An investigation of the relationship between Bipolar Disorder and Cannabis use

A thesis submitted to the University of Manchester for the degree of Doctor of Clinical Psychology in the Faculty of Medical and Human Sciences

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WORD COUNT

Thesis Section	Text	Abstracts, tables, figures, references	Appendices	Total
Thesis abstract	434	----	---	434
Paper one (Literature Review)	6,230	3,171	---	9,401
Paper two (Empirical Paper)	5,879	2,248	---	8,127
Paper Three (Critical review)	6,371	1,895	4,838	13,104
Total	18,914	7,314	4,838	31,066

ABSTRACT

Substance abuse is very common in Bipolar Disorder (BD) and can lead an individual having an increased range of difficulties. Studies have indicated that cannabis is used very frequently, but most research into substance use and BD has focused on either alcohol use or substance use disorders generally. The relationship between BD and cannabis use specifically has received far less attention. This thesis specifically explored the co-occurring relationship between BD and cannabis use.

In the first section the author examines and critically evaluates studies that have reported on the relationship between BD and cannabis use. The initial phase included a literature search of the area and the identification of relevant papers. A total of 13 research studies were identified and included in the final review. The studies varied considerably in terms of their research questions, design and methodological quality. The findings from the studies were synthesised in relation to a number of existing hypotheses for why BD and substance use in general co-occur. On the whole, the 13 studies contributed sufficient evidence both for and against the existing hypotheses. The findings suggest that there are a number of factors that contribute towards the high co-occurrence of BD and cannabis use (e.g. the use of cannabis to self-medicate symptoms).

The second section was designed to investigate a number of the factors derived from the literature which might explain the high co-occurrence of BD and cannabis use. The Experience Sampling Methodology (ESM) was utilised to provide a close investigation of a number of factors over the course of daily life. Twenty-three participants with BD type I and type II completed diary entries for 6 days using ESM. The procedure allowed a close investigation into the associations between cannabis, mood, BD symptoms and Behavioural Activation System (BAS) sensitivity. Self-reported BAS was also measured to indicate the extent to which this predicted changes in mood, BD symptoms and cannabis use. The findings indicate that cannabis use is associated with a number of psychological effects, although no evidence for the self- medication of mood and BD symptoms was revealed in the daily life of the participants. An association between BAS sensitivity and positive affect and manic symptoms was revealed and this is consistent with the findings in current literature.

The final section provides a critical reflection of the research process. This includes a rationale for the development of the literature review and the main research paper. This is followed by a description of the study context and then a reflection on the methodological and ethical issues which were faced. Finally it discusses theoretical, clinical and future implications for research in this area.

DECLARATION

No portion of this work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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PAPER ONE

The co-occurrence of Bipolar Disorder and Cannabis use: A review paper

ELIZABETH TYLER

PREFACE

The work for this paper was carried out between December 2010 and June 2011. The literature search was completed at the beginning of January 2011. Professor Christine Barrowclough provided overall supervision for the thesis which included reading drafts of the manuscript.

The author intends to publish the review paper in 'Bipolar Disorders - An International Journal of Psychiatry and Neurosciences' and the paper has been prepared in accordance with their requirements (see appendix A for author guidelines). The authors will be: Elizabeth Tyler and Professor Christine Barrowclough.

ABSTRACT

Objectives: Cannabis use is very common in Bipolar Disorder (BD). However, most research into substance use and BD has focused on either alcohol use or substance use in general. The relationship between cannabis use and BD has received far less attention.

Method: In this review the author examines and critically evaluates studies which report on the specific relationship between BD and cannabis. These findings are synthesised in relation to a number of existing hypotheses for why BD and substance use in general co-occur.

Results: From a systematic search of the literature 13 relevant studies were identified and were included in the review. These studies varied considerably in terms of the research questions and design (e.g. longitudinal, cross-sectional, experimental, and qualitative), as well as the methodological quality.

Conclusions: Taken as a whole, the studies contribute sufficient evidence with which to re-consider the existing hypotheses in the context of cannabis use and BD. The findings suggest that there appear to be a number of factors that contribute to the high occurrence of BD and cannabis use, including the use of cannabis to self-medicate symptoms of BD. The review highlighted a number of areas which warrant further attention and these are discussed further in the paper.

Keywords: bipolar disorder, mania, cannabis use, substance use, self-medication

INTRODUCTION

Approximately 50-60% of individuals with Bipolar Disorder (BD) have a lifetime history of substance use disorder (1, 2). Furthermore, studies report that rates of substance use are elevated in people with BD compared to the general population (1, 3). Co-occurring BD and substance use often show a more severe course of illness including poor insight and denial (4); increased suicide attempts (5) and higher levels of symptom severity (6).

A review paper investigating the co-occurrence of BD and substance use disorders (7) examined 4 possible hypotheses for the high levels of co-morbidity reported. [1] Substance abuse is a symptom of BD due to the nature of the condition, which may lead to 'risky' behaviour and poor judgement (8, 9). [2] Substance abuse is developed as a way of coping with BD, 'the self medication hypothesis' (10, 11, 12). [3] Substance abuse causes BD by repeated use, inducing changes in the brain, subsequently altering affect (13, 14). [4] Substance use disorders and BD share common risk factors such as genetic vulnerabilities (9), elevated levels of impulsivity (15) or sensation seeking (12). However the authors conclude that none of the 4 hypotheses have clear support for explaining all cases of co-occurrence and suggest all 4 mechanisms may play a role in the excessive substance abuse observed in individuals with BD.

Overall, research has revealed that cannabis is the most frequently used drug in individuals with BD (2, 16, 17); this pattern mirrors rates in the general population (18).

The major psychoactive component in cannabis is Δ9-tetrahydrocannabinol (THC). THC replicates the actions of natural cannabinoids produced in the body and binds itself to cannabinoid receptors CB_1 and CB_2. These receptors are found within several regions of the brain, including the frontal cortex, striatum and hippocampus (19, 20, 21). Neuro-anatomical findings suggest CB_1 modulates and interacts with the function of dopamine (22). Whilst evidence suggests this interaction modulates a variety of areas, including affect, appetite, learning and memory (23, 24), little is understood regarding the underlying molecular mechanisms. Further understanding of the interaction and the mechanisms involved may have important implications for individuals with BD who use cannabis, since the disorder is characterised by difficulties with affect regulation.

Estimates of current cannabis use for individuals with BD range from 8% to 22% and for lifetime use the estimates range from 30% to 64% (25). In a number of studies, particularly those with a younger participant sample, cannabis use equalled or exceeded alcohol use disorders (1, 17,

26). However, most research into substance use and BD has focused on either alcohol use or substance use disorders generally and the relationship between BD and cannabis use specifically has received far less attention.

Whilst Strakowski and DelBello's (7) paper provided a comprehensive review of studies investigating the co-occurrence of BD and substance use disorders generally, to the author's knowledge there are no published reviews exploring the specific relationship between BD and cannabis use. The present paper focuses exclusively on BD and cannabis use and aims to evaluate the 4 hypotheses of Strakowski and DelBello's (7) through examining and critically evaluating studies which report on the relationship between BD and the use of this specific drug.

METHOD

Literature search

The following databases were searched from inception to January 2011: EMBASE, MEDLINE, Psych info and the Web of Science. Search terms included 'bipolar' OR 'manic depression' OR 'mania' AND 'cannabis/ marijuana use' OR 'cannabis/marijuana abuse' OR 'cannabis/marijuana misuse'. The reference lists of abstracts were also searched.

Study selection

All titles and abstracts were examined and full text papers of potentially relevant studies obtained. All papers were read to determine whether they met the following inclusion criteria for the review.

Study samples / inclusion criteria

All studies that investigated individuals with BD and co-occurring cannabis use were included. These examined individuals with a diagnosis of BD or sub-threshold BD symptoms at baseline or who were at risk of developing BD or BD sub-threshold symptoms post-baseline.

Studies were also included which examined individuals with a different mental health diagnosis (e.g. anxiety disorders). However for the purpose of this review the participant sample had to include 50% or more people with BD or BD sub-threshold symptoms.

The following diagnostic groups for BD were included in the review: BD type I or II, rapid cycling BD, BD not otherwise specified (NOS) and also studies which included sub threshold BD conditions that required either a reduced duration or number of symptoms, as verified by the Diagnostic and Statistical Manual of Mental Disorders -revised 4th ed. (DSM-IV: 27) criteria. All levels of cannabis use were included in the review.

Studies in languages other than English were not considered for inclusion.

RESULTS

The original search yielded 81 papers of which 68 were excluded for not meeting the inclusion criteria outlined above. Reasons for exclusion were as follows:

- Investigations of cannabis use and psychosis
- Investigations of cannabis use and other mental health difficulties (did not include 50% or more individuals with BD)
- Investigations of substance use in general and BD
- Review papers of cannabis and mental health difficulties in general
- Review papers of substance use and BD
- Not in the English language

A total of 13 papers therefore were included in the final review, none of which were included in Strakowski and DelBello's (7) review paper. These studies employed a range of designs, including case, case-control, cohort and cross-sectional. Further details of these studies can be found in table 1.

Authors	Study	N	Age range (years)	BD diagnosis at baseline?	Cannabis use at baseline?	Methods-Design	Time period	Results
Henquet et al (29)	Cannabis use and expression of mania in the general population	4815	Adults (18-64)	No lifetime mood disorders	Yes	A longitudinal population based study	3 year follow up period	Cannabis use at baseline increased the risk for manic symptoms during follow up period (adjusted OR = 2.70, 95% CI: 1.54-4.75).
Van Laar et al (31)	Does cannabis use predict the first incidence of mood and anxiety disorders in the general population?	3881	Adults (18-64)	No lifetime mood disorders	Yes	A prospective longitudinal study	3 year follow up period	Cannabis use at baseline predicted an increase in the risk of a first BD (adjusted OR =4.98; 95% CI: 1.80-13.81).
Tijssen et al (32)	Risk factors predicting onset and persistence of sub threshold expression of BD psychopathology among youth from the community	543	Young adults (14-24)	No lifetime mood disorders	Yes	A prospective cohort study	8 year follow up period	Cannabis use at baseline was associated with the onset of manic symptoms (OR= 4.26; 95% CI: 1.42-12.76, P = 0.010).
Merikangas et al (28)	Specificity of BD spectrum conditions in the co morbidity of mood and substance use disorders	591	Young adults (19-20)	A percentage of the sample had sub-threshold mania (either a reduced duration <4 days or number of symptoms <4).	No	A prospective longitudinal cohort study	20 year follow up period	Manic symptoms at baseline predicted the later onset of cannabis use/abuse/ dependence(OR = 4.82; 95% CI: 2.0-11.60).

Gao et al (67)	Independent Predictors for Lifetime and Recent Substance Use Disorders in Patients with Rapid-Cycling BD: Focus on Anxiety Disorders	564	Young adults -adults (16+)	DSM-IV diagnosis of rapid cycling BD	Yes	Cross sectional design	----	Patients with co-occurring BD and anxiety disorders (n=261) had significantly increased rates of lifetime (OR = 3.4, 95% CI: 1.91-6.01, P = 0.0001) and recent (OR = 2.5, 95% CI: 1.14 – 5.77, P = 0.188) cannabis dependence compared to those without anxiety disorder. Specifically GAD was associated with lifetime (OR = 3.36, 95% CI: 1.646 – 6.856, p = 0.0009) and recent (OR = 3.28, 95% CI: 1.214 – 8.863, P = 0.0191) cannabis dependence. A history of physical abuse was associated with recent cannabis dependence (OR = 3.47, 95% CI: 1.385-8.673, p = 0.0079).
Baethge et al (35)	Sequencing of substance use and affective morbidity in 166 first episode BD I patients	166	Adults (18-72)	First-episode BD I - manic or mixed episode	Yes	Prospective follow-up study	4.7 years follow up.	Manic or hypo-manic morbidity was associated with cannabis use during the preceding quarter (RC = 0.111; 95% CI: 0.05-0.17; z-score = 3.80, p < 0.001) or the same quarter (RC = 0.11; 95% CI: 0.05-0.18; z-score = 3.63, p < 0.001).
Strawkowski et al (34)	Effects of co-occurring Cannabis use disorders on the course of BD after a first hospitalization for mania	144	Adolescents/ adults (12-45)	First psychiatric hospitalization for mania - BD I	Yes	Prospective inception cohort study	8 years follow up	Identified associations between cannabis use and affective symptoms but could not determine causality. Seventy percent of patients using cannabis did not resume use for at least 8 weeks following admission.
Grinspoon and Bakalar (36)	The use of cannabis as a mood stabilizer in BD. Anecdotal evidence and the need for clinical research	5	Adults (18-47)	BD (type not specified)	Yes	Case series	----	5 cases of individuals with BD that indicate they find cannabis useful in the treatment of their symptoms, both manic and depressive.
Gruber et al (37)	Do patients use Marijuana as an antidepressant?	5	Young adults (16-28)	BD (type not specified)	Yes	Case series	----	3 cases if individuals with BD where patients report that cannabis produces a direct antidepressant effect.

Healey, et al (42)	Reason for substance use in dual diagnosis and substance use disorders: A qualitative study	15	Adults (18+)	BD I	Yes	Semi structured interview	----	Reasons for substance use were idiosyncratic; one participant used cannabis to reach elated state, whilst others used it to alleviate symptoms.
Van Rossum et al (66)	Does Cannabis Use Affect Treatment Outcome in BD? A Longitudinal Analysis	3459	Adults (18+)	BD I inpatients and outpatients – meeting criteria for manic/mixed episode	Yes – cannabis users versus none users	Prospective observational study	2 years	Cannabis users with BD exhibited less compliance with medication and higher levels of overall illness severity compared to BD non-users.
Gonzalez et al (67)	Assessment of medication adherence in a cohort of patients with BD.	1831	Adults (18+)	BD I inpatients and outpatients – meeting criteria for manic/mixed episode	Yes – cannabis users versus none users	Prospective observational study	2 years	Patients were less likely to be adherent to medication if they had cannabis abuse/ dependence during the acute treatment phase.
Jarvis et al (68)	Neuroanatomic comparison of Bipolar Adolescents with and without cannabis use disorders	14	Adolescents (12-18)	BD I	Yes – cannabis users versus none users	Cross sectional	---	BD with cannabis use disorder demonstrated evidence of greater structural abnormalities than BD alone

Table 1: Thirteen studies included in the review paper

Hypothesis 1: Substance abuse occurs as a symptom of BD

BD is characterised by extreme contrasts in mood, recurrent episodes of acute mania, depression and mixed state emotions. Signs of depression include feelings of guilt and worthlessness, insomnia or hypersomnia, impaired concentration and thoughts of death and suicide. Mania, in contrast is associated with increased self-esteem, pressured speech, a decreased need for sleep, flight of ideas, distractibility and an increase in risk- taking behaviours. These characteristics, particularly the increase in risk taking behaviours, have led investigators to hypothesise that the high levels of substance abuse observed in people with BD may be due to the nature of the condition (8, 9).

Strakowski and DelBello (7) hypothesise that substance abuse may be a symptom of BD and suggest that this leads to two predictions:

[1] substance abuse begins after the onset of BD

[2] substance abuse is state dependent, therefore the amount of substance use changes depending on the individual's current mood state

The community based Zurich cohort study (28) provides data to test the first prediction of Strakowski and DelBello (7) that cannabis use begins after the onset of BD. Merikangas et al (28) aimed to examine the degree to which BD spectrum conditions increased the risk for various substance use disorders. Previous epidemiological research investigating the co-morbidity of mood disorders and substance use often relied on either cross-sectional design, making it difficult to ascertain causal inferences or retrospective estimates of disorder onset, which may be open to bias. In response to the methodological issues that can arise from using such data, a prospective study design was utilised.

Over a 20-year period, young adults (age 19-20) were interviewed at six time points in their home environment. Substance use, mood disorders and sub-threshold symptoms of these disorders, based on DSM-IV (27) criteria were assessed at each interview. Participants meeting criteria for cannabis abuse and dependence at baseline were excluded from analyses. The development of later cannabis abuse/ dependence (OR, 4.82; 95% CI, 2.0-11.06) was significantly predicted by the presence of sub-threshold manic symptoms at baseline. However the study did not control for the influence of factors such as gender and personality traits (for example impulsivity). An adjustment

for such factors may affect the associations reported as trait impulsivity has been identified as a shared risk factor for the development of BD and substance use disorders (15).

As the authors highlighted, the 20-year attrition rate of 38% in the Zurich study (28) may indicate that the sample is self-selected and therefore unrepresentative, which could lead to difficulties generalising results from this study to other populations. Additionally, whilst the cohort was assessed until their 40th year, in fact the last assessment of mood was made in the participants' 35th year due to the prospective nature of the analyses. It follows that their findings may not generalise to older populations.

