below for discussion of age of onset, and Table 2). This is consistent with late adolescent modal onset.

Morbidity and mortality are both increased in BD, recent UK data indicating increased mortality compared to the general population, at least 12 times increased suicide risk (more than schizophrenia) and 50 times the risk of self-harm (14). Data

from the WHO Global Burden of Disease study ranked BD as the 4th leading cause of disability adjusted life years in people aged 10-24 (15).

There is a dearth of representative studies examining first episode manic psychosis, especially within first episode psychosis (FEP) services. Recent three year follow-up of a Hong Kong sample showed 37% of people with first episode manic psychosis (FEMP) attained functional remission, FEMP patients being more likely to be hospitalised than people with first episode schizophrenia (16).

This contrasts with studies in other countries, one study finding no significant difference in days spent in hospital at 10-year follow-up between similar cohorts, with better GAF scores in those with bipolar disorder (17).

Age of onset

Determining age of onset is problematic, as first onset of mild depression, major depression, hypomania and mania may all occur at different time points; illness may have onset before elevated poles that define BD. Age of onset occurs at different time points, with three groupings proposed; late adolescence, mid-twenties and in middle life (18). In a review of eight admixture analyses studies (identifying normally distributed cases across age groups), three sub-groups were identified (early, intermediate and late) in all but one analysis (19). In their pooled analysis, 45% had onset before 21.33 years and 81% experienced first episode before 34.67 years.

Using retrospective design, Berk et al identified median age of onset of mania of 24.1 years, with median age of diagnosis of BD or schizoaffective disorder and initiation of diagnosis-appropriate treatment at 30 years (20). Participants had their first depressive episode aged 21.2, with onset of any symptoms nearly 4 years prior to that. While retrospective data from adult and persistently unwell participants indicate later age of onset of mania, prospectively studied familial high-risk youths

suggest earlier age of first (hypo) mania (21). A recent meta-analysis of 27 studies suggested the interval between onset of BD and management was 5.8 years, high heterogeneity illustrating differences in definition of onset and management (22). Delay between onset of symptoms (of both depression and mania) and initial diagnosis underlines need for early identification and intervention(s). For first presentation of bipolar depression, this would focus on identifying clinical variables such as family history of BD, reverse vegetative symptoms (“atypical” symptoms, e.g., hypersomnia, hyperphagia, leaden paralysis), psychotic features (23), and treatment factors such as poor response to antidepressants and manic switching (24). For first presentation of mania, persistent symptoms, impairment and relapses are common (see below).

Clinically, the perception that phenomenology of hypomania/mania differs depending on age of onset is borne out by evidence. A review of 9 studies suggested more irritability in childhood onset, increased activity more prevalent in adolescent onset, and increased pressure of speech in adult-onset illness. The authors identified lack of direct comparison between childhood and adult onset illness and heterogeneity amongst studies (25). Early age of onset (defined by the cut-off given by Geoffroy et al, above 18), is associated with increased suicide attempts, rapid cycling, drug abuse, obsessive–compulsive disorder and increased familial risk for affective disorders. Though focused discussion on cognitive function is outside the scope of this article, we note results of a recent longitudinal study of youths with bipolar disorder, followed over 2.5 years. This found no difference in measures of the Cambridge Neuropsychological Test Automated Battery (CANTAB) compared to CANTAB normative data, identifying three subtypes, the subtype with poorest function having more mood episodes (26). Several other studies and meta-analyses

have pooled data together, demonstrating cognitive impairments even during euthymia, after recovery from first manic episode versus controls (in cognitive flexibility, though not response inhibition and verbal fluency), as well as established illness (27,28).

Natural history; is bipolar disorder a recurrent illness?

Modern theories of the natural and recurrent course of BD date back to 1851 and Falret's concept of "folie circulaire"(28), where he described melancholic and manic episodes, interspersed with symptom free periods and generally poor outcome, though Kraepelin is generally credited with the distinction between affective psychoses and schizophrenia. To ascertain possible benefits of prophylactic treatment and natural course of illness requires examination of historical cohorts who did not receive prophylactic medication. We then examine studies conducted in the modern era, highlighting methodological considerations.