The study outlined above provides some support for the prediction that substance abuse begins after the onset of BD. However this is limited to manic symptoms (below current diagnostic thresholds) rather than a clinical diagnosis of BD. In addition, analyses were limited to investigating the risk posed by BD to the later development of cannabis use disorders. Merikangas et al (28) recognise the need to take into account the bidirectional associations that may be present in the data but were not investigated in this study.

In contrast, a longitudinal population based study (29), utilizing the Composite International Diagnostic Interview (CIDI: 30), found that over a 3-year follow up period, manic symptoms at baseline did not predict the onset of cannabis use during follow up (OR = 2.70, 95% CI: 1.54-4.75). Furthermore they found that cannabis use at baseline in-fact increased the risk for manic symptoms during follow up (OR = 2.70, 95% CI: 1.54-4.75). Participants did not meet criteria for a mood disorder at baseline.

Similarly, two additional studies (31, 32) used the CIDI (30) to assess whether lifetime cannabis use predicted increased risk for first incidence of mood disorders over specific time periods; likewise participants did not meet criteria for a mood disorder at baseline.

Using a longitudinal study design with an 8 year follow up, Tijssen et al (32) investigated risk factors for predicting onset and persistence of sub-threshold BD symptoms in adolescents. Participants (n = 543) did not have a history of manic symptoms at baseline. They found onset of manic symptoms was associated with lifetime cannabis use (defined as minimum usage of five times at baseline; OR 4.26; 95% CI 1.42-12.76, P = 0.010). Both Tijssen et al (32) and Henquet et al (29) examined sub-threshold manic symptoms in the general population. Therefore there may be difficulties with generalising the reported association to people with a clinical diagnosis of BD.

Van Laar et al (31) interviewed participants (n= 3881) over a three year period and found any use of cannabis at baseline predicted first incidence of BD (OR = 4.98%, 95% CI: 1.80-13.81), based on DSM-III-R (33) criteria. The association remained significant, even when they adjusted for strong confounders such as alcohol and other substance use disorders, lifetime psychotic symptoms and lifetime anxiety symptoms.

Taken together, the studies reviewed so far provide a complex picture of co-occurring BD and cannabis use. It appears to be the case that cannabis use can occur before or after the development of BD. Whilst one study (28) indicates that the BD symptoms predict later cannabis use, one study fails to support this direction of effects (29) and several other studies indicate a the reverse causation; with cannabis use at baseline predicting the later development of BD symptoms (29, 31,32).

Data from these studies (29, 31, 32) challenge the first prediction of Strakowski and DelBello (7) that cannabis use begins following the onset of BD, since a high proportion of participants had begun to use cannabis prior to the onset of BD symptoms.

The second prediction from Strakowski and DelBello's (7) hypothesis (that substance use may be a symptom of BD) is that substance abuse is state dependent, therefore the amount of substance use changes depending on an individual's current mood state.

Unfortunately, none of the studies in the current review investigate the actual amount of cannabis used over the course of BD. However, there is data available which investigates periods of cannabis use versus non-use. Strakowski et al (34) studied the sequence of onset of BD and cannabis use disorder, based on previous studies that focused on co-occurring alcohol use and BD (8, 26). They investigated the course of BD and cannabis use disorders after a first psychiatric hospitalisation of mania by comparing patients whose BD onset preceded the development of cannabis use disorder and patients whose cannabis use began before onset of BD. The 2 groups demonstrated significant differences in their improvement, the cannabis first group exhibited better recovery. However when adjusted for potential mediator variables (i.e. age, gender, education, rates of other substance use disorders and age of onset of BD) these results did not remain significant. More than 70% of the patients using cannabis prior to hospitalisation did not resume use for at least 8 weeks following discharge.

This study provides some support for the second prediction; that substance use changes depending on the person's mood state. However there may have been other factors involved which led to a change in their typical cannabis use, such as access to money or loss of contacts to purchase cannabis following their discharge from hospital.

Another prospective study (35) followed 166 people with first episode BD I over the course of 4.7 years, using the Longitudinal Interval Follow up Evaluation (LIFE), based on DSM-IV (27) criteria. Participants were rated for the presence or absence of affective morbidity or substance use within three-month (quarterly) intervals. Findings revealed manic or hypomanic morbidity was associated with cannabis use during the same quarter (RC = 0.116; 95% CI = 0.053-0.178; z-score = 3.63, $p < 0.001$) and the preceding quarter (RC = 0.111; 95% CI = 0.054-0.168; z-score = 3.80, $p< 0.001$) but not in the following quarter. Cannabis use was not related to changes in depressive symptoms. For analysis manic and hypomanic morbidity was dichotomised as either present or absent, regardless of severity and included sub-syndromal mania or hypomania. This approach may have reduced the accuracy of the reported associations.

Whilst a number of methodological issues have been raised in the 2 studies above (34, 35) their results nonetheless provide some evidence to support the second prediction. Their findings are consistent with the suggestion that there is a selective association of particular substances depending on the mood state of the individuals with BD, (since participants were using cannabis at different stages of their illness).

Data to support this prediction can also be drawn from the self-report literature (36, 37) which will be discussed further in the next section. Individuals have reported using different substances at different times to manage symptoms of their conditions. However there is currently no data to indicate whether such self-reported "self-medication" represents an increase in their typical use. In the two studies mentioned above (34, 35) data for cannabis use has been dichotomised to being present or absent, regardless of quantity or frequency of use. In future studies it would be important to investigate how amount and frequency fluctuate as a function of mood.

Hypothesis 2: Substance abuse is an attempt by individuals with BD to self-medicate symptoms

For substance abuse in general, several theorists have suggested a 'self-medication hypothesis', where patients attempt to reduce the intensity of their symptoms through using particular substances (7, 11, 12, 38). As regards to BD, this hypothesis assumes that when the symptoms such as hyperactivity, restlessness, over-excitability and poor sleep (that often characterise mania) become unbearable then individuals may turn to alcohol or cannabis for their sedative effects, to relieve symptoms or reduce the tension or anxiety related to their mood state. Similarly when individuals feel low, hopeless and worthless, they may use stimulants (e.g. cocaine or ecstasy) to enhance their mood, self-esteem and confidence.

In their paper, Strakowski and DelBello (7) state that this second hypothesis leads to two predictions:

> [1] that substance abuse occurs after the onset of BD (c.f. Hypothesis 1)
>
> [2] that the specific type of substance is state dependent, whereby an individual uses different drugs according to their specific properties, depending on mood state

As previously discussed, data from studies reviewed so far is inconsistent as regards to the onset of cannabis use and BD. One study (28) did find that cannabis use commenced after the onset of BD symptoms, which lends some support to the prediction. This was limited to sub-threshold manic symptoms. Additionally whilst those meeting criteria for cannabis abuse and dependence at baseline were excluded, they did not control for potential confounders or explore for reverse causality.

However, despite there being only a limited number of studies bearing on cannabis use and BD they nonetheless contain evidence to support the suggestion that cannabis use predates the onset of BD, which does not support the first prediction. Van Laar et al (31) used participants with no prior mood disorders and found that any level of cannabis use at baseline predicted first incidence of BD. Additionally, Henquet et al, (29) and Tijssen et al (32) also used participant samples with no prior mood disorders and found significant associations between cannabis use at baseline and the onset of BD symptoms at post baseline. These associations remained significant even when adjusted for potential confounders

Strakowski and DelBello (7) provide one explanation for substance abuse appearing to occur prior to the onset of BD. They suggest that in fact substance abuse may begin very early in the onset of BD during the prodromal or sub-syndromal phases. They argue that individuals may be masking the affective symptoms so that it appears their substance use occurs before the onset of BD, when in fact, it does not. Data from the Zurich study (28) lends some support to the masking hypothesis where cannabis use occurred after the onset of sub-threshold mania (defined as either a duration of less than 4 days, or as less than 4 symptoms with impairment), suggesting perhaps that individuals were indeed in the prodromal/ sub-syndromal phase when they began using cannabis.

The second prediction for the 'self-medication' hypothesis is that the specific type of substance used is state dependent, by which individuals use drugs with specific properties, depending on mood state. A review paper of this area (39) focused on the therapeutic use of cannabis or cannabinoids in BD, suggests that key constituents of cannabis, THC and cannabidiol (CBD) may have mood stabilising properties. The authors found no systematic studies of cannabinoids in BD, but they do propose that cannabinoids; THC and CBD may produce a range of sedative, hypnotic, anxiolytic, anti-depressant, and anti-psychotic effects. They also suggest that the use of cannabinoids warrants controlled clinical trials to investigate their therapeutic potential. This would mirror studies of patients with acute and chronic pain conditions and those with multiple sclerosis (40, 41), where patients reported improvements in the severity of their symptoms and of their mental health.

Grinspoon and Bakalar (36) provided 5 case histories, which indicated that patients commented that they found cannabis to be useful in the treatment of their BD. They reported that patients found using cannabis helped relax and control manic behaviour and relieved the effects of other medication. Similarly Gruber et al (37) described cases where cannabis appeared to have a direct anti-depressant effect, based on self-reports. In the cases of 3 patients with BD, cannabis was found to be superior to anti-depressants in relieving their depression. However this should be interpreted with caution due to the small sample size and potential bias produced from using data that has been unsystematically collected.

A recent systematic qualitative study (42) utilising semi-structured interviews, had findings differing with Gruber et al (37). They reported that cannabis was not always perceived as useful when individuals were depressed due to its association with mood enhancing qualities. They also found

that patients' reasons for using cannabis were idiosyncratic. Some used it to alleviate and reduce symptoms of mania, whilst others used it prior to entering a manic state and once elated, felt satisfied and experienced a decreased need for cannabis.

The findings from the self-report literature indicate that individuals appear to use cannabis when both manic and depressed for a variety of reasons. This may contradict the second prediction of Strakowski and DelBello (7) that individuals use different drugs, depending on their mood state. However individuals with BD may use cannabis in discrete mood states due to the various pharmacological properties it may contain, as noted by Ashton et al (39). Whilst manic, people may use cannabis for the sedative effects and when depressed, for the anti-depressive effects proposed by Ashton et al (39).

If true, the suggestion that cannabis may produce anti-depressant effects could cause additional complications for individuals with BD. Anti-depressants have previously been associated with the induction of manic episodes (43, 44, 45), additionally impacting on the course of the illness (46). Anti-depressant effects exerted by cannabinoids could have the potential to induce manic-like episodes. A number of case studies have presented patients who appeared to experience manic symptoms following cannabis use (47, 48, 49).

Links between cannabis use and manic symptoms are consistent throughout the literature. Exploring causality, Henquet et al (29) and Tijssen et al (32) found cannabis use at baseline predicted later onset of manic symptoms. Over the course of BD, Baethge et al (35) found cannabis use preceded and also coincided with manic morbidity but did not follow a change in mood state.

A further investigation into the effect of cannabis use on the symptoms of people with BD is indicated. A recent study (50) used experience sampling methodology (ESM) to investigate the effects of cannabis use on psychotic symptoms and mood in individuals with psychosis and a non-clinical sample, over the course of daily life. For individual's with BD, tracking the daily patterns of cannabis use and affective symptoms may provide insight into the range of effects which have been reported in the literature - for example whether cannabis use leads to an increase in manic or depressive symptoms or whether a change in affective symptoms leads to an increase or decrease of cannabis use.

Hypothesis 3: Substance abuse causes BD

The third hypothesis for why substance abuse is so common in individuals with BD is that substance abuse may in fact cause the illness. The effects of substance use have been noted to imitate affective disorders (9). The euphoria and elation brought on by stimulants, mirrors the high of mania, which is typically followed by post drug effects such as low mood and lack of energy, which are characteristic of depression.

Strakowski and DelBello (7) hypothesise that firstly substance abuse may directly cause symptoms that resemble BD or secondly may actually initiate BD in vulnerable individuals who might not otherwise have developed the illness. For this hypothesis Strakowski and DelBello (7) make 3 further predictions:

[1] substance abuse begins prior to onset of BD

[2] there is less familial affective illness in people with BD with substance abuse than those without

[3] BD will resolve once substances are no longer abused

As noted earlier in this review, there appears to be conflicting evidence regarding the sequencing of onset of cannabis use and BD. From reviewing the current research there appears to be more evidence to suggest that cannabis use begins prior to the onset of BD (29, 31, 32) which supports the first prediction. However there is some evidence to suggest that cannabis use does commence after the onset of BD symptomology (28).

The second prediction proposes that if substance use causes BD in people that might not have developed the illness otherwise, then those people should demonstrate lower rates of BD in their relatives, than those who do not use substances. Unfortunately no studies to date have investigated the use of cannabis exclusively in relation to rates of familial BD.

The third prediction relating to substance abuse causing BD, states that once substance use is resolved then affective symptoms should cease. Few studies have examined the longitudinal course of co-occurring BD and cannabis use. As discussed previously Strakowski et al (34) studied the course of BD and cannabis use disorders after a first psychiatric hospitalisation for mania. Seventy percent of the participants did not resume cannabis for at least 8 weeks following discharge, which provides some support for this prediction. However authors found the recurrence of cannabis

abuse was rapid and common. In addition, 16 patients developed a new cannabis use disorder during follow-up, though it is not clear whether this was triggered by a change in their affective symptoms during this period.

The second element of the third Strakowski and DelBello (7) hypothesis suggests that substance use may initiate BD in vulnerable individuals who might not otherwise have developed the illness. Unfortunately they do not define vulnerability, though one can assume this refers to those who have an additional risk factor (e.g. biological) that may make them more susceptible to developing BD or BD symptoms if they use substances.

Unfortunately, none of the studies included in the review have investigated if there are any specific risk factors which make individuals who use cannabis more vulnerable to developing BD, than those who do not go on to develop BD. Research in this area is far more advanced in relation to psychosis and cannabis use. Research has identified a number of factors which interact with cannabis use and play a causal role in the development of psychosis or psychotic symptoms. These include those individuals already vulnerable to pre-existing psychotic symptoms (e.g. 51, 52) childhood trauma (53) and individuals that carry the catechol-*o*-methyltransferase gene (54).

Strakowski and DelBello's (7) further view is that substance abuse may affect the course of BD in that it initiates either the initial or first few episodes. They suggest this could occur through the kindling or sensitisation process suggested by Post et al (55). As noted earlier, neuro-anatomical findings suggest CB_1 interacts and alters the function of dopamine, which modulates a number of areas including affect. It has been proposed that both psychosis and mania may share a genetic vulnerability to a dysregulated dopamine system, which may be precipitated by pharmacological stress, such as cannabis use (56). The repeated use of cannabis and subsequent production of the cannabinoids, may lead to permanent changes in the dopaminergic system in the brain (57, 58). This process called 'sensitisation' refers to a change in dopaminergic state that may lead to random releases of dopamine in the brain. This, it has been suggested, may contribute to the development of psychosis (59, 60).

Authors have suggested that this same mechanism may apply to mania (29, 31). Therefore once there has been a permanent alteration in the central nervous system, individuals will continue to display affective symptoms, regardless of continued cannabis use (7). Studies, which have revealed

that baseline cannabis use is associated with the later development of manic symptoms, support this hypothesis (29, 32).

However further investigation of these interactions and the role of genetic and environmental factors, which may lead to the development of BD, is indicated. Henquet et al (29) suggest such studies should focus on individuals who have been exposed to cannabis use and have a pre-existing vulnerability to a dysregulated dopamine system.

Hypothesis 4: Cannabis use and BD share a common risk factor

Strakowski and DelBello's (7) final hypothesis is that BD and substance use disorders may share a common risk factor. For example the genes that cause BD, may also contribute to substance abuse (9). Previous studies have found BD and substance use share common risk factors such as elevated levels of impulsivity (e.g. 15) sensation seeking (12); co-morbidity with anxiety disorders (61) or enhanced Behavioural Activation System (BAS) sensitivity (62).

A recent study (63) investigated independent predictors for lifetime and recent substance use disorders in a sample of patients with rapid-cycling BD. The authors highlight that their study is the first to investigate the association between anxiety disorders and recent/ lifetime prevalence of particular substances, in a sample of BD individuals. Patients with co-occurring anxiety disorders (n=261) had significantly increased rates of lifetime (OR = 3.4, 95% CI: 1.91-6.01, p = < 0.0001) and recent (OR=2.5, 95% CI: 1.14 – 5.77, p = < 0.018) cannabis dependence compared to those without anxiety disorder (n=303). Specifically, Generalised Anxiety Disorder (GAD) was associated with lifetime (OR = 3.36, 95% CI: 1.646 – 6.856, p = 0.0009) and recent (OR=3.28, 95% CI: 1.214 – 8.863, p = 0.0191) cannabis dependence. They also found that a history of physical abuse was associated with recent cannabis dependence (OR = 3.47, 95% CI: 1.385-8.673, p = 0.0079). These results remained significant even when adjusted for potential confounder variables such as gender, age, number of episodes, history of alcohol use and psychosis.