In their careful review of 11 studies of over 6500 people with BD (using the Kraepelinian construct of both unipolar and bipolar illness) not taking prophylactic medication, Goodwin and Jamison concluded that recurrence is the rule, as opposed to the exception (29). Rates of single episode varied from 0-55%, older studies indicating higher rates, with significant numbers of single "episodes" being chronic and unremitting. They noted rates of recurrence had apparently increased in the 35 years prior to their 2007 textbook (speculating antidepressants may have contributed to this). Interpretation of older studies is difficult, on account of factors such as Slater's paradox, where analyses of Kraepelin's cohort included total number of recurrent cases, as opposed to individual cases. **This may have led to erroneous assertions, such as the rate of cycling increasing over time and periods of euthymia decreasing with more recurrences** (30). In the Zurich longitudinal study,

219 patients with bipolar disorder, with median age at follow-up/death of 68 years, only 16% were considered to have sustained recovery (functional outcome measured by score on the Goal Attainment Scale (GAS) >60 and no episodes in the prior 5 years), approximately a quarter in remission (with an episode in the last 5 years), and 27% with incomplete remission. Furthermore, rates of recurrence after first episode of illness appeared consistent over time (forty-year follow-up from first episode) (31). A strength of this study is the catchment area design, with follow-up of individual cases over time, as opposed to only those requiring hospitalisation (a possible bias of older studies.)

Data on outcome after first episode mania in recent cohorts are limited by length of follow-up (longest follow-up 4 years), and it should be acknowledged that remission of episode does not necessarily reflect symptomatic or functional remission. For example, following remission of an initial manic syndrome, although 90% of subjects had syndromal recovery at 1 year, 40% were still experiencing anxiety and depression and nearly 60% failed to return to prior functioning (32). Regarding first episode mania studies, a recent systematic review of 8 studies estimated recurrence at 1 year at 41% and 59.7% at 4 years (33). A similar conclusion was reached by another systematic review, which included adolescents with first manic/mixed episode. This pooled data from 5 studies in adults, 3 studies giving recurrence rate of 35% at one year. Three studies in child and adolescent populations gave one year recurrence of 48%, 2 year recurrence of 46% and 4-5 year recurrence of 65% (34). If one considers that episodes accumulate over time (as in the Zurich longitudinal study), findings are in accordance with high recurrence risk over the lifetime. Recurrence rates also appear higher in established BD. An indirect measure of recurrence comes from the SPaRCLE trial, where 1172 people with bipolar I illness

(experiencing mania, depression or mixed episode) had illnesses stabilised with quetiapine and subsequently randomised to quetiapine, lithium or placebo.

Quetiapine and lithium both increased time to recurrence of depression and manic symptoms over placebo at two-year follow-up (quetiapine HR 0.29, lithium HR=0.46), with recurrence in placebo group of approximately 48-56%, depending on index episode (mania, depression, mixed) (35).

An influential model (the “kindling” hypothesis) postulates that life stress triggers the initial episode of illness, though these episodes eventually occur autonomously (36).

This model incorporates animal work, relating to seizure stimulation, with less electrical stimulation required to elicit seizures in mice, with less electricity required to provoke seizure with each progressive seizure, with eventual spontaneous seizure activity (ie without stimulus). Behavioural sensitisation refers to the process whereby mice respond to psychomotor stimulants such as cocaine, both in the short and longer-term, with increased intensity of behavioural response over time. This has been used to explain the natural history of relapses in bipolar disorder, such as increased recurrence of episodes, independent of life-stress. Extrapolating this to clinical studies is difficult, on account of methodological issues, including quantification of life stress (both negative and positive), measurement of recurrence (as noted above) and inclusion of help-seeking populations. This was emphasised in a recent review which concluded that 8 of 15 studies in BD showed kindling effect, and methodological issues limited interpretation (37).