A number of limitations of the study were identified. Not all Axis I anxiety disorders were assessed in the study, history for post traumatic stress disorder and social phobia were not available for analyses. Therefore whilst an association was revealed between 'anxiety disorders', Rapid Cycling BD and cannabis dependence, results may not generalise to all types of anxiety. Data from the

study was cross sectional, so whilst a relationship between anxiety disorders, in particular GAD and cannabis dependence was revealed, causality cannot be established. A longitudinal prospective study is indicated to investigate this further. Additionally, as the authors noted, differences between BD patients with rapid cycling BD and without have been reported (64, 65), therefore findings from the study may not generalise to other BD populations.

Unfortunately no further studies in the review examined whether exclusively cannabis use and BD share a common risk factor and thereby providing additional evidence required for this fourth hypothesis. However a number of studies reviewed have found evidence to suggest that co-occurring BD and cannabis use are in fact a risk factor for poorer outcomes; including increasing severity of symptoms and non-medication compliance, compared to BD alone.

A prospective observational study (66) of both inpatients and outpatients with BD, aimed to investigate the exposure of cannabis use on clinical and social treatment outcomes over the course of one year. During this time period, cannabis users exhibited less compliance and higher overall symptom severity (mania and psychosis symptoms) in comparison to the non-users. Furthermore, cannabis users experienced less satisfaction with life and experienced a lower probability of developing a relationship.

A recent prospective observational study (67) investigated factors that influenced medication adherence in people with BD during initial uptake or a change in treatment. They found that the patients less likely to comply with medication adherence were those with cannabis abuse/dependence during the first 12 weeks of treatment.

Unfortunately, due to the nature of the designs, it is impossible to determine true causality in either of the 2 studies (66, 67). Therefore whilst significant differences were revealed between users and non-users, it is impossible to affirm that this was due solely to the effects of cannabis use.

Investigating neuro-physiological links between co-morbid cannabis use and BD, Jarvis et al (68) compared brain morphometry between BD adolescents with co-occurring cannabis use disorders and without. Using whole brain structural magnetic resonance imaging scans (MRI) they found adolescents with co-occurring BD and cannabis use demonstrated evidence of greater structural abnormalities in the frontal and temporal cortical areas, as well as in the sub-cortical regions, linked to emotional and motivational regulation. Due to the cross-sectional nature of the study, it remains difficult to ascertain causal inferences from the results, though they do tentatively suggest there

may be underlying differences involved in cannabis use. This research may provide clues to the possible reasons for non-compliance (66, 67), as repeated cannabis use may affect an individual's motivation and ability to make decisions about taking their medication, which in turn may have an affect on their symptom severity and future outcomes.

Whilst a number of methodological issues were raised, Gao et al (63) provide evidence to suggest co-occurring rapid-cycling BD and cannabis use may share common risk factors such as anxiety disorders (specially GAD) and past physical abuse. This mirrors results from previous studies which have found high levels of co morbidity of anxiety disorders in individuals with BD and substance use in general (61). Further research is needed to explore whether individuals with co-occurring BD and specifically cannabis use may share other common risk factors (e.g. impulsivity), like substance use in general. Additionally a number of studies (66, 67, 68) appear to suggest that the co-occurrence of BD and cannabis use may increase the risk of a range of difficulties being experienced and reduce the likelihood of positive outcomes, compared to BD alone.

SUMMARY

Thirteen studies reporting on the relationship between BD and cannabis use were examined and critically reviewed. The studies vary considerably with regards to the methods and samples used, ranging from case series (e.g. 36) to longitudinal prospective studies (e.g. 29) and individuals with sub-threshold manic symptoms (e.g. 28) to those with a DSM-IV (27) diagnosis of BD disorder (e.g. 35).

A number of limitations were highlighted throughout the review. Firstly, 4 of the 13 studies reviewed used sub-threshold symptoms of BD (28, 29, 35, 32), based on existing literature which suggests that there are expressions of mania distributed within the general population (69, 70). However this may lead to an overestimation of associations reported in these studies when compared to those that include individuals with a clinical diagnosis of BD.

The identification participant's level of cannabis use/abuse/dependence varied throughout the studies. Some studies required a SCID diagnosis or cannabis abuse or dependence (e.g. 28, 35, 68), whilst in others lifetime use was determined as 5 times or more at baseline (31, 32). The diagnostic instrument used for assessment varied throughout the studies, some used the SCID (e.g. 34, 35, 68)

others used the CIDI (e.g. 29) and one study used the Structured Diagnostic Interview for Psychopathologic and Somatic Syndromes (e.g. 28). However, all the above instruments were based on either DSM-III (33) or DSM- IV (27) criteria.

All of the studies relied on self-report data, which may lead to underestimations due to the illegal nature of drug use. Hair sample analysis may be a more reliable method of assessment in future research (71). The studies did not report on the type of cannabis used and data indicates that level of THC (the major psychoactive compound in cannabis) varies depending on type of cannabis (72, 73). In one study (28) data was collected over a number of decades. Reports indicate that the concentration levels of THC found in cannabis have risen over time (from 9% in 1999 to 18% in 2005) according to Niesink et al (74).

Despite the limitations already discussed, studies reviewed here do provide further evidence both for and against Strakowski and DelBello's (7) original hypotheses. Like Strakowski and DelBello's (7) findings, there appear to be a number of factors that contribute to the high occurrence of BD and cannabis use and specific reasons for this co-morbidity remain equivocal. There is a conflict in evidence regarding the sequencing of onset of BD and cannabis use. However from reviewing the available research, there appears to be more evidence to suggest that cannabis use begins prior to the onset of BD (29, 31, 32). This fails to support the prediction that substance use originates as a way of coping with BD ('the self-medication' hypothesis), since in many cases cannabis use occurred before the onset of BD. However the self-report literature indicates that patients do indeed find cannabis useful in the treatment of their BD. Whilst cannabis use was perceived as helpful in the management of BD, reasons for its use appeared idiosyncratic.

Some individuals, for example, appeared to use cannabis when both manic and depressed. This is not consistent with the self-medication hypothesis, which states that individuals use different drugs depending on their mood state. Reasons for use from the self-report literature are consistent with the pharmacological properties of cannabis outlined in a review (39). The paper suggests that THC and CBD, the key constituents of cannabis may produce a range of effects (39). Therefore whilst manic, individuals may use cannabis for the sedative effects and when depressed for the anti-depressive effects.

Links between manic symptoms and cannabis use were consistent throughout the literature (29, 32, 35). One possible explanation for this is that cannabis use can induce mania, though this requires further investigation into the pharmacological properties of cannabis and the potential subsequent effects. As discussed previously the interaction between CB_1 and dopamine can lead to a permanent change in the central nervous system and may have important consequences for individuals with BD.

The studies reviewed have made a significant contribution to our understanding of co-occurring cannabis use and BD. However, the literature review has highlighted a lack of research focused specifically on cannabis use and BD. There are a number of areas which warrant further attention. Research should focus on whether there are additional factors which interact with cannabis use and make individuals more 'vulnerable' to developing BD. This includes an investigation of the interaction between THC and dopamine in the brain and whether this leads to the development of BD or whether it further complicates affect regulation. The relationship between cannabis use and BD also requires further investigation - whether individuals are using cannabis to self-medicate a change in symptoms or whether cannabis use itself leads to a change in symptoms. Additional research in this area may offer a clearer understanding of why there are such high levels of cannabis use in individuals with BD.

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PAPER TWO

The relationship between Bipolar Disorder and Cannabis use in daily life: An experience sampling study

ELIZABETH TYLER

PREFACE

This work for this paper was completed between January 2010 and May 2011. A number of individuals made significant contributions towards the research study. Firstly, Professor Christine Barrowclough provided overall support and supervision for the study. She also read the manuscript, gave advice and was involved in the formulation of items for the experience sampling diary. Professor Steven Jones was the field supervisor for the study and was also involved in the formulation of the items for the experience sampling diary. Miss Nancy Black assisted with the identification and recruitment of research participants for the study. Miss Lesley-Anne Carter provided statistical support and supervision for the study.

The author intends to publish the research paper in 'Bipolar Disorders - An International Journal of Psychiatry and Neurosciences' and the paper has been prepared in accordance with their requirements (see appendix A for author guidelines). The authors on this paper will be: Elizabeth Tyler, Professor Christine Barrowclough, Professor Steven Jones, Nancy Black and Lesley-Anne Carter.

ABSTRACT

Objectives: Although cannabis use is common in bipolar disorder (BD) and may contribute to worse clinical outcomes, little is understood about the relationship between this drug and BD over the course of daily life.

Methods: Twenty-three participants with BD type I or type II completed diaries for 6 days using Experience Sampling Methodology to provide a close investigation into the associations between cannabis, mood, BD symptoms and Behavioual Activation System (BAS) sensitivity. Self-reported BAS was also measured and the extent to which this predicted changes in mood, BD symptoms and cannabis use.

Results: The results indicated that positive affect predicted the likelihood of subsequent cannabis use (OR:1.25 ,CI:1.06–1.47, P=0.008). However, neither negative affect, manic nor depressive symptoms predicted the use of cannabis. Cannabis use was associated with subsequent increases in positive affect (β=0.35, CI:0.20-0.51, P=0.000), manic symptoms (β=0.20,CI:0.05-0.34, P=0.009) and depressive symptoms (β= 0.17,CI:0.04-0.29, P=0.008). BAS sensitivity (ESM diary) was associated with increases in positive affect (β=0.18, CI:-0.09-0.26, P=0.000) and manic symptoms (β=0.27,CI:0.19-0.35, P=0.000). Similarly a higher self-reported BAS (questionnaire) was associated with increases in positive affect (β = 0.06, CI: 0.02–0.89, P=0.001) and manic symptoms (β = 0.08, CI: 0.04–0.12, P=0.000).

Conclusion: The findings indicate that cannabis use is associated with a number of psychological effects, however no evidence for the self medication of mood and BD symptoms was revealed in daily life. Associations between BAS sensitivity and positive and manic symptoms are consistent with current literature. The findings in relation to existing literature and clinical implications are discussed in the paper.

Keywords: bipolar disorder, mania, cannabis use, experience sampling methodology, ESM, behavioual activation system, self-medication.

INTRODUCTION

Cannabis is the drug most frequently used by individuals with Bipolar Disorder (BD: 1, 2, 3). Estimates of current use range from 8% to 22% and lifetime use from 30% to 64% (4). In comparison to BD alone, co-occurrence with cannabis use is a risk factor for poorer outcomes, including increased symptom severity (5) and poorer medication compliance (5, 6). Therefore individuals with co-morbid BD and cannabis use represent an important group to study from both a clinical and a public health perspective.

Specific reasons for this co-morbidity remain equivocal and are not yet fully understood. A number of prospective cohort studies (7, 8, 9) have found evidence to suggest that cannabis use begins prior to onset, which might suggest a causal role in the development of BD. However there is also evidence to suggest that for some, cannabis use commences following the onset of BD symptomatology (10). The self-report literature suggests that individuals with BD use cannabis as a form of self-medication to alleviate manic symptoms (11, 12) and to relieve depression (13). These studies (11, 12, 13) suggest that individuals with BD may use cannabis for the differing pharmacological properties outlined by Ashton et al (14) who proposed that Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), (the key constituents of cannabis) may produce a range of effects (e.g. sedative, anxiolytic, antidepressant). Therefore whilst manic, individuals may use cannabis for the sedative effects and when depressed for the anti-depressive effects.

In accordance with the Behavioural Activation System (BAS) hypersensitivity model of BD (15, 16), the high rates of BD and substance use reported may be partially due to a hyper-reactive BAS. The model suggests that vulnerability to BD may be reflected in an overly sensitive BAS that is hyper-active to relevant cues such as reward incentive or goal striving (17). It is therefore hypothesised that excessive BAS activation and increased sensitivity can lead to hypo(manic) symptoms such as euphoria, optimism, distractibility, excessive goal seeking and increased self-confidence (15, 18). Alloy et al (19) hypothesise that high BAS activation should also be associated with greater substance abuse, which occurs as a product of an individual's pursuit for rewarding stimuli (i.e. drug-induced 'highs'). They found that higher BAS sensitivity, measured by the BIS/BAS scale (20), predicted BD status and increased substance use difficulties.

A number of factors appear to contribute towards the high level of cannabis use reported in BD. Similarly, rates of cannabis use in individuals with psychosis are high (21, 22) and there is no single model available which fully explains this co morbidity (23). A recent study (24) used the experience

sampling method (ESM) to provide further insight into the complicated dynamics of cannabis use and its effect on individuals with psychosis, in the context of daily life. Henquet et al (24) found that cannabis use predicted an increase in positive affect in both individuals with psychosis and a non-clinical control group. Cannabis use predicted a decrease in negative affect and an increase in the number of hallucinatory experiences in the psychosis group alone. They found no evidence to support the self-medication hypothesis as neither psychotic experiences or mood was found to predict cannabis use. Similarly to Henquet et al (24), the current study was designed using ESM to allow a close investigation into BD and cannabis use over the course of daily life and to aid further understanding of this seemingly complex relationship.

ESM is a structured diary method where individuals are asked to report their thoughts, feelings and symptoms over the course of daily life. ESM was pioneered in mental health research by a group of researchers at the University of Maastricht (25, 26). It offers a number of advantages in comparison to traditional assessments of mental health experiences (27, 28), which rely on using retrospective data, and may be open to recall bias. With ESM, the short space between an event occurring and reporting of the details reduces the possibility of memory bias (29). ESM examines phenomena in the real world as they occur and therefore has a high level of ecological validity. It provides a rich and descriptive data set, detailing a participant's daily experience and has the capacity to assess the temporal relationship between numerous variables (28).

ESM has previously been used to investigate the perception of daily 'hassles' and 'uplifts' in individuals with BD (30). Furthermore, Knowles et al (31) used a diary method, where individuals with BD or unipolar depression plus a non-clinical sample reported on self-esteem and positive and negative affect twice a day, over the course of a week.

To the author's knowledge there are no published studies that have used ESM to examine the relationship between BD and cannabis use. In the current study, the use of ESM aimed to provide an in-depth investigation into the associations between cannabis use, mood, BD symptoms and BAS sensitivity in individuals with BD, over the course of daily life, and to test a number of predictions suggested in the literature outlined above.

The aims of the study were to explore whether:

1] the frequency of cannabis use would increase as a function of mood and BD symptom change (i.e. self medication effects)

2] cannabis use would be associated with subsequent changes in mood and BD symptoms

3] an increase in BAS sensitivity (measured by the questions in the ESM diary) would lead to an increase in manic symptoms and / or cannabis use

4] individuals scoring higher on the BAS total, (from the BIS/ BAS questionnaire; 20) would experience higher levels of manic symptoms and were more likely to use cannabis

METHOD

Participants

Ethical approval for the study was obtained from the National Health Service (NHS) and the University of Manchester research ethics committees. Twenty-seven participants were recruited for the study from a number of sources. These included 4 mental health trusts in the North-West of England, self-help organisations (Manic Depression Fellowship and Mood Swings), self-referral from the online University of Manchester research volunteering website and from the PARADES[1] participant panel (a confidential database of individuals with BD who have taken part in previous PARADES research and have expressed an interest in taking part in further research).

All individuals met criteria for BD-I or BD-II, as determined by the Structured Clinical Interview for Axis I Disorders (SCID) based on the DSM-IV diagnostic criteria (32). Researchers were trained in the SCID and received regular supervision from a consultant psychiatrist. Substance use disorders were assessed using the substance use module of the SCID (32). To be included, participants were required to report using cannabis on at least two occasions per week (in at least half the weeks in the 3 months prior to assessment). Exclusion criteria for the study included meeting criteria for a current episode of mania or depression (if currently met criteria they were kept on a waiting list until out of episode), aged below 18, evidence of an organic brain disease or moderate to severe learning disability.

[1] The study is part of the PARADES programme, Spectrum Centre, University of Lancaster, funded by the National Institute for Health Research. A research programme focused on BD and comorbid problems.

Power calculations are difficult and complicated to estimate in ESM analyses due to the multi-level nature. This is because there is a sample size for each level and therefore statistical power is determined at more than one level (33). It was expected that the sample size in the current study was nevertheless enough to detect effects.

Experience Sampling Method

At the beginning of this study, participants were given a paper diary and a digital wristwatch. In accordance with previous research (e.g. 34, 35), the ESM period lasted for six consecutive days and the watch emitted a signal on ten occasions throughout the day at pseudo-random times, between the hours of 8am and 10pm.

Each time participants heard the beep they were required to fill out a page of the diary. The diary consisted of questions on thoughts, mood, BD symptomatology, BAS sensitivity, contextual information regarding their current situation and substance use. Participants were required to fill out the diary within 15 minutes of hearing the beep and to record the time of completion. Any entries completed outside this time frame were excluded from analyses. Previous research has demonstrated that entries completed after the 15 minutes are less reliable and valid (26). A minimum of 20 valid diary reports were required by each participant, to ensure the data was representative (28).

Procedure

During the initial visit informed consent was gained from the participant and the SCID (32) interview was completed. Where all inclusion criteria were met, a second visit was arranged, one day prior to the ESM period. During the second visit, the participant was introduced to the watch and paper diary and briefed about the study. The general procedure described above was explained in detail.

During the briefing session the researcher discussed the layout of the diary in detail and asked the participant to fill out a trial page. Each response was checked carefully, thus ensuring that the participant fully understood what was required.

The researcher left contact details with the participant in case any queries arose regarding the study. Participants were contacted via telephone and text message twice during the 6-day ESM period in order to facilitate motivation and discuss any queries regarding the study.

On the seventh day a final meeting was arranged to collect the watches and diaries and debrief the participant. The diaries were checked for any ambiguity and whether the participant had completed 20 or more entries. Information was recorded on whether it had been a typical week and if the experiment had influenced their mood, cannabis use and usual activities. Participants filled out the BIS/BAS scale (20) at this final meeting.

MEASURES

The experience sampling diary

Mood items

Current mood was assessed using ten items, rated on a 7-point Likert scale (where 1= 'not at all' and 7 =' very much so'). Items were drawn from previous ESM studies (34, 36) using participants with psychosis and healthy controls. A principal components analysis revealed two separate scales: the items 'cheerful', 'excited', 'relaxed', 'satisfied', 'happy' formed the positive affect scale ($\propto$ = 0.85) and the items 'lonely', 'anxious', 'irritate', 'sad', 'guilty', formed the negative affect scale ($\propto$ = 0.82). The mean scores for each scale were used in the analyses.

BD Symptoms

Current BD symptomatology (mania and depression) was assessed using 7 items rated on a 7-point Likert scale. The formulated items were chosen in accordance with guidelines for selection of ESM items (28) and to assess momentary experiences of BD symptoms that might occur and fluctuate during the flow of daily life. A service-user group of 4 people with a BD diagnosis verified the appropriateness of the questions and members felt the language reflected how they would describe their own behaviour and experiences. A principal components analysis revealed two distinct subscales. The mania scale ($\propto$ =0.75) consisting of the items: I am 'full of energy', 'high', 'good ideas' and the depression scale ($\propto$ = 0.82), consisting of items: I feel 'slowed down', 'low', 'bad about myself', 'fearful'. The mean scores for each scale were used in the analyses.

BAS sensitivity

Current BAS sensitivity was assessed using three items rated on a 7-point Likert scale. The mean of these items was used to form the 'BAS sensitivity scale' ($\propto$ = 0.76), consisting of items: 'I want to try

something new', 'Nothing can stand in my way' and 'I'm craving excitement'. The mean scores for the scale were used in the analyses.

Substance use

Cannabis use, referred to as a 'cannabis moment' was reported in the diary after each beep (the period between the current beep and previous beep) from the question 'since the last beep I've used cannabis?' Cannabis use $_{previous}$ was defined as cannabis use during the period between previous beep and the beep before that. The type of cannabis used was also recorded.

Alcohol and other drug use (other than cannabis) were reported in the diary after each beep, termed 'alcohol moment' and 'other drug moment' respectively.

Questionnaire

BIS/ BAS scale (20)

The BIS/BAS scale (20) is a 20-item measure consisting of three BAS subscales: Reward Responsiveness (RR), Drive (D) and Fun Seeking (F) and one Behavioural Inhibition System (BIS) scale. Each item has four possible options ranging from "strongly disagree" to "strongly agree". The scale measures an individual's tendency to respond to threatening events with fear, anxiety or negative affect. It includes items such as 'I feel pretty worried or upset when I think or know somebody is angry at me'. Overall the BAS scale measures positive affect and motivation in response to incentives or rewards. The RR subscale assesses positive affect in response to expected or experienced desired events, e.g. 'it would excite me to win a contest'. The D subscale measures individuals motivation to pursue desired goals such as 'I go out of my way to get what I want'. The F subscale measures willingness / impulsivity to pursue or approach novel and rewarding stimuli, e.g. 'I will often do things for no other reason than they might be fun'. Carver and White (20) report internal consistencies of between (α's) from .59 to .74 for the subscales.

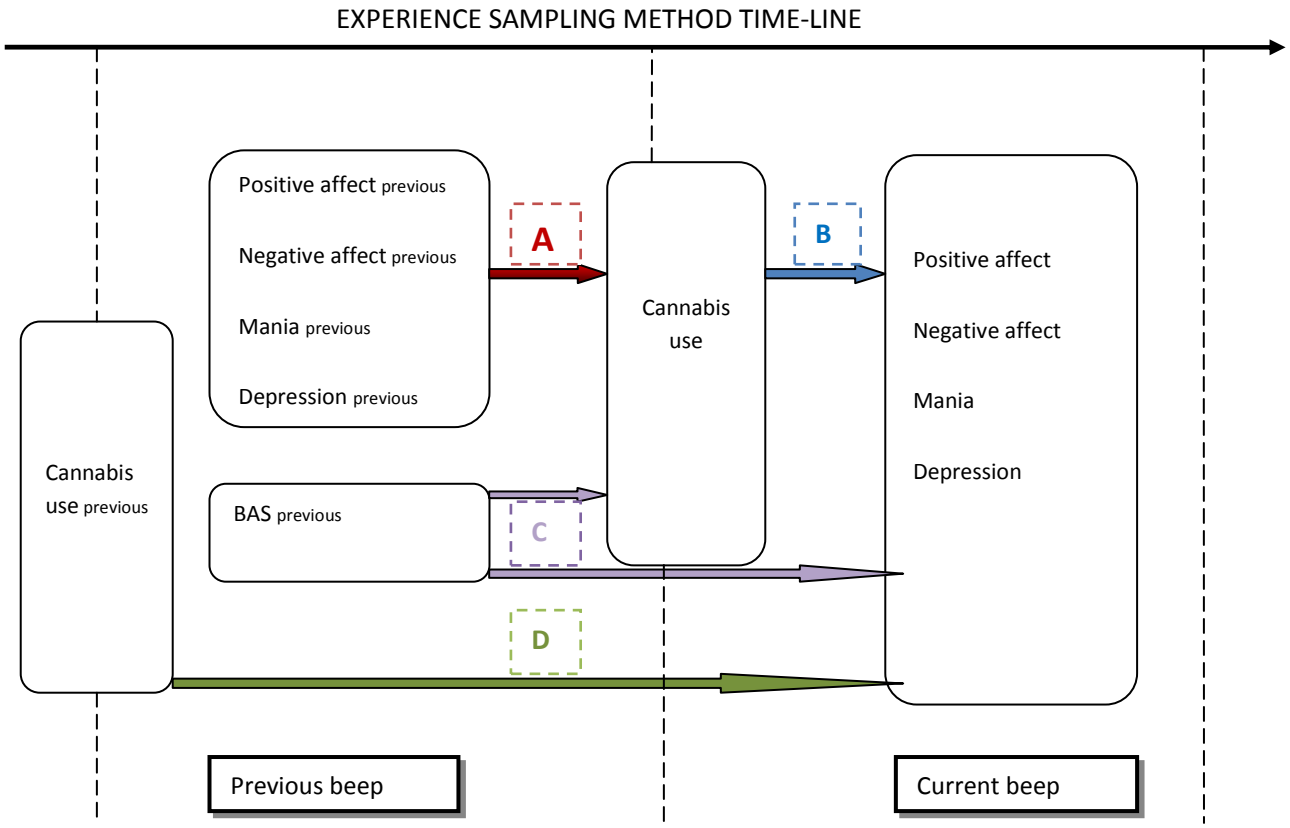
The scale has been widely used to measure individual differences in sensitivity of the BAS and the BIS in a number of populations including community samples (37) depressed mothers (38) and BD spectrum disorders (16, 19, 39).

Two studies (37, 40) found factor analyses supported a two-factor structure reflecting separate behavioural inhibition (BIS) and behavioural activation systems (BAS). The BAS total (consisting of the 3 subscales; RR, D and F) was used in the present study, the internal consistency in the present sample was, $\alpha = 0.76$ (BAS total).

STATISTICAL ANALYSIS STRATEGY

STATA 11 (41) was used for the analyses. ESM data has a hierarchical structure with the repeated participant observations (level one), nested within days (level two), nested within participants (level three). Responses for one individual or for one day are more likely to be similar than those for a different individual or for a different day. Multilevel random regression analysis was used as it takes the whole data set into account and can estimate the amount of variation that is associated with the three different levels. The multilevel regression XTMELOGIT routine was used for the dichotomous variables and the XTMIXED routine for the continuous variables. Therefore the odds ratios (dichotomous variables) and the betas (continuous variables) are the associations between the independent and dependent variables in the multilevel model. Figure 1 demonstrates the main analyses conducted.

Figure 1: **STATISTICAL ANALYSES** -Adapted from Henquet et al (24) A: analysis to investigate self medication effects, with positive affect $_{previous}$, negative affect $_{previous}$, mania $_{previous}$ and depression $_{previous}$ as the independent variables and cannabis use as the dependent. B: analysis to investigate the effects of cannabis with cannabis use as the independent variable and positive affect, negative affect, mania and depression as the dependent variables. C: analysis to investigate the effects of BAS, with BAS$_{previous}$ as the independent variable and cannabis use, negative affect, positive affect, mania and depression as the dependent variables. D: analysis of temporal dynamics of cannabis effects to investigate the short and long term effects of cannabis use.



Preliminary analyses

Multi-level regression analyses were conducted to identify whether age, gender, alcohol use at the same beep, other drug use at the same beep, type of cannabis used and total cannabis use for the ESM period were associated with changes in mood, BD symptoms and cannabis use. The results were used to identify which variables would be adjusted for in the main analyses.

Self medication effects (See Figure 1 – Analysis A)

To investigate whether mood or BD symptoms predicted cannabis use; multilevel analyses were conducted using the XTMELOGIT routine. Positive affect $_{previous}$, negative affect $_{previous}$, mania $_{previous}$

and depression previous were entered as the independent variables and cannabis use as the dependent variable. Overall cannabis use during the ESM week was adjusted for in these analyses.

Cannabis effects on mood and BD symptoms (See figure 1 – Analysis B)

The main effects of cannabis use on mood / symptoms were investigated with cannabis use as the independent variable and positive affect, negative affect, mania and depression as the dependent variables. Alcohol use at the same beep and overall cannabis use during the ESM week were adjusted for in these analyses.

BAS sensitivity effects on cannabis use, mood and BD symptoms (See figure 1 – Analysis C)

The main effects of BAS sensitivity on mood / symptoms were investigated with BAS previous as the independent variable and positive affect, negative affect, mania and depression as the dependent variables. Alcohol and cannabis use at the same beep and overall cannabis use during the ESM week were adjusted for analyses.

To investigate the effect of BAS sensitivity on cannabis use, BAS previous was entered as the independent variable and cannabis use as the dependent variable.

Temporal analyses of cannabis use (See figure 1 – Analysis D)

Post hoc analyses were conducted to further investigate the duration of cannabis effects on mood and symptoms. To investigate these, cannabis use at the current beep and cannabis use previous were entered simultaneously into the model, predicting positive affect, negative affect, mania and depression.

Investigating the association between BAS total score and mood / BD symptoms / cannabis use

To investigate associations between the BAS total and mood and symptoms, BAS total was entered as the independent variable and positive affect, negative affect, mania and depression as the dependent variables.

RESULTS

Participants

Twenty-seven participants initially participated in the study. However 2 participants were subsequently excluded as they had fewer than 20 valid reports and a further 2 dropped out due to personal circumstances. The final study sample consisted of 23 participants, 16 males and 7 females (mean age 36.8, SD: 12.8). Twenty-one of the participants met criteria for BD-I and 2 met criteria for BD-II. The majority of the participants (87%) were from a white British background and over half of the sample (56%) was unable to work due to their mental health difficulties. Six of the sample had a current co-morbid anxiety disorder and 5 had a current co-morbid personality disorder. See table 1 for further demographic details of the participant sample.

Table 1: Socio-demographics of the participant sample (n =23)	
Gender (F:M)	7:16
Age Mean (SD)	36.8 (12.8)
Diagnosis (BD I: BD II)	21:2
Ethnicity	
White British	20 (87.0%)
Other White Background	1 (4.3%)
Black Caribbean	1(4.3%)
White and Asian	1(4.3%)
Living status	
Living alone	12 (52.2%)
Living with friends	5 (21.7%)
Living with partner and/or children	5(21.7%)
Living with close relative	1(4.3%)
Occupation	
Sick/ Disability	13 (56.5%)
Student	4 (17.4%)
Employed/ self employed	3 (13.0%)
Employed voluntary	2 (8.7%)
Unemployed	1(4.3%)
Co-morbidity	Current
Anxiety disorders *	6 (26.1%)
Personality disorders **	5 (21.7%)

* Anxiety disorders included panic disorder (with and without agoraphobia), generalised anxiety disorder, obsessive compulsive disorder, post traumatic stress disorder, social phobia, specific phobia.
** Personality disorders included Borderline personality disorder and anti-social personality disorder

Substance use

Three participants met current criteria for cannabis abuse disorder and 12 met criteria for current cannabis dependence disorder. Over the course of the six-day ESM period, the mean number of cannabis moments for the sample was 15.4 (SD: 8.6, range: 2 – 30). During this period all participants reported only using one type of cannabis.

Two participants met criteria for current alcohol abuse and one for current dependence. The mean number of alcohol moments over the ESM week was 3.5 (SD: 5.6, range: 0-21). One participant met current criteria for other drug use and 1 met criteria for other drug dependence. The mean number of other drug moments over the ESM period was 0.9 (S.D: 2.5, range: 0-12). See table 2.

Table 2: Substance abuse in the participant sample (n = 23)	
Cannabis	
Current abuse	3 (13.0%)
Current dependence	12 (52.2%)
Type of cannabis used	
Skunk	12 (52.2%)
Resin	8 (34.8%)
Grass	3 (13.0%)
Cannabis moments over ESM period	
Mean (S.D)	15.4 (8.6)
Range	2 - 30
Alcohol	
Current abuse / dependence	2/1
Alcohol moments over ESM period	
Mean (S.D)	3.5 (5.6)
Range	0-21
Other drug	
Current abuse / dependence	1/1
Other drug moments over ESM period	
Mean (S.D)	0.9 (2.5)
Range	0-12

BIS/BAS scale (20)

The mean BAS total from the BIS/BAS scale (20) was 39.52 (SD 7.7). This score is consistent with other BD samples (19, 39).