Staging bipolar disorder and linking this to treatment

Staging mental illness is a method of linking knowledge about the natural history of mental illness to putative treatments. This is in keeping with concepts in general medicine (e.g., oncology)(38). A staging model has been proposed for BD,

incorporating phases from those at increased risk of developing BD, through to initial presentation, recurrence and possible progression (39).

It is crucial to recognise early clinical phenotypes for a range of traditional disorders, including BD, overlap. Syndromes such as mania and psychosis are typically late phenotypes, and need for care precedes emergence of these 'defining' labels.

Therefore, to be relevant, clinical staging models must be designed within a transdiagnostic context, rather than traditional silos.

Stage 0 denotes people who are asymptomatic but at increased risk, stage 1 with subthreshold symptom and decreased functioning, with stage 2 indicating first onset illness, in keeping with recognised diagnostic criteria. Stages 3 and 4 indicate recurrent and persistent illness, with accruing disability.

This is intuitively appealing, enabling clinical phenomena to be linked to treatments as well as neurobiological biomarkers and targets of treatment response/non-response, across diagnostic boundaries (40,41). This model is neither deterministic nor pessimistic and incorporates a "reverse gear"; one can move from stage 4 back to stage 3, if persistent and recurrent illness stabilises with optimal therapy, and represents an optimistic shift in thinking from earlier staging models. It also alleviates concerns about theories of inevitable progression and worsening facets of illness, such as cognitive functioning (as illustrated above). This is dependent on validity and reliability of "stages" and demonstrable efficacy of treatments, preventing further progression. Concurrent with this is evidence that suggests some interventions are more efficacious for people who have experienced fewer illness episodes. This consists of predominantly post-hoc analyses, with dichotomising data (and resultant caveats). Re-analysis of a group psychoeducation trial found a cut-off of 6 episodes affected 5 year recurrence of mood episode in euthymic BD (42) and a large, multi-

centre RCT of cognitive behaviour therapy (CBT) found decreased recurrence in people experiencing 12 episodes or less (HR=0.51)(43). Similar analyses exist in trials of olanzapine (decreased time to remission in first episode compared to multi-episode mania at 12 weeks (44) and lithium prophylaxis in unipolar and BD, finding reduced recurrence in BD of less than ten years' duration (45). These studies are, however, cross sectional, and people with longer illness are more likely to have treatment resistance. Furthermore, recent literature from prospective follow-up of people with history of one manic episode, that relapse prevention (i.e., lack of recurrence) may be associated with less grey matter volume loss (46) and improvement in neuropsychological functioning (47), though teasing apart effects of confounders such as antipsychotics and substance misuse will require larger studies, and longer-term follow-up.

Direct trial evidence for specific interventions in first episode mania

Pharmacological

Conus et al compared chlorpromazine and olanzapine as adjuncts to lithium in first episode mania in an 8 week RCT, finding similar safety but possibly earlier and higher remission rates with olanzapine (48). The only maintenance trial in people with post-first episode mania recruited 61 people with FEMP whose symptoms had been well controlled with quetiapine and lithium and randomised them to quetiapine (mean dose 437.5mg) or lithium (mean level 0.6mM). Using a mixed-model, repeated measures design they found lithium superior to quetiapine on clinical measures (Young Mania Rating Scale (YMRS), Brief Psychiatric Rating Scale (BPRS), clinical global impression), and functioning (49). What can be taken from these two pharmacological studies is that lithium does exert a beneficial effect in this patient group, at a relatively low dose, in keeping with the doses of antipsychotics

needed in first episode schizophrenia (50). It is also acknowledged that any intervention studies are difficult to recruit to, and possibly large drop-out rates and smaller number of potential participants than first episode populations in general.

Psychological

As pointed out by Vallarino et al, most psychotherapy studies have focused on samples outside the age range of first onset illness (51). Taking an evidence-mapping approach they identified 5 studies in people with first episode BD, four of which were case series, one a controlled trial (52). Here we will consider only trial data. The first RCT, an adjunct to the pharmacotherapy trial, above, was an open label trial of manualised CBT versus treatment as usual (TAU), with 20 in each group. A significant difference was found in depression, though not manic symptoms, at 18-month follow-up. We identified a further pilot RCT of recovery-focused CBT versus TAU, which recruited 67 people (33 to CBT), with onset of BD in the last 5 years, around 80% having BD. The authors found decreased time to relapse of any mood episode in the CBT group at 15 months (HR=0.37), and better self-reported recover (53). Although better than TAU, interpretation is difficult, given lack of an active control intervention (54).