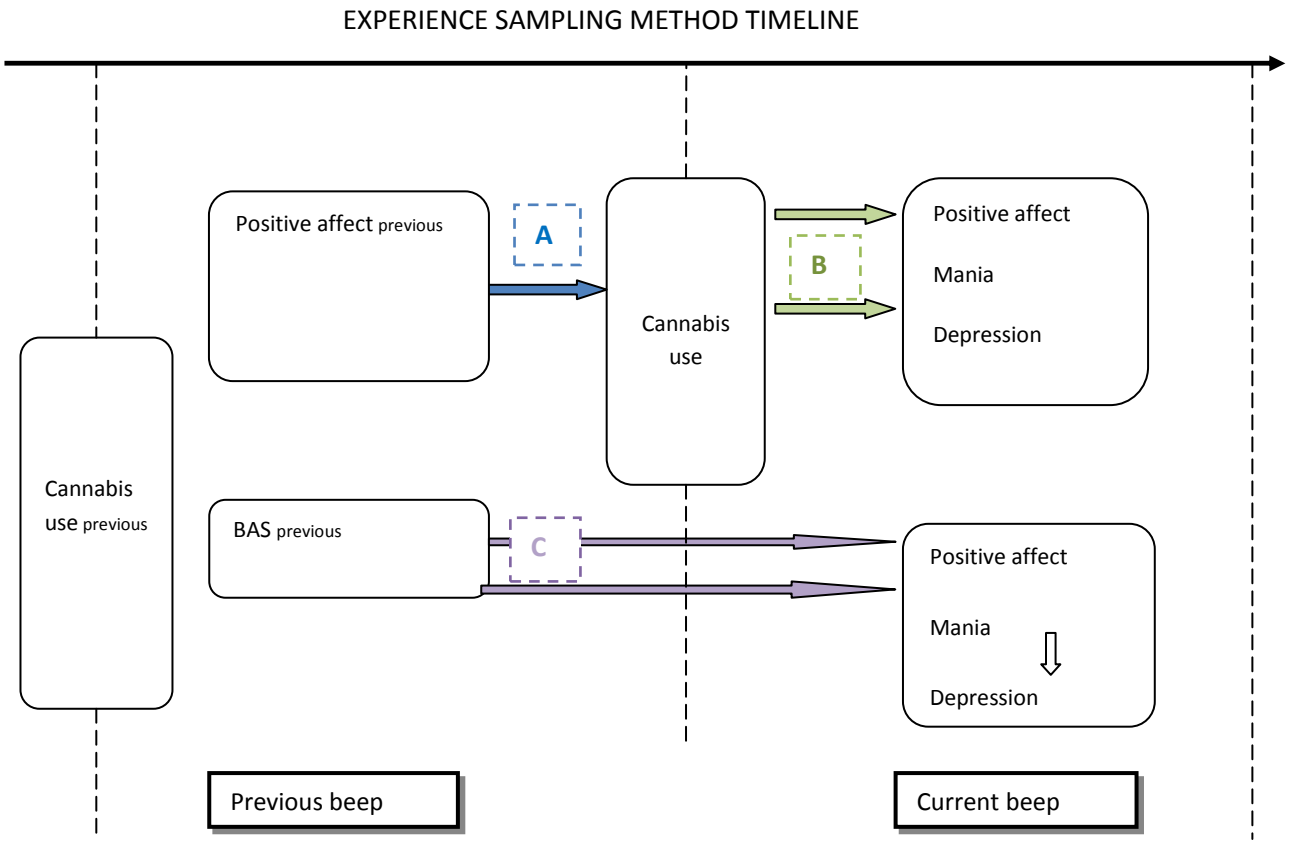
Individuals' scores on the BAS total from the BIS/BAS scale (20) were associated with BAS sensitivity from the ESM diary (β = 0.11, 95% CI: 0.06 – 0.16, P = 0.000).

Preliminary analyses

Total cannabis use for the ESM period (number of cannabis moments) was associated with cannabis use at the current beep (β = 0.12, 95% CI: 0.10 – 0.15, P = 0.000), therefore this was adjusted for in all the main analyses. Alcohol use (at the same beep) was associated with subsequent increases in positive affect (β = 0.44, 95 % CI: 0.17 – 0.72, P = 0.002) and manic symptoms (β = 0.32, 95% CI: 0.06 – 0.58, P = 0.015), therefore it was adjusted for in the analyses which investigated the effects of

cannabis. Figure 2 demonstrates the significant associations that were revealed from the main analyses.

Figure 2: **RESULTS** - A: Positive affect previous predicted the likelihood of cannabis use at the next beep. B: Cannabis use was associated with subsequent increases in positive affect, manic symptoms and depressive symptoms. C: BAS previous was associated with subsequent increases in positive affect and manic symptoms and a subsequent decrease in depressive symptoms.



Self – medication effects (See figure 2 – Result A)

There was a significant relationship between positive affect $_{previous}$ and cannabis use at the current beep. (OR: 1.25, 95% CI: 1.06 – 1.47, P = 0.008). The odds of cannabis use at the current beep were increased for those with higher scores of positive affect at the previous beep. Negative affect $_{previous}$ did not significantly predict cannabis use at the following beep (OR: 0.88, 95 % CI: 0.74 - 1.05, P = 0.147). Similarly no association was found between manic symptoms $_{previous}$ (OR: 1.08, 95% CI: 0.93 - 1.26, P= 0.291) or depressive symptoms $_{previous}$ (OR: 0.92, 95 % CI: 0.78 - 1.08, P= 0.303) and cannabis use. See table 3.

Table 3: Effect of cannabis use on mood/ BD symptoms (Self medication effects)	
Positive affect	OR: 1.25, 95% CI: 1.06 - 1.47, P = 0.008
Negative affect	OR: 0.88, 95 % CI: 0.74 - 1.05, P = 0.147
Mania scale	OR: 1.08, 95% CI: 0.93 - 1.26, P= 0.291
Depression scale	OR: 0.92, 95 % CI: 0.78 - 1.08, P= 0.303

Cannabis effects on mood and BD symptoms (See figure 2 – B)

Cannabis use was associated with subsequent increases in positive affect (β = 0.35, 95 % CI: 0.20 - 0.51, P=0.000). Cannabis use was also associated with subsequent increases in manic symptoms (β = 0.20, 95 % CI: 0.05 - 0.34, P= 0.009) and depressive symptoms (β= 0.17, 95% CI: 0.04 - 0.29, P= 0.008). Overall, cannabis use had no effect on negative affect (β= -0.01, 95 % CI: -0.13- 0.10, P = 0.806). (See table 4).

Table 4: Effect of mood/ BD symptomatology on cannabis use	
Positive affect	β = 0.35, 95 % CI: 0.20 - 0.51, P=0.000
Negative affect	β= -0.01, 95 % CI: -0.13 - 0.10, P = 0.806
Mania scale	β = 0.20, 95 % CI: 0.05 - 0.34, P= 0.009
Depression scale	β= 0.17, 95% CI: 0.04 - 0.29, P= 0.008

BAS sensitivity effects on mood/BD symptoms/ cannabis use (see figure 2 -C)

BAS $_{previous}$ did not significantly predict the likelihood of cannabis use at the following beep (OR = 0.99, 95 % CI: 0.80 -1.21, P = 0.907).

BAS $_{previous}$ was associated with an increase in both positive affect (β = 0.18, 95 % CI: -0.09 - 0.26, P = 0.000) and manic symptoms (β = 0.27, 95 % CI: 0.19 - 0.35, P=0.000). BAS $_{previous}$ was also associated with a decrease in depressive symptoms (β = -0.09, 95 % CI: -0.16 to -0.02, P = 0.014). However there was no significant association between BAS $_{previous}$ and negative affect (β = - 0.01, 95 % CI: -0.08 - 0.06, P = 0.712). See table 5.

Table 5: Effect of BAS sensitivity on subsequent cannabis use/ mood/ BD symptoms

Cannabis use	OR = 0.99, 95 % CI: 0.80 -1.21, P = 0.907
Positive affect	β = 0.18, 95 % CI: -0.09 - 0.26, P = 0.000
Negative affect	β = - 0.01, 95 % CI: -0.08 - 0.06, P = 0.712
Mania scale	β = 0.27, 95 % CI: 0.19 - 0.35, P=0.000
Depression scale	β = -0.09, 95 % CI: -0.16 to -0.02, P = 0.014

Temporal dynamics of cannabis effects

Follow up post–hoc analyses were conducted to investigate the duration of cannabis effects on mood and BD symptoms. This was achieved by entering cannabis use and cannabis use $_{previous}$ simultaneously into the model. The results suggested that increases in positive affect were observed in the short term (β = 0.29, 95% CI: 0.10 – 0.48, P=0.003 for cannabis use) but not the long term (β = 0.01, 95% CI: -0.18 – 0.20, P=0.943 for cannabis use $_{previous}$). Similarly increases in depressive symptoms were observed in the short term (β = 0.18, 95% CI: 0.03 – 0.33, P=0.019 for cannabis use) but not the long term (β = 0.11, 95% CI: -0.04 – 0.27, P=0.138 for cannabis use $_{previous}$). See table 6.

Table 6: Temporal dynamics of cannabis effects	
Positive affect	
Cannabis use	β = 0.29, 95% CI: 0.10 – 0.48, P=0.003
Cannabis use $_{previous}$	β = 0.01, 95% CI: -0.18 – 0.20, P=0.943
Negative affect	
Cannabis use	β = -0.040, 95% CI: -0.18-0.10, P=0.579
Cannabis use $_{previous}$	β= -0.01, 95% CI: -0.15 – 0.13, P=0.925
Mania scale	
Cannabis use	β = 0.07, 95% CI: -0.10 – 0.24, P=0.393
Cannabis use $_{previous}$	β = -0.08, 95% CI: -0.25 – 0.09, P=0.359
Depression scale	
Cannabis use	β = 0.18, 95% CI: 0.03 – 0.33, P=0.019
Cannabis use $_{previous}$	β = 0.11, 95% CI: -0.04 – 0.27, P=0.138

Investigating the association between BAS total score and mood / BD symptoms / cannabis use

A higher reported BAS total was associated with increased positive affect (β = 0.06, 95% CI: 0.02 – 0.89, P = 0.001) and manic symptoms (β = 0.08, 95% CI: 0.04 – 0.12, P = 0.000). However there was no significant association between BAS total and negative affect (β = 0.05, 95 % CI:- 0.02 – 0.11, P = 0.143) or depressive symptoms (β = 0.05, 95% CI: - 0.02 – 0.11, P = 0.18).

There was no significant association between BAS total and cannabis use (β = -0.01, 95% CI: - 0.07 – 0.05, P = 0.643). See table 7.

Table 7: The association between BAS total and mood / symptoms / cannabis use	
Positive affect	β = 0.06, 95% CI: 0.02 – 0.89, P = 0.001
Negative affect	β = 0.08, 95% CI: 0.04 – 0.12, P = 0.000
Mania scale	β = 0.05, 95 % CI:- 0.02 – 0.11, P = 0.143
Depression scale	β = 0.05, 95% CI: - 0.02 – 0.11, P = 0.182
Cannabis use	β = -0.01, 95% CI: - 0.07 – 0.05, P = 0.643

DISCUSSION

In relation to the first prediction, positive affect was associated with the increased likelihood of cannabis use. However, negative affect, manic symptoms or depressive symptoms did not predict the use of cannabis at the subsequent beep. This fails to support the hypothesis that cannabis is used to self-medicate symptoms of BD in the context of daily life. In line with the second prediction, the findings from the study indicate that the use of cannabis in daily life was associated with subsequent increases in positive affect, manic symptoms and depressive symptoms. In addition, the data suggests that increases in positive affect and depressive symptoms were only experienced in the short-term, as cannabis use at the previous beep did not predict a significant increase in mood or symptoms at subsequent time points. In line with the third hypothesis, an increase in BAS sensitivity, as measured by the ESM diary, was associated with increases in positive affect, manic symptoms and a decrease in negative affect. However in contrast, increases in BAS sensitivity were not associated with an increased likelihood of cannabis use. Consistent with the final hypothesis, individuals scoring higher on the BAS total from the BIS/BAS scale (20), experienced higher levels of manic scores and positive affect, however in contrast to the hypothesis they were not more likely to use cannabis.

Cannabis effects

The findings that cannabis use was associated with an increase in positive affect, manic and depressive symptoms is consistent with current literature that suggests cannabis can produce a range of psychological effects (42, 43, 44). It has been suggested that the psychological and physiological effects of cannabis are primarily due to its main chemical compounds, THC and CBD. The effects of cannabis have previously been found to be bidirectional (42, 45), causing effects such as euphoria and dysphoria; this may partially explain why cannabis use was associated with both manic and depressive symptoms in the current study. The bidirectional effects of cannabis have been found to depend on a range of factors such as dose, route of administration and personality differences (42, 45).

The effect of cannabis use on individuals with psychosis has received rather more investigation than the effects of the drug on those with BD. Research suggests that compared to 'healthy' control participants, individuals with high expressed psychosis liability may be more sensitive to THC (46,

47). Barkus and Lewis (48) found that individuals scoring higher on Schizotypal traits were more likely to experience both psychosis-like experiences and more pleasurable experiences after smoking cannabis. Individual differences in sensitivity to the effects of THC may explain the range of experiences (24). In a similar way, individuals with BD may also differ in their sensitivity to the effects of THC, which may explain why there was a range of effects in the current study.

The increase in symptoms following cannabis use in the current study may be due to the effect of THC on dopamine levels in the brain. Once ingested, THC replicates the actions of natural cannabinoids produced in the body and binds itself to cannabinoid receptors CB_1 and CB_2, found within several regions of the brain. Neuro-anatomical findings suggest CB1 modulates and interacts with the function of dopamine (49). The repeated production of cannabinoids, following cannabis use may lead to a permanent change in dopamine levels (50, 51). It has been suggested that this process called 'sensitisation' may contribute to the development of psychosis (52, 53). Authors have suggested that this same mechanism may apply to mania (7). However further research in this area is clearly indicated as little is understood regarding the underlying interaction between cannabinoids and dopamine (54).

<u>Effects of mood / BD symptoms on cannabis use (Self-medication effects)</u>

Positive affect predicted the likelihood of cannabis use, and it appears that individuals were using cannabis when they were feeling good. Alternatively, higher positive affect prior to cannabis use may have been experienced due to the expected enjoyment of the effects of substance use.

Data from the current study does not support the idea that cannabis is used for self-medication effects in the context of daily life. An increase in negative affect and BD symptoms did not predict cannabis use at the following beep. This finding is consistent with Henquet et al (24) who similarly did not find evidence to support the self-medication hypothesis for psychosis, as changes in hallucinations, delusions and negative affect did not predict cannabis use.

The interpretation of the findings of this study is limited to the associations between the current beep and the previous beep. It is possibly the case that self-medication effects appear further down the chain of events, following a longer period of mood / symptom changes. Alternatively, failure to find self-medicating effects from cannabis may have been due to the nature of the participant

sample. BD is characterised by shifts in affect regulation and therefore over time individuals may have become accustomed to subtle changes in mood. Therefore, within the context of daily life, cannabis may not be used as a way to cope with these slight fluctuations. Participants in the study were currently well and out of episode and therefore it may be that cannabis is used to self-medicate more pronounced symptoms or the onset of manic / depressive episodes. This would be consistent with the self- report literature where individuals have found cannabis useful in the management of their BD (11, 12, 13).

Effects of the BAS

Data from the current study does support the prediction that an increase in BAS sensitivity was associated with an increase in manic symptoms. This finding is consistent with the BAS hypersensitivity theory of BD (15, 55) which suggests that excessive activation of the BAS is reflected in hypo (manic) symptoms such as euphoria, excessive goal seeking and self confidence. Interestingly, BAS sensitivity was also associated with an increase in positive affect and a decrease in negative affect, which too is consistent with the original BAS theory (56) where BAS is hypothesized to be associated with positive affect.

Contrary to predictions, this study did not find that an increase in BAS sensitivity (as measured in the ESM diary), led to an increase in the likelihood of cannabis use. It may be that as individuals in the study had overall elevated levels of BAS (derived from the BAS total), consistent with other BD populations (19, 39) and the subtle fluctuations in BAS sensitivity (which the diary measures) were not strong enough predictors of whether an individual would use cannabis.

Similarly, the study did not find support to suggest that higher levels of BAS total from the BIS/ BAS scale (20) would be associated with an increased likelihood of cannabis use. However, interestingly, and as predicted, those with higher scores on the BAS total experienced higher levels of manic symptoms, and also experienced higher levels of positive affect. This finding is similar to Meyer and Hoffman (57) who found that high self reported BAS predicted levels of positive affect and hypo-manic symptoms in a sample of students over a 17-day diary study.

Overall the findings from this study provide further evidence for an association between higher levels of BAS and manic symptoms and positive affect. The data from the study did not find an association between higher levels of BAS and cannabis use, on either the BAS total from the BIS/ BAS scale (20) or the BAS sensitivity from the ESM diary. Alloy et al (19) suggest that high BAS

activation should lead to increased substance abuse; therefore it may be that the BAS was not fully activated in participants in the current study. The mean BAS total was consistent with other BD samples, though this was at the lower end (19, 39). In addition, it may be that in comparison to other drugs of abuse, cannabis is not perceived as highly 'rewarding', being more easily accessible. A recent study (58) found that two thirds of 15 year olds reported that they knew where they could easily buy cannabis. Therefore individuals that use cannabis may not experience as heightened levels of BAS sensitivity in pursuit of cannabis compared to other drugs.

LIMITATIONS

Several limitations need to be taken into account in interpreting the results of the study. First, details of cannabis use were based on self-report. Cannabis use remains illegal in the United Kingdom, and this may have led to underestimations in reported use. Hair sample analysis may have offered a way to confirm usage (59). Additionally, whilst type of cannabis was reported and adjusted for in analyses, the individual potency of the drugs consumed was not controlled for. There are in excess of 100 different strengths of cannabis and research has revealed that on average, cannabis resin and herbal (grass) contains around 2-4 % THC, however Sinsemillia (Skunk) contains around 12-18 % THC (60, 61). Data for cannabis use at each bleep was dichotomized into 'yes' or 'no'; future studies might attempt to collect and report information regarding the amount of cannabis ingested and route of consumption at each beep. However the collecting of this additional information must be balanced against the further burden of data collection for the participant.

This is the first time that ESM methodology has been used to examine changes in mood, symptoms and BAS sensitivity in a sample of individuals with BD. The items used on the scales for mania, depression and BAS sensitivity were formulated specifically for the study. However, to overcome any potential difficulties, items were chosen in accordance with guidelines for selection of ESM items (28). Items were also reviewed by a service user panel with BD who felt they accurately described their experience when manic and depressed. Additionally, scores on the BAS total from the BIS/BAS scale (20) were significantly associated with an increase on the BAS sensitivity scale in the ESM booklet ($\beta = 0.11$, 95% CI: 0.06 – 0.16, $P = 0.000$).

Cannabis is known to have an impact on cognition (e.g. 62, 63) and as suggested by Henquet et al (24) this may therefore have impacted on the ability to report information accurately in the diaries. However one of the main advantages of using ESM is the short space and time between an event occurring and the recall, which reduces memory bias (29). Additionally, a recent study (64) found cannabis use was associated with better neuro-cognitive functioning in participants with BD, particularly executive functioning.

ESM can be a demanding methodology and requires sustained attention and motivation to fill out diary entries. This may deter some individuals, and thereby result in a selection bias. In addition, like other ESM studies (e.g. 65, 66) the sample size was relatively small hence the results for the study may not generalise to all individuals with co-occurring cannabis use and BD.

Additionally, the majority of the sample was from a white British background and had a diagnosis of BD-I. It is therefore questionable how much the findings of this study may generalise to people from different ethnic minorities or other BD groups

Finally, the inclusion of a control group may have provided insight into whether the findings from the study relate exclusively to those with a diagnosis of BD, compared to a non-clinical sample.

CLINICAL IMPLICATIONS

Overall results from the present study indicate that cannabis use can cause a range of psychological effects for individuals with BD, including an exacerbation of both manic and depressive symptoms. Co-occurring BD and substance abuse is highly prevalent (6, 67) and it is associated with worsened outcomes (5, 6). Therefore, as previously highlighted, this group of people represents an important group to study from both a clinical and public health perspective. However intervention research for BD and substance abuse is in its infancy (68, 69, 70, 71) and demonstrates a limited evidence base (68). The results from this study may help to inform future interventions.

Clients often find it difficult to reduce their substance intake and the literature suggests that some individuals perceive cannabis as a useful coping strategy in the management of their BD symptoms. However results from this study may help to counter these positive expectations of their substance use. The findings suggest that cannabis is not being used to self medicate changes in symptoms, within the context of daily life, and in fact it may be further complicating affect states. Services and clinicians should be educated around the potential impact of using cannabis. They should be skilled

up to provide psycho-education to inform clients of the risks. Alongside this clinicians should be offering more helpful strategies to help clients cope with changes in BD symptoms, which may in turn increase an individual's confidence to reduce their substance intake.

Similar to Henquet et al (24), the majority of participants in this study found the ESM diary a useful and reflective tool to monitor their mood and cannabis use. Therefore the methodology used here may also be of great clinical use. A number of participants reported that tracking patterns of mood and cannabis use led them to question their substance use and in some cases reduce intake. ESM could provide an invaluable therapeutic tool, particularly with clients who are ambivalent about changing their drug use habits. Tracking the course of symptoms and cannabis use may provide insight into unhelpful patterns of behaviour, which may contribute towards the maintenance of their difficulties.

FUTURE RESEARCH

BD is classified as a serious and enduring mental health difficulty and results from the present study indicate that the use of cannabis may in fact complicate the course of symptoms. Reasons for this may be due to the effects of THC in the central nervous system. Further research is indicated with individuals with BD to investigate the interaction between cannabinoids and dopamine. BD is characterised by difficulties with affect regulation, and whether the cannabinoid-dopamine interaction contributes towards the development of BD, or whether it further complicates affect states continues to be poorly understood.

Further research is also need to see whether the results from this study would generalise to another sample of individuals with co-occurring BD and cannabis use. The inclusion of a control group would also provide further insight into whether the results relate exclusively to those with a diagnosis of BD.

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PAPER THREE

A critical reflection of the research process

ELIZABETH TYLER

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OVERVIEW

This section provides a critical reflection of the research process. It includes a rationale for the development of the literature review and the main empirical paper. This is followed by information regarding the study context and an examination of methodological and ethical issues which arose during the research process. Finally it discusses theoretical, clinical and future implications for research in this area.

THE LITERATURE REVIEW

Bipolar disorder (BD) is characterised by extreme shifts in mood from mania to depression. Whilst it is associated with achievement and artistic creativity (1), it can also be linked to a range of problems. These include difficulties with work performance (1, 2), higher rates of suicide in comparison to the general population (3) and elevated levels of substance use, particularly cannabis use (4, 5, 6).

Strakowski and DelBello (5) provided a comprehensive review of studies exploring the co-occurring relationship between BD and substance use. However to the author's knowledge there are no published review papers examining studies on the relationship between BD and cannabis use. A review of studies in this area was considered to be important since rates of cannabis use are elevated within the BD population (7) and are associated with a number of difficulties, including increased symptom severity (8) and non-medication compliance (8, 9).

The production of the literature review highlighted a relative lack of research studies focusing specifically on BD and cannabis use, especially when compared to cannabis use and psychosis for which there is a large body of research available. There were a number of studies which explored the use of cannabis and mental health difficulties in general, however the author decided to only include studies where the sample included 50% or more individuals with BD. This was so the majority of the sample had a diagnosis of BD and the findings could be generalised to other individuals with the disorder.

Following the exclusion of relevant papers, the final 13 included studies where the methodological quality varied. The studies reviewed employed a range of designs (e.g. longitudinal, cross-sectional, experimental, qualitative) and this led to both strengths and weaknesses for the paper. The use of

both quantitative and qualitative observations provided different ways of exploring the subject area, both complementing one another. However due to the range of methodologies used it was not possible to apply a common rating scale to critique the studies and was therefore difficult at times to draw comparisons between the studies. The papers were therefore critiqued on their individual quality and the findings were synthesised in relation to Strakowski and DelBello's (5) hypotheses.

The 13 studies reviewed provided new evidence with which to re-evaluate Strakowski and DelBello's (5) 4 hypotheses in the context of cannabis use and BD (none of the 13 papers were included in their original review). Similar to their findings for substance use in general, the literature review highlighted a number of factors which appear to contribute towards the co-occurring relationship between BD and cannabis use.

THE EMPIRICAL PAPER

The review demonstrated that there are a number of factors which may contribute to the relationship between BD and cannabis use. The research paper was designed to investigate a number of these factors derived from the literature, which may explain the high co-occurrence of BD and cannabis use.

This paper extended previous research by providing an in-depth investigation into the relationship between BD and cannabis use, over the course of daily life. There has been an increase in the number of researchers interested in investigating mental health difficulties within the realm of daily life (10, 11). This study utilized the Experience Sampling Methodology (ESM) to investigate associations between mood, BD symptoms, BAS sensitivity and cannabis use. The use of ESM provided many advantages when compared to traditional assessments - this will be discussed further in the next section.

Overall the literature review and study contributes to a furthering of our understanding of what would seem to be a complex relationship between BD and cannabis use. A number of associations between cannabis use and aspects of BD were revealed which support the findings of other researchers. However the study did not find evidence to support the view that cannabis is used to self-medicate a change in symptoms over the course of daily life. The findings in relation to existing literature will be discussed further in the theoretical implications section.

THE STUDY CONTEXT – PARADES PROGRAMME

The study was part of the PARADES programme (Spectrum Centre, Lancaster University) which is funded by the National Institute for Health Research (NIHR), and focuses on the development and implementation of psychological approaches to BD and co-morbid problems. The study sat within the substance misuse stream (1 of 2 studies investigating co-morbid BD and substance use) and being part of the PARADES programme offered a number of advantages which included; additional supervision from two of the grant holders (SJ: Professor of Clinical Psychology, Lancaster University and PARADES PI and RM: Professor of Psychiatry and Community Mental Health, University of Nottingham) and access to the service user panel of individuals with BD. Additionally, due to the large scale of the study for a clinical psychology doctoral thesis, a great advantage was having support from the Mental Health Research Network (MHRN) and from a research assistant (RA), in identifying and recruiting participants for the study.

The RA and author worked closely together throughout the identification and recruitment stages of study, and this help and support was invaluable. In the identification stages, both parties attended team meetings individually and jointly. However due to time constraints for the author, the RA was able to attend more meetings and therefore was able to identify a larger number of participants for the study. The study also received support with the identification of participants (n=2) from clinical skills officers (CSO) who were part of the MHRN. During the recruitment stages the RA and author completed some joint participant visits (n=6) and the author completed a number alone (n=10).

METHODOLOGICAL CONSIDERATIONS

Experience sampling methodology(ESM)

An advantage of using ESM is the amount of rich and descriptive data it can provide. In the context of the study within this thesis, ESM allowed participants to report on their mood, BD symptoms and cannabis use - in the 'moment', and in their everyday settings. It thereby provided a high level of ecological validity. Previous studies investigating the relationship between BD and cannabis predominantly have used longitudinal study designs and participants have reported on their symptoms and cannabis use during follow-up assessments (12, 13). The information gathered in this manner may be open to recall biases and may not accurately depict the patterns of symptoms and

cannabis use. Stone et al (14) examined the correspondence between accounts of coping strategies following a stressor, using ESM diary methods versus a retrospective report produced 48 hours later. They found that there was poor correspondence between the two measures and the different representations suggest that information collected after a time period may be significantly different to information gathered just after an event.

Limitations of ESM

Whilst ESM offered a comprehensive, detailed investigation of the associations between aspects of BD and cannabis use, there were also a number of limitations which had to be taken into consideration. ESM could be perceived as a demanding methodology since completion of the diary entries requires sustained concentration, and can be time consuming for participants. ESM lends itself to being used by individuals who are motivated to complete the diary entries, and may therefore be open to a selection bias. ESM may also deter individuals who are not comfortable with reading and writing.

This study used the paper-based diary and watch method. An alternative approach would be to use personal digital assessments (PDAs). The use of PDAs provides superior control over diary entries as data can only be inputted at certain times, thereby preventing participants 'backfilling' entries at a later date. However certain individuals could find the technology daunting and difficult to use. Additionally, research suggests that using the paper-based diary and watch method yields similar results to PDAs (15). That being the case it was decided that the paper-based diary and watch method would be adequate for the study.

There is also the potential that ESM could induce experiences for individuals (10), therefore a participants' reaction to the study methods could change their experiences during the study. During the 'debrief' the participants were asked a number of questions about their experience of completing the research. A number of participants reported that the study had made them think more and focus on the way they were feeling, which will be discussed further in a following section.

Additionally during the ESM week, participants were expected to act independently in accordance with the research protocol, without the presence of a researcher; therefore compliance was not always guaranteed (10). Nevertheless, to overcome some of the difficulties this may have presented, the watches were programmed to beep at according to a time schedule (which changed each day so the participants did not become accustomed to filling in their diaries at certain times

during the day). Participants were required to record the time after each diary entry. Once the study was completed, each diary entries were matched with the time schedule and any completed outside the 15 minute window were excluded from the analyses. Additionally a great deal of care was taken during the briefing stages of the study to ensure participants fully understood what was required - this involved reading through all the questions in the diary and practicing an entry. Overall, compliance was good for the study. When the data in the diary was checked according to the time schedules, the author had to exclude very few entries (n=8). Additionally, there was a relatively low drop-out rate for the study. Two participants did not complete due to personal circumstance and 2 participants did not fill in enough diary entries during the week.

Developing items for the ESM diary

Developing items for the diary was a key part of the research process (see appendix G for booklet questions). Items for the study were formulated and chosen in accordance with past research (e.g. 16, 17) and recent guidance (11).

The mood items had been used in previous studies, investigating cannabis use and psychotic experiences (18). Given that factor analytic studies of these items had been done using data from people with schizophrenia diagnoses, a principal component analysis (see appendix I) was conducted for the present study and two distinct components were revealed. These were identified as a positive and a negative affect scale (See appendix). This, coupled with the cronbach's alpha for each scale (positive $\alpha = 0.82$, negative $\alpha = 0.85$) suggests that they are measuring separate constructs. Additionally, the high alphas' indicate that the items in the scales are closely related.

The mania and depression items were chosen by a team of researchers at the University of Manchester and from the PARADES programme (SJ, CB, ET). All of whom had considerable experience of working with people with BD and hence were familiar with the symptomatology. There were originally 8 items for BD; 'full of energy', 'restless and fidgety', 'high', 'full of good ideas', 'slowed down', 'low', 'bad about myself' and 'fearful'. A principal component analysis (see appendix I) revealed two separate scales. However 'restless and fidgety' (originally mania) loaded onto both factors and therefore this item was excluded from analyses. This left 3 items in the mania scale 'full of energy', 'high' and 'full of good ideas' and the remaining 4 items listed above for the depression scale. The internal consistency for both scales was high, mania ($\alpha = 0.75$) depression ($\alpha = 0.82$), indicating that the items were closely related.

A correlation matrix (See appendix J) was computed to investigate the relationship between the positive affect, negative affect, mania and depressive scales. There was a strong correlation between the negative affect and depressive scales were highly associated (r = 0.82). This indicates that there may have been a high degree of overlap between the scales. However during the main analyses the scales produced different results (e.g. cannabis use was significantly associated with depressive symptoms but not with negative affect). This provided some predictive validity to support the use of separate scales: and it suggests that they were measuring different emotional states. Items from the positive and negative affect scales were considered to reflect everyday mood fluctuations as expected within the 'normal' range. The items formulated for the mania and depression scales were deemed to reflect symptoms specific to BD that would fluctuate over the course of daily life.

Items for the BAS sensitivity scale were also developed specifically for the study. Three items were used to form the scale, 'I want to try something new', 'Nothing can stand in my way', 'I'm craving excitement'. These were formulated using the same guidance as noted above (11) and were adapted from questions from the BIS/ BAS scale (19). Items were considered to measure levels of BAS sensitivity that would fluctuate over the course of daily life. The internal consistency for the scale was high ($\alpha = 0.76$), again, indicating that the items were closely related. Additionally, as mentioned in the main paper, increases in scores on the BAS sensitivity (ESM diary) were associated with higher individual scores from the BIS/BAS scale (19).

<u>Service user involvement in the ESM diary</u>

A meeting was arranged with a group of service users who had a diagnosis of BD (n=4). Involving service users in the development of the study was seen as a key component and the author was keen to receive feedback on the wording of the questions in the diary. All members practised filling out the questions in the diary and they felt that the language reflected how they would describe their own behaviour and experiences.

The study was also piloted with a single member of the group. Overall, feedback indicated that the participant had found the study interesting and enjoyable. They felt that the questions in the diary were appropriate and some reported that after filling out a diary entry, they recognised that their mood was becoming increasingly elevated and had found it helpful to recognise this change. They noted that the

text message and phone call during the week helped with motivation and made them feel appreciated and recognised. This feedback emphasised the need to ensure that participants were contacted during the ESM week. Feedback from the services users was very positive and this gave the author confidence that the ESM diary had face validity in measuring individuals' BD symptoms.

BIS/BAS scale (19)

The BIS/BAS scale (see appendix H) was originally developed by Carver and White (19) to assess individual differences in the sensitivity of the Behavioural Activation System (BAS) and the Behavioural Inhibition System (BIS). Their original factor analysis revealed 4 separate subscales. The BIS and three subscales which formed the BAS total (Drive, Fun Seeking, and Reward responsiveness).

However more recent studies have conducted factor analyses and revealed two distinct factors, which correspond to the BIS and the BAS (20, 21). There is ongoing discussion over whether to use the BAS as three separate subscales; Ross et al (22) suggest that they should be considered as distinct constructs. However for the present study the BAS total was used as a number of other studies using a BD population have used the two factor structure and the BAS total was therefore comparable to these studies (e.g. 23, 24).