Service level interventions

Kessing et al examined a specialist mood disorder clinic (specialist pharmacological and psychological treatment, including group psychoeducation) versus TAU in an RCT of 158 people admitted to hospital with 1st, 2nd or 3rd episode mania/BD. They found significant improvement in rehospitalisation after follow-up of 2.5 years. Post-hoc analysis identified non-statistically significant improvement for younger patients (aged 26 and below (55)).

Current service level interventions for young people with first episode mania/bipolar disorder.

There is substantial international variability in care for people with first episode mania. Several classifications exist (56), with limited focus on low and middle-income countries (LMIC). For this review, systems include those with a) universal health care (UHC) systems- including social health insurance with 'residual' systems, b) UHC systems with Specialised Streams of Care (SSC) for early psychosis or BD, c) managed care systems or voluntary health insurance (VHI), d) systems in LMIC settings and e) University or tertiary research clinical settings.

Several European, Canadian and Oceanic health systems follow the UHC model. Here, those with BD and early stage BD access hospital and outpatient care through existing pathways for severe mental illness. Services are based on age, with CAMHS for those under 18 and adult services. Pertinently, this falls in the middle of peak age of onset (19). Additionally, limited resources and prioritisation of more severely unwell can lead to EI being neglected. Furthermore, those with early BD typically do not identify themselves as having enduring or severe mental illness. Therefore, poor access to, and engagement with services can occur, with consequent worse outcomes.

Specialised access and care pathways can create clearer care, minimise stigma and improve availability and EI uptake. This is possible in the UK, Canada and Australia, where established Early Psychosis programmes exist. Additionally, Ireland, UK and Australia have youth-specific care, which may improve access (57). Complex managed care systems (e.g. United States) also incorporate early psychosis programmes (e.g. Co-ordinated Specialty Care centres) (58). In several LMICs, modified voluntary health insurance and 'residual' governmental health care provides

care for BD, often in later illness. Lower acceptance of mental illness as a health issue, higher stigma and resources pose problems, making EI less pragmatic (59). Several University affiliated research clinics offer early intervention for those at high-risk of BD, and children and adults with BD (60). While these settings generate valuable evidence, substantial improvement in dissemination to scale within local health systems is required. Intervention trials across services could help develop evidence to inform best practice within services. Outcomes, including quality of life, satisfaction with care and costs will all need to be understood to inform policy makers and clinicians regarding future services.

Clinical practice guidelines and early stage BD: current status

Clinical guidelines are relatively silent on treatment in first or early treatment seeking episodes of mania or BD. In our examination of guidelines published (or updated) in the last decade, eight guidelines refer to the first manic episode or early intervention. Three of these guidelines refer to indications for maintenance pharmacotherapy in first-episode mania; the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines on Maintenance treatments in BD (61), the Taiwanese (62) and South African (63). The British Association for Psychopharmacology (BAP) guidelines *do* make comment on early intervention for BD, at individual and service level (64) . At an individual level BAP note lack of evidence, suggesting similar treatments to “mature” illness, and at service level suggest access to EI services, and a specifically trained psychiatrist. BD-specific guidelines recommend maintenance treatment for first episode mania depending on illness severity (WFSBP (61)), persistent disability (63), family history of BD (61, 62), suicide attempts and comorbid psychotic features (62).

The Canadian Network for Mood and Anxiety Treatments (CANMAT)/ International Society for Bipolar Disorders (ISBD) 2018 guidelines incorporate discussion on staging, first episode and recommend maintenance treatment early in illness course, after a first manic episode (65). Similarly, the Royal Australian and New Zealand College of Psychiatrists recommend consideration of maintenance treatment from the very first episode of mania (66). Conversely, the International College of Neuropsychopharmacology (CINP) guidelines suggest that those with first episode mania may be exempt from maintenance treatment recommendations (67).