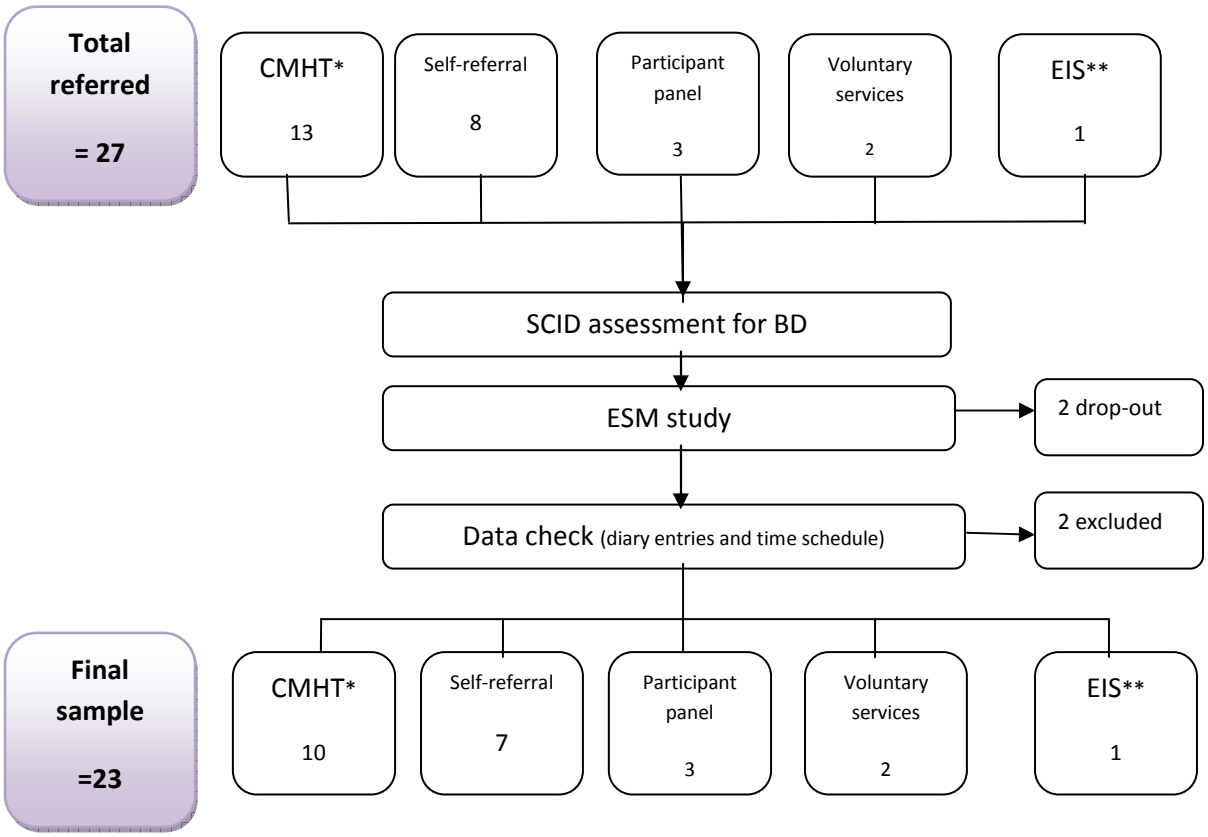
It would have been interesting to run further analyses with the separate three subscales to see if any differences were found in relation to BD symptoms and cannabis use. However within the time constraints of the current thesis this was not possible.

Recruitment

The study recruited participants from a number of different sources (See figure 1) including community mental health teams (CMHT). During the recruitment stages there were a number of research studies recruiting individuals with BD and psychosis in the Greater Manchester area. This led to a few difficulties as some of the team managers who were approached were resistant to researchers attending team meetings, feeling that their teams had already been subject to a lot of research activity.

The author was mindful of interacting with team members in a sensitive manner and was acutely aware of the time pressures and demands facing care coordinators, particularly within the current NHS climate. Many of the teams that were approached were friendly and welcoming to research. However at a number of meetings, difficulties were experienced. In some cases team members appeared disinterested in the research and on a few occasions some were challenging about the study feeling that the ESM might be too demanding for their clients. This raised an important issue as it appeared that some members of the team were selecting clients whom they felt could take part in the research, rather than giving their clients the choice. This, of course could lead to a potential selection bias. This caused some frustration for the author as it was felt that some teams were putting up additional barriers to the research process and that all clients should have had been able to make their own decision about whether they wanted to be involved in the study (see appendix E for referrer information sheet).

Figure 1: Referrals/ final participants included in the study.



*CMHT – Community Mental Health Teams

**EIS – Early Intervention Services

Cannabis use

Cannabis use and possession remains illegal in the United Kingdom and therefore the design of a study which involves individuals who use cannabis creates immediate difficulties. An ICM poll for BBC online (25) found that whilst 49 % of respondents supported the decriminalisation of cannabis, 36 % were against it and a further 15 % were undecided. Therefore the use of cannabis remains a contentious issue within our society and from a researcher's perspective it has to be treated sensitively.

When introducing the study to potential referrers and participants, a particular emphasis was placed on confidentiality. Whilst the majority of team members were open and welcoming, there was a minority, as mentioned previously, who appeared to be unreceptive regarding the study. In the process of trying to understand this ambivalence, a number of potential reasons, in relation to cannabis use were formulated:

-Some care coordinators felt that part of their role should be to support clients in reducing their drug-taking habits - admitting that one of their clients was using cannabis might look like a shortcoming.

-They disapproved of their clients' drug taking habits and did not want to expose them.

-They were not aware of their clients' drug taking habits.

When presenting the study at team meetings, in an attempt to overcome any of these potential barriers, particular emphasis was placed upon discussion of research which reported on the high numbers of substance use within mental health populations. The aim was to ensure that team members felt comfortable talking about substance use. In some cases this did open up a range of discussions. Some teams were very receptive to the research study and felt that substance use by clients was a problem within their teams. They hoped that the research would provide more insight into why there were such high levels of use by individuals with mental health problems.

Once referred into the study, participants seemed to be very open and honest regarding their drug use habits and happy to share information. Participants reported enjoying the chance to talk and reflect on their experience of taking drugs. This openness may have been facilitated by a non-judgemental attitude from the author and the RA.

Assessment of cannabis use/ other substances

The Structured Clinical Interview (SCID) based on the DSM-IV diagnostic criteria (26) was used to assess cannabis abuse and dependence. The SCID has been used in numerous research studies. There was a range of cannabis dependence within the sample (3 individuals currently met criteria for abuse and 12 for dependence). Similarly the number of times participants used cannabis over the ESM period ranged from 2 to 30, which was adjusted for in the analyses. However, overall, cannabis use was moderate for the sample. The mean number of 'moments' for the sample was 15.4 (S.D 8.6) over the 6 day period.

The type of cannabis used by the participants was recorded at each 'moment' (e.g. Resin, Grass or Skunk). To the author's knowledge this is one of the first studies to adjust for this information in the analyses when investigating co-occurring BD and cannabis use. Previous studies have dichotomised cannabis use into 'yes' or 'no' (e.g. 12). However, there are many different types of cannabis which contain various concentrations of Δ9-tetrahydrocannabinol (THC) and cannabinol (CBD: 27, 28). These cannabinoids are thought to be responsible for the range of psychological and physiological effects produced by cannabis.

Type of cannabis was not significantly associated with a change in mood, symptoms or cannabis use. Previous research had indicated that cannabis containing higher levels of THC (e.g. skunk) could cause more adverse psychological effects (29), therefore it was expected that individuals using the higher strengths may experience more mood/ symptom changes. However whilst the type of cannabis was recorded, the amount and frequency of use at each beep was not. Therefore some individuals may have been using a larger quantity of the lower strength cannabis between the beeps, as compared to those using the higher strength cannabis. Future studies should aim to collect information on the amount, frequency and the route of consumption of cannabis at each beep, as this would provide a more accurate measure of cannabis use.

The effect of other substances was also adjusted for in the analyses (alcohol and use of other drugs at the same beep). However, similarly to cannabis use, the amount and frequency of the alcohol/ other drug use was not recorded between beeps. Alcohol at the same beep was associated with subsequent increases in positive affect and manic symptoms; therefore it was adjusted for in the analyses that investigated the effects of cannabis use on mood and symptoms. Other drug use was not associated with changes in mood or symptoms. There was overall low usage of alcohol (mean

number of moments = 3.5) and other drugs (mean number of moments = 0.9) over the 6 day study period.

The participant sample

The majority of the participant sample had a diagnosis of BD-I and were from a white British background. Research has highlighted differences between BD populations, for example Kupka et al (30) found that patients with rapid cycling BD differed significantly from those without rapid cycling on a number of variables such as: number of lifetime manic/ depressive episodes, history of drug abuse, history of childhood sexual/physical abuse. It may not therefore be possible to generalise results from this study to other BD populations.

Previous research has reported high incidence rates of mania within ethnic minority communities in the UK, especially those from African-Caribbean and African ethnicity (31, 32). Research has shown that there are major differences in the way individuals from different ethnic minorities access mental health services (33). Therefore the under-representation of people from different backgrounds in the study may reflect this. Additionally, because only 3 people with non-white British backgrounds were included in the study, the results are not generalisable to individuals from different ethnic backgrounds.

The sample size for the study was relatively low. This was nevertheless enough to detect effects (due to the multilevel nature of ESM data). However it is questionable how much the findings would relate to other individuals with co-occurring BD and cannabis use.

The inclusion of a control group may have provided insight into whether the associations revealed in the study relate exclusively to individuals with BD or whether they relate to non-clinical samples. Henquet et al (18) found significant differences between their patient sample and control group. Daily cannabis use predicted subsequent increases in positive affect and increased levels of hallucinatory experiences in the patient only group.

Statistical analyses

The statistical analyses were conducted by the author. Supervision for the multi-level modelling techniques was provided by a research methods fellow (LC).

Henquet et al (18) used ESM to provide insight into the complicated dynamics of cannabis use and its effect on mood and psychotic experiences. In the main, the present study replicated the statistical analytic strategy that Henquet et al (18) used in their study. However in the Henquet et al (18) paper when they investigated the self-medication effects (mood/ symptom change predicting cannabis use), they additionally adjusted for cannabis use at the previous beep, due to the fact that cannabis use at the previous beep was strongly associated with cannabis at the current beep. Likewise, when investigating the effects of cannabis on mood / symptoms, they adjusted for mood and symptoms at the previous beep. This was based on the fact that mood/ symptoms at the previous beep were strongly associated with mood/ symptoms at the current beep.

However, after seeking statistical advice, it was advised that the inclusion of previous beep values (e.g. cannabis/ mood/ symptoms) of the dependent variable as a covariate in a longitudinal multilevel model can lead to false correlations due to mathematical linkage. Previous beep values of the dependent variable estimate the random effect term of the current dependent variable. Therefore this effect will be larger, particularly if the cluster size is small and the clustering effect is large. Therefore it was decided not to include previous beep variables in any of the models as the inclusion may have led to the effect sizes been underestimated.

Participant feedback on the study

Feedback regarding the study process was gathered at the end during the debrief session. The majority of the sample reported they had enjoyed the study. Twenty of the participants reported that it had been a typical week in relation to their symptoms - this was an important finding as it increased the validity of the reported associations. The majority of the sample (21 out of 23) reported that filling the diaries out had not affected their cannabis use. Two individuals reported that filling out the diary had led to a change in their cannabis use. These 2 individuals found that they had become more aware of the effect of cannabis on their mood and this had motivated them to want to reduce their usage.

Eight of the participants felt that the study had influenced their mood. The reasons for this included reflecting and focusing more on their mood - the diary made them think and concentrate more on how they felt. A number of participants reported that they had used more cannabis after the beeps had finished for the day. A visual scan of the data confirmed that the majority of missing beeps were at the beginning of the day. This would need to be taken into account when designing studies

with similar populations and possibly the time schedule would need to be altered to fit more accurately with lifestyle.

Receiving the feedback from the participants at the end of the study was a very important part of the process. The finding that the majority of individuals had enjoyed participating in the study was pleasing for the author. The feedback regarding timings was useful and should be taken into consideration in the design of future studies in this area.

ETHICAL CONSIDERATIONS

Ethical approval was sought and granted from the National Research Ethics Service committee (NHS: see appendix B for the ethics approval letter and appendix C for research governance letter – an example from one of the trusts). A number of ethical issues had to be taken into consideration when designing and conducting the study.

Consent

All participants were given an information sheet (see appendix D) with details of the study, prior to signing the consent sheet. This gave the participant and author time to discuss the objectives of the study and also gave the participants an explanation of what the process would involve. Both parties signed two copies of the consent sheet (see appendix F), one for the participant and one for the author, which were kept in a locked filing cabinet. Participants were informed that they were free to withdraw from the study at any point, without giving any reason and that they had the option for their data to be destroyed.

Confidentiality

All information gathered from participants during the research study was kept confidential, including information about their substance use. Any identifiable information was kept separately from study measures in a locked filing cabinet. At the first meeting participants were informed that everything they discussed during the research process would be kept confidential. However they were informed that if the author was concerned that the participant might be a risk to themselves or others, then this information would have to be shared with another party (though they would always aim to discuss this with the participant first).

Individuals with both BD and substance use do present as an increased 'risky' population, due to the nature of the conditions. There are reported higher rates of suicide in comparison to the general population (3). Therefore monitoring the clients risk to self was an important part of the research process. On one occasion, during a second visit, the author was concerned about a participant's welfare as there had been an apparent deterioration in mood between the two visits. Permission was granted from the participant to contact the named care coordinator.

STUDY IMPLICATIONS

Theoretical and future implications

The findings from the study might be discussed in relation to the stress-vulnerability model which was first proposed by Zubin and Spring (34). This model was not discussed in the main paper; this was due to the format of the 'paper-based' thesis which does not permit space to fully elaborate on the theoretical implications. The model proposes an aetiological mechanism for mental health disorders as well as an explanation for relapse; and its basic premise suggests that some people (those with an underlying predisposition) are vulnerable to developing /relapsing into mental health difficulties if they are exposed to enough stressors. Stress may come in many forms and can include, biological, developmental, psychological, environmental and socio-cultural and different people are thought to be vulnerable to different stressors. Therefore, for some individuals in the study, cannabis use may have been a 'stressor' and contributed to the exacerbation of their BD, however for others, different factors may have contributed towards their mental health difficulties. In the context of every day life, each individual's vulnerability and sensitivity to the effects of cannabis use may be different, which may explain why a range of effects in the study were reported. This will be explored further in the following section.

Effects of Cannabis

The findings from the empirical paper suggest that within the context of daily life, cannabis use is associated with an increase positive affect and manic and depressive symptoms for individuals with BD. However due to the nature of the study design, this finding is limited to the associations between cannabis use at the current /previous beep and these variables, therefore cannot indicate causation. The results suggest that the effects of cannabis on positive and depressive symptoms

were experienced only in the short term as cannabis use at the previous beep did not predict a significant increase in mood or symptoms at subsequent time points.

These findings are consistent with current literature that suggests that cannabis use is associated with manic symptoms (12, 35, 36), with depressive symptoms (37, 38) and positive affect (18). The findings are also consistent with research which has suggested that cannabis can cause bidirectional effects (39, 40, 41), causing effects such as euphoria and dysphoria. Barkus and Lewis (42) found that individuals scoring higher on Schizotypal traits were more likely to experience both psychosis-like experiences (negative) and more pleasurable experiences (positive) after smoking cannabis.

A study with 'healthy' participants, under placebo-controlled laboratory conditions found that THC (one of the key constituents that are present in cannabis) was reported to produce relaxation and there was a decrease in subjective ratings of depression (40). The current study found that cannabis was associated with an increase in depressive symptoms. However Ashton et al (40) utilised a non-clinical sample which may explain why cannabis was associated with different psychological effects from those in this study. Henquet et al (18) found that cannabis use was significantly associated with subsequent increases in hallucinations in their patient sample compared to their non-clinical student sample.

As mentioned previously, it has been suggested that the main psychological and physiological effects of cannabis are due to its key constituents, THC and CBD. Recent experimental work with 'healthy individuals' has found that intravenous infusions of THC can produce mild to transient psychotic like symptoms, anxiety and feelings of detachment (43). Once ingested, THC mimics the actions of natural cannabinoids and binds itself to cannabinoid (CB_1 and CB_2) receptors. Neuro-anatomical findings suggest CB_1 modulates and interacts with the function of dopamine (44). The repeated production of cannabinoids may lead to a permanent change in dopamine levels (45, 46).

A recent study found that THC did induce dopamine release in the human striatum in a sample of 'healthy' participants (47). However, Stokes et al (48) found that THC did not produce significant dopamine releases in the striatum. Henquet et al (18) suggest that the differing findings may be because individuals differ in their sensitivity to THC. The effects of cannabis are known to differ depending on dose, personality and degree of tolerance (39, 40, 41).