Another guideline referring to care for those with first episode manic psychosis in EI services is the Australian Clinical Guideline on Early Psychosis (ACGEP) (68). This specifically identifies sodium valproate as second-line mood stabiliser for acute treatment of a first manic psychotic episodes (It is considered first-line treatment in many other BD-specific guidelines (e.g., CANMAT, 2018, WFSBP). While ACGEP permits use of sodium valproate in women of child-bearing age (albeit with caution), NICE recommend against use altogether (69).

The ACGEP contains general recommendations regarding access, risk management, CBT, case management and supporting vocational recovery. This, the Royal Australian guideline for schizophrenia (70) and NICE guidelines on psychosis and schizophrenia (71) do not distinguish between recommended duration of maintenance medication between schizophrenia spectrum disorders and BD in first episode psychosis.

Similarly, the principle of gradual medication dosing ('start low, go-slow') recommended by ACGEP may contradict loading-doses used for sodium valproate, where early use of higher doses is recommended (WFSBP 2009); this probably reflects differences in use of antipsychotic and mood stabiliser medications.

There is a similar lack of clarity in the NICE Guidelines for Psychosis and Schizophrenia, suggesting following the NICE Bipolar guideline which offers no advice on maintenance antipsychotic/mood stabiliser medication after first episode (NICE's Psychosis guideline suggesting review after one to two years.)

Recommendations and future directions

When FEP services exist, people with first episode mania should be incorporated into these services, and care tailored individually.

People presenting with first episode mania should be offered the following interventions.

Pharmacological treatment for acute mania should be in keeping with recommendations for established illness, though once in remission thought should be given to making maintenance treatment as tolerable as possible, with monitoring of side-effects. Lithium could be considered the gold standard for maintenance treatment, though individually there may be concerns regarding adherence and tolerability. Here, low dose antipsychotics could be considered, with more tolerable medications with less propensity for weight gain considered. Cautious initial use of medications and slow titration is preferable, as early experiences of tolerability prime later expectations and subsequent adherence, with major long-term consequences. Initiating (and continuing) maintenance treatment should be based on natural course of illness, acknowledging people presenting to services usually have prior experience of depression/hypomania/mania, and also take into account variability in efficacy of antipsychotics as maintenance therapy in BD (72). Psychological interventions might be more efficacious if given early, and should emphasise on psychoeducation, at group or individual level.

Other principles of early intervention should be considered; holistic case management, family intervention, vocational recovery, physical health interventions and treatment for co-morbid drug and alcohol misuse/dependence.

Before definitive guidance can be given more research is required, to provide level 1 evidence.

First, determining specific interventions (pharmacological and psychological), their dosage, timing and effectiveness in early illness stages and phases is critical. At a service level, monitoring of people who have experienced first episode mania within FEP services will be necessary, to evaluate effectiveness against outcome measures such as relapse, functioning and vocational outcomes (as seen in non-affective psychosis). Greater public and systemic education, emphasising importance of EI in BD and associated disorders is critical. A specific focus on improving access to care within locally available services is paramount, as well as maintaining care to prevent relapse and deterioration in functioning.

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Conflicts of interest

AHY-paid lectures and advisory boards for the following companies with drugs used in affective and related disorders

Astrazenaca, Eli Lilly, Lundbeck, Sunovion, Servier, Livanova, Janssen

No share holdings in pharmaceutical companies

Lead Investigator for Embolden Study (AZ), BCI Neuroplasticity study and Aripiprazole Mania Study. Investigator initiated studies from AZ, Eli Lilly, Lundbeck, Wyeth, Janssen

LY has been on speaker/advisory boards for, or has received research grants from Allergan, Alkermes, AstraZeneca, Bristol Myers Squibb, CANMAT, CIHR, Dainippon

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PM (McGorry) reports he is a Member of a Janssen Advisory Board.

PM (McGuire) reports receiving investigator-initiated research funding from or participating in advisory or speaker meetings organized by Sunovion, Janssen, GW Pharmaceuticals, Takeda, and Roche.

SJ, AR and CD report no conflict of interest.

Contributors

SJ and AR conceptualised the manuscript, with additions by CD, PM, MB, PM, LY and AHY.

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Tables

Table 1

Clinical differences between first episode mania and schizophreniform psychosis

	Bipolar psychosis	Schizophreniform psychosis
Duration of untreated psychosis	Shorter (73)	Longer
Treatment response (pharmacological)	Acute and maintenance lithium response	Antipsychotics
Treatment response (psychological)	Psychoeducation	CBT for psychosis (74)

Table 2

Current clinical guidelines encompassing first episode mania

Guideline Group (Year)	Guidance relating to first episode mania?	Intervention suggested
British Association of Psychopharmacology (BAP) (2016)	Yes	<p>Monitor for risk of BD in those with Unipolar MDD</p> <p>Aim to prevent recurrence, and further disability</p> <p>Those with acute mania should be offered early intervention, including hospitalisation</p> <p>Assessment should be undertaken by a trained psychiatrist</p>
Canadian Network of Mood and Anxiety Treatments (CANMAT-International Society for Bipolar Disorders (ISBD) guideline (2018)	Yes	<p>To initiate comprehensive treatment from the first episode</p> <p>Effective maintenance treatment should be</p>

		considered from an early stage
International College of Neuro-Psychopharmacology (CINP, 2017)	Yes	Those with first episode mania are considered eligible for exemption from the recommendation for lifelong prophylaxis- especially if the risks of medications on physical health are high
Royal Australian and New Zealand College of Psychiatrists (2015)	Yes	<ul style="list-style-type: none"> - Maintenance treatment should be considered from the first episode of mania - People should be provided with support to come to terms with the illness (acceptance)
World Federation of Societies of Biological Psychiatry (WSFBP)- Guidelines for Maintenance Treatment (2018)	Yes	Adopts recommendations from Dutch guidelines, that those with first episode mania should be considered for maintenance treatment

		if they have a positive family history or a severe episode
Australian Clinical Practice Guidelines on Early Psychosis- 2 nd Edition (2016)	Yes	<p>Recommendations specific for first episode mania with psychosis</p> <ul style="list-style-type: none"> - Provides pharmacologic treatment algorithm for acute treatment of manic psychosis - Recommends consideration of maintenance treatment based on several factors.

Table 3

Summary Table

- 1. First episode mania is recurrent and presents many years before diagnosis.**
- 2. Further studies are required, examining pharmacological, psychological and social interventions.**
- 3. Treatment guidelines for bipolar disorder and first episode psychosis should incorporate tailored care for first episode mania and suggestions for not only acute but prophylactic treatment.**

My Experience with Bipolar Disorder

My struggles with mental health began at age 14 when I started to experience some symptoms of depression; however, it was when I started to develop episodes of hypomania at 16 when things began really getting out of hand. These episodes came as a shock to everyone around me as I was always known as a stable, stoic, polite young boy.

In my first episode of hypomania, I had seemingly boundless energy levels and was fascinated (perhaps I should say obsessed) with business. I admired Richard Branson and decided that I was capable of doing well in school whilst forming a business. I led my school's Young Enterprise project and was getting very good grades, but it was short-lived. I began to get too high and felt like I was good enough to build a huge business and wanted to go to China to make my business flourish. I began to skip school and didn't do my school work, as I thought my business goals should take precedence and believed that I didn't need to put much effort in to be able to achieve good grades at school. Alongside this, I began to experience insomnia, had a constant need to pace and was getting very frustrated. My behaviour began to alienate everyone around me.

I felt depressed, was guilt-ridden and tried to make amends with people, feeling confused about what had overcome me during that period of time. This realisation, however, didn't prevent future episodes. I had another episode where my new fascination was with the rapper Eminem. I was determined to go to Detroit and make a career for myself as a rapper. At this stage, my friends had had enough of my behaviour and left me completely. I felt isolated and began to realise that something was seriously wrong with me. I was plagued by questions within my head, like: 'Am I crazy? Am I weak? Am I a bad person?' I questioned whether I

should see a professional, but was worried about the stigma attached to seeking psychological help. I tried to muster up the courage, but my priorities changed as my sister was diagnosed with Leukaemia. I tried to be there for my sister whilst doing a lot of school work to catch up with work I'd neglected the year before. I enjoyed spending a lot of time with my sister, knowing she may not have much time left. I made an effort to put on a brave face, but my mental health was still poor. It was, in some ways, even worse. My insomnia was still very bad, and I began experiencing rapid cycling symptoms. I knew people around me could see behind the mask, but I managed to do well in my education while seeing my sister frequently. It would have been what she wanted- but I burnt out.

At the end of the year, once she was better, a severe mixed episode took over my life. I experienced hallucinations (visual and auditory), odd delusions including grandiose delusions as well as all of the symptoms I had experienced up to that date, but to a higher level. I was referred to see a mental health team, where I had weekly sessions. A psychiatrist sat at the back of the room taking notes, while a therapist and I discussed how I was feeling.

During this episode, I was a huge threat to myself and engaged in risky behaviour as I thought I would be invulnerable to the repercussions. This is an example of my delusions of grandeur; I thought nothing anyone or anything could do would be able to break me. I am appalled, looking back, that I wasn't hospitalised. These behaviours included walking at all hours of the night, hanging around with dangerous people and spontaneously taking a dangerous quantity of drugs or alcohol. During that episode, if I had been mugged, I would have started a fight and could have potentially been seriously hurt.

At other times during this episode I felt completely alone, anxious and unable to move from my room. I felt sad and depressed and unable to do anything. Yet, I was angry, full of energy and felt a need to pace and be on the move. This oxymoron was beyond frustrating and made me feel desperate, like I had no hope.

The psychiatrist explained to my family that he was confused about my symptoms, saying: 'Sam paints a very complex picture.' They prescribed Phenergan to help me with my sleep and I took this at 100mg. It seemed to help with the sleep, but the rest of my symptoms persisted. As several weeks had passed without any progress on diagnosis, my mum asked whether I could possibly have bipolar disorder, since she had observed periods of extreme high and low moods. They disregarded this idea as they felt that the current episode couldn't be explained by bipolar disorder. They failed to enquire further on episodes in the past and failed to ask my family whether any of my relatives had bipolar disorder. I have two relatives who have suffered from bipolar disorder. After approximately 12 weeks of work together, they explained that I might have borderline personality disorder, but that they were still uncertain. They said they would refer me to the "MAP" team (for Mood, Anxiety and Personality disorders).

At the time, I felt positive about the experience with my initial team. I believed the psychiatrist's opinion that I painted a complex picture and accepted the suggestion of looking into borderline personality disorder. I felt unaware of what was happening to me, so even though I didn't see many parallels, I accepted that they must be right. However, when I mentioned the illness to my girlfriend at the time, she said that she didn't believe I could have this disorder and said that I didn't seem insecure in our relationship at all. She felt like my issues didn't have anything to do with interpersonal relationships.

It took a long time for me to be transferred to the MAP team. They explained the transition time was due to difficulty in transferring a patient from adolescent to adult mental health services. I felt abandoned and hopeless, but was glad that the major episode had ended. Once I was under their care, I saw a social worker there every few weeks. She treated me in quite a patronising manner. She said: 'I think you'll be happy that they are thinking of changing the name from borderline personality disorder to emotionally unstable personality disorder.' This

frustrated me a lot and I felt like my issues were not being taken seriously at all. For this reason, I started to question whether I was making out I was more ill than I was. I questioned whether they were correct and wondered if I had something wrong with my personality. This knocked my self-esteem and made me believe in myself less than I ever had before.

From the time that I left my first team, it took approximately 8 months to be seen by a psychiatrist at the MAP team. I was adamant to take medication, but she refused my request for a long while. After some time, she prescribed 500mg of Sodium Valproate. I began to feel a little hyper at this low dose, but nowhere near as manic as I had been in previous episodes. I wasn't aware that this was a low dose as I trusted the psychiatrist's opinion. I wondered why I am still ill and this made me question further whether it was a personality issue that couldn't be solved by medication.

At this time, I took part in a research project at Kings College. The doctor in charge of the project took me under his wing. We had chats and within a few times of meeting with him, he realised that a lot of my symptoms and my history were compatible with a diagnosis of bipolar disorder. He was kind enough to send a letter to the MAP team, describing my history and saying that they should reassess whether I fit a diagnosis of bipolar disorder. I researched into bipolar disorder extensively and when I asked people if this fit me, people said that this diagnosis made more sense. The diagnosis made me feel a lot more comfortable and made me feel understood. This reduced the amount of time I spend questioning whether I was a bad person. I could accept myself more. I participated in other research projects within Kings College. All of the researchers were fantastic and they all treated me with respect. I felt understood and felt like there was no judgement from them.

The MAP team gave me a new diagnosis of bipolar disorder and incrementally brought me up to a high dose of 2g of sodium valproate. On this very high dose, I was very lethargic and down, but I felt relieved that I wasn't suffering from mania anymore. I was happy that my

highs weren't hurting me or those around me. I would meet with the psychiatrist once a month and we decided to keep me on the same medication. After a while I became quite frustrated on this dose, yet my psychiatrist tried to convince me to stay on it. I felt depressed and my voice wasn't being heard, so I began to slowly taper off from the sodium valproate. I then experienced another severe mixed episode. I was seen by a crisis team and they gave me someone to speak to at the time. I was happy that I was given someone to talk to twice a week and this made me feel that someone cared which helped considerably. When I say the experience was very positive, I mean that one of the workers there helped me a lot. He was only available within the sessions though and when I would ring up asking to see anyone, they would be cold and tell me I should just go to A&E.

During this episode, I felt suicidal and I made a number of suicide plans. I was very frustrated and was very worried that I would severely hurt someone and so I was adamant to be hospitalised. I needed to pace at all times and my frustration was severe. I was brought up in a way that developed a lot of self-control within me and I tried my very hardest to keep it all in. I went to the hospital on several occasions (St Georges and Kings College), but they refused me. This deeply saddened me, but I managed with time to get out of this episode. This made me feel like I wasn't being heard and I felt like people weren't taking my mental health seriously enough.

The MAP team then started me on a small dose of 50mg of Quetiapine. I experienced another hypomanic episode. They upped my Quetiapine to 100mg and then to 150mg as my doctor saw that I needed more sedation. I was involved in sales and was working 70 to 80-hour weeks. My frustration levels were high and I barely slept at night. When I made it out of the episode, I got very depressed and felt more guilt than I ever had done before.

My mum, who was very worried at the time, contacted the research psychiatrist and told him what had transpired. He was quite shocked at the prescription of 150mg of Quetiapine as this

dose is too low to properly prevent manic episodes. At my mother's request he referred me to another psychiatrist, another researcher at Kings College, who accepted me as a private patient. My experience with him has been fantastic. I am now on 300mg Quetiapine and 200mg Lamotrigine and I have since been symptom free for the past 18 months.

My levels of guilt have improved due to feeling more accepted and realising that this issue is not part of my personality; it is a physical issue which needed to be solved through medication. Both Sameer and Paul have helped me accept that I have bipolar disorder, that it can be managed and that I can lead a productive, meaningful life. Family therapy helped my family to understand my illness and accept it.

My concentration and cognitive abilities began to improve once I was stable for longer than a few months, but I still had work to do to get back to where I was before. I realised this when I initially began cognitive remediation therapy (CRT) and found a lot of the cognitive tasks difficult. During the sessions I worked hard, slowly developing my metacognitive skills. I then began reading and doing psychological research on my own. Now I am able to do well in my degree. I'm still not at my peak, but eager to carry on trying hard. I am able to get on with tasks, but more importantly I am consistent and able to focus on one thing without switching goals frequently. I am passionate about my psychology course and am very happy and content overall.