There is limited evidence that suggests that (mesolimbic) dopaminergic hyperactivity may contribute towards psychosis/ and mania (49), therefore it has been suggested that dopaminergic

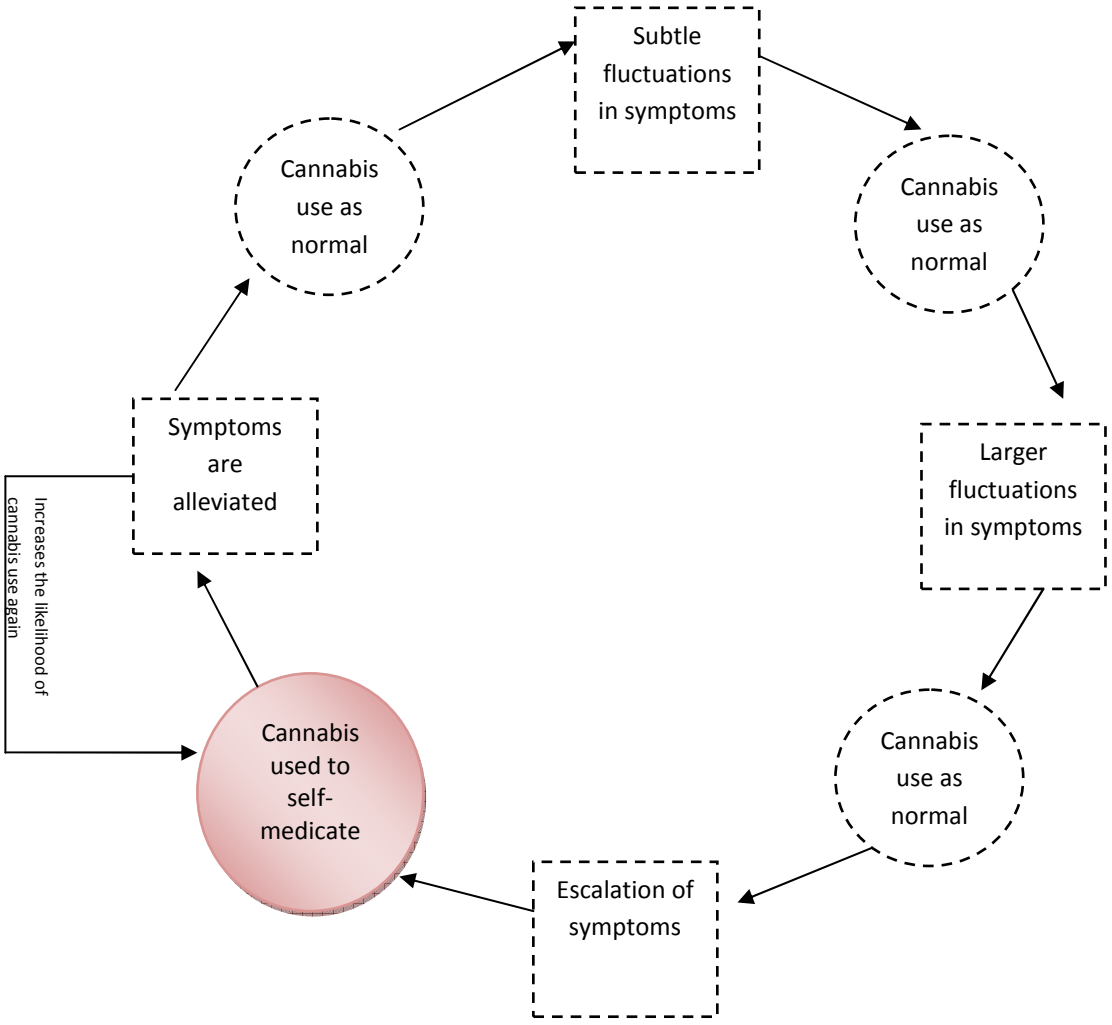
hyperactivity may underlie the link between cannabis and BD (36, 50). Compared to BD, the relationship between THC and vulnerability to developing psychosis has been subject to far more investigation. A number of factors have been identified which in combination with THC, increase the likelihood of causing psychosis. These include pre-existing psychotic symptoms (51) and exposure to childhood trauma (52, 53). Further research is clearly indicated firstly to investigate the interaction between cannabis and its effect on dopamine in the brain and secondly to investigate which factors may make individuals with BD more vulnerable to the effects of cannabis use.

Self-medication

The study did not find evidence to support the use of cannabis to self-medicate fluctuations in symptoms over the course of daily life. However, as discussed in the main paper, this may be because cannabis is used further down the chain of events, when symptoms escalate or become more pronounced. As discussed previously this is the first known study to investigate the relationship between BD and cannabis use in daily life. Therefore it may be that cannabis is used only when there is a dramatic change in symptoms, which potentially may not be measurable using the ESM diary (since it is designed to measure fluctuations in symptoms which occur in the moment). Previous self-report studies have found that cannabis is used to self medicate symptoms of both mania and depression (54, 55, 56). However these reports are completed retrospectively and may be open to recall bias.

Further research in this area should focus on at what stage in the course of BD individuals use cannabis as a form of self-medication, and also what impact self-medication has on an individual's symptom levels. It may be that individuals with co-occurring BD and cannabis use find themselves trapped in a vicious cycle of mood instability and cannabis use. An individual may experience subtle fluctuations in mood and continue with their cannabis use as normal. However these symptoms may begin to escalate and once they have become more noticeable and pronounced, cannabis may be used as a form of self medication. This may be perceived as helpful (since symptoms are alleviated) and in consequence increasing the likelihood of cannabis being used again the next time a significant change in mood is experienced.

See figure 2 below:



BAS theory

The Behavioural Inhibition System (BIS: 19) and the BAS (57) are proposed to be the two major motivational systems. It is hypothesised that the BAS is related to goal attainment behaviour, reward seeking and positive affect (e.g. 57). According to Depue and colleagues (58, 59) the BAS regulates behaviours and moods typically observed in mania and depression. Therefore a dysregulated BAS may lead to a vulnerability to BD and those who are vulnerable may react strongly when faced with rewarding stimuli.

Findings from the study revealed an association between both the BAS sensitivity scores from the ESM diary and the BAS total scores from the BIS/BAS scale (19) and an increase in manic symptoms.

This association provides further support for the BAS hypersensitivity theory of BD (58, 59) which suggests that a sensitised BAS is reflected in (hypo) manic symptoms such as euphoria and excessive goal seeking. A number of other studies have revealed an association between individuals with BD spectrum disorders reporting elevated self-report scores of BAS sensitivity and exhibiting (hypo) manic symptoms (e.g. 24, 60).

Individuals with substance abuse also exhibit higher self-reported BAS sensitivity (61, 62), leading several theorists (63, 64) to hypothesise that increased levels of reward sensitivities or drive (i.e. BAS) may also contribute towards the development and maintenance of substance abuse problems. In a longitudinal study comparing BD spectrum and 'healthy' individuals, Alloy et al (60) found that higher BAS sensitivity predicted BD status and increased substance use problems. The authors concluded that higher BAS sensitivity may represent a shared personality vulnerability for both BD and substance use disorders, which may partially explain their co-occurrence

The findings from the study did not reveal a significant association between higher levels of BAS (measured by BAS sensitivity scale from ESM diary and BAS total from BIS/BAS scale) and cannabis use. As noted in the main paper it may be that the BAS was not fully activated in participants in the current study - the mean BAS total was at the lower end, compared to other BD samples (24, 60). Furthermore, as also noted in the main paper, it could be due to an individual not perceiving cannabis as 'highly' rewarding compared to other drugs – therefore they might not experience such heightened levels of BAS activity in pursuit of cannabis.

A further understanding of these personality vulnerabilities does warrant further attention as they may provide opportunities for future intervention. One way of further investigating the role of the BAS in BD and cannabis users would be to compare scores on the BIS/BAS (19) and ESM data for 'healthy' individuals who use cannabis, individuals with BD and individuals with co-occurring BD and cannabis use. This may provide some insight into which individuals are more likely to experience increases in mood/ symptoms/BAS sensitivity as a result of cannabis use and visa versa.

Implication of the study for clinical practice

As previously discussed co-occurring BD and substance abuse is highly prevalent (4, 5, 6) and it is associated with worsened outcomes (1, 2, 3). However intervention research for this particular

group of people is still in its infancy (67, 68, 69, 70). The data from the main study may help inform future interventions.

Overall the findings indicate that cannabis use can lead to a range of psychological effects for individuals with BD, including an exacerbation of both manic and depressive symptoms. Researchers have reported on the potential therapeutic role for cannabis in the management of BD, due to the pharmacological properties contained in THC and CBD (65). Those authors report that cannabis may exert a number of effects such as sedative, hypnotic, anxiolytic, anti-depressant and anti-psychotic. It therefore appears that cannabis may be perceived as useful for some individuals with BD as Ashton et al (65) and the self-report literature suggests that people often use cannabis as a coping strategy in the management of their BD (54, 55, 56). However results from the study indicate that it may further complicate mood for some individuals with BD. Individual differences in sensitivity to cannabis may explain the complexity of this relationship and as discussed previously further research in this area is indicated.

The results from the study may help to counter some individual's positive expectations of their cannabis use. Clients often find it difficult to reduce their substance intake and one of the reasons for this may be due to the perception that cannabis is a useful coping strategy. Firstly services and clinicians should be educated around both the potential impact of using cannabis. They should be skilled up to provide psycho-education to inform clients of the risks. Subsequently the development of behavioural experiments may be one useful way to target client's beliefs about their cannabis use. This could be achieved by asking clients to make predictions about their mood/ symptoms following cannabis use and then use self-monitoring to track their actual experiences. Alongside this clinicians should be offering more helpful strategies to cope with BD symptoms, which may in turn increase an individual's confidence to reduce their substance intake.

As discussed in the main paper, the use of ESM may provide an invaluable therapeutic tool. When participants were asked about their experience of taking part in the study, 8 of the sample reported that using the diaries had increased their awareness of their symptoms and cannabis use. Additionally, two participants made an association between changes in mood and their cannabis use and this realisation had initiated a change in their cannabis use. The service user that piloted the study reported that on one occasion he had become aware that his mood was becoming high, and therefore was able to put some coping strategies in place to prevent further escalation.

The feasibility of using of PDAs as a self-help tool for individuals with BD warrants further investigation. The use of technology is becoming gradually more prevalent in psychological research and clinical practice (66). PDAs could be programmed to beep throughout the day and upon hearing the beep participants could be instructed to respond to brief questions. If participants scored above a certain cut-off point, they could be offered an intervention (e.g. a coping strategy specific to their symptoms). The use of PDAs in the form of 'relapse prevention' could provide an invaluable therapeutic tool for individuals who find it difficult to access psychological services.

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APPENDICES

APPENDIX A

Bipolar Disorders

An International Journal of Psychiatry and Neurosciences

Author Guidelines

Bipolar Disorders - An International Journal of Psychiatry and Neurosciences will consider for publication full length research papers, brief reports, invited editorials, new and views, review articles, rapid communications, case reports, and letters to the editors.

Full length research papers and review papers should generally not exceed a total of 7,500 words. Brief reports, news and views, invited editorials and case reports should generally not exceed 2,000 words. Letters to the editors should be less than 600 words. Rapid communications may have the length of either a full length paper or a brief report.

Manuscripts with all tables and figures may be submitted electronically to kocandj@upmc.edu and any written correspondence should be addressed to:
Donna Kocan
Managing Editor, Bipolar Disorders
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As a general rule, papers will be evaluated by four independent reviewers. One copy of the manuscript will be kept in the editorial office in case revision is recommended. Revised manuscripts should be accompanied by a point-by-point reply to the recommendations of reviewers and editor, specifying the changes made in the revised version.

Authors should include in a cover letter the names and complete addresses, including fax or email, of five potential reviewers, which will be used at the discretion of the editors.

The journal does not hold itself responsible for loss or damage to mailed manuscripts, or for statements made by contributors.

Rapid Communications will be considered for important scientific contributions; authors should explain in their accompanying letter why they intend to publish their paper as a rapid communication.

ABOUT MANUSCRIPTS

Manuscripts with all tables and figures may be submitted electronically to kocandj@upmc.edu. The following rules are in general agreement with 'Uniform requirements for manuscripts submitted to biomedical journals' accepted by an International Steering Committee (see ref. 1 below).

The paper should be submitted in English. Begin each manuscript component (title page, etc.) on separate pages. The pages of the manuscript - text, reference list, tables and legends to figures, in that order, should be numbered consecutively.

Title page
The title page should contain: 1. a concise informative title; 2. author(s)'s names; 3. name of department(s)/ institution(s) to which the work is attributed; 4. name, address, telephone and fax numbers, and e-mail address of the author to whom correspondence about the manuscript, and requests for offprints should be referred; 5. if the title exceeds 40 characters (letters and spaces), a running head of no more than 40 characters; 6. a word count for the whole paper.

Funding Sources
All funding sources supporting the work submitted should be properly acknowledged. Authors are expected to disclose any commercial associations that might pose a conflict of interest in connection with the submitted manuscript or indicate that there are no conflicts. This information will be published as a footnote on the title page of the published manuscript.

Abstract and key words
The abstract should not exceed 250 words and should be arranged in a structured fashion to include objectives, methods, results and conclusions. It should state the purpose of the study, basic procedures (study subject /patients / animals and methods), main findings (specific data and statistical significance), and principal conclusions. For the News and Vies articles, a short (up to 100 words) non-structured abstract should be provided. Below the abstract, provide 3-10 key words that will assist indexers in cross-indexing your article. Use terms from the Medical Subject Headings list from Index Medicus, whenever possible.

Introduction
Present the background briefly, but do not review the subject extensively. Give only pertinent references. State the specific questions you want to answer.

Patients and methods / Materials and methods
Describe selection of patients or experimental animals, including controls. Do not use patients' names or hospital numbers. Identify methods, apparatus (manufacturer's name and address), and procedures in sufficient detail to allow other workers to reproduce the results. Provide references and brief descriptions of methods that have been published. When using new methods, evaluate their advantages and limitations. Identify drugs and chemicals, including generic name, dosage and route(s) of administration. Authors must indicate that the procedures were approved by the Ethical Committee of Human Experimentation in their country, and are in accordance with the Helsinki Declaration of 1975. All papers reporting experiments using animals must include a statement in the Materials and Methods section giving assurance that all animals received humane care. The authors accept full responsibility for the accuracy of the whole content, including findings, citations, quotations and references contained in the manuscript.

Results
Present results in logical sequence in tables and illustrations. In the text, explain, emphasize or summarize the most important observations. Units of measurement should be expressed in accordance with Système International d'Unite (SI Units).

Discussion
Do not repeat in detail data given in the Results section. Emphasize the new and important aspects of the study. Relate the observations to other relevant studies. On the basis of your findings (and others') discuss possible implications / conclusions. When stating a new hypothesis, clearly label it as such.

Acknowledgements
Acknowledge only persons who have made substantive contributions to the study. Authors are responsible for obtaining permission from everyone acknowledged by name because readers may infer their endorsement of the data and conclusions. Authors are expected to disclose any commercial or other relationships that could constitute a conflict of interest. All funding sources supporting the work should be acknowledged.

Tables
Tables should be numbered consecutively with Arabic numerals. Type each table on a separate sheet, with titles making them self-explanatory.

Illustrations
All figures should clarify the text and their numbers be kept to a minimum. Details must be large enough to retain their clarity after reduction in size. Illustrations should preferably fill single column width (81 mm) after reduction, although 2/3 page width (112 mm) or full page width (168 mm) will be accepted if necessary. Magnifications should be indicated in the legends rather than inserting scales on prints. Line drawings should be professionally drafted and photographed; halftones should exhibit high contrast.

Where possible, authors should send digital versions of each figure saved as a separate file in TIFF or EPS format. Please provide best quality figures. Digital files in accordance with our instructions at http://authorservices.wiley.com/prep_illust.asp can be used by production. EPS (illustrations, graphs, annotated artwork; minimum resolution 800 dpi) and TIFF (micrographs, photographs; minimum resolution 300 dpi) are recommended, although in some cases other formats can be used. Files should be at print size. Figures and illustrations for accepted papers can be submitted electronically. Full instructions can be found on our digital illustration pages. Figures and tables can be embedded into the Word document, but they must be grouped at the end of the document rather than embedded within the text.

It is recommended that authors check the quality of their figures prior to submission using Sheridan's Digital Expert tool. The site is also a good place to learn about image reproduction in more detail.

Color illustrations in small numbers may be accepted free of charge at the discretion of the Editors. Otherwise the author must pay for color reproduction and printing of the illustrations at a rate of GBP 150 for the 1st figure, and GBP 50 each for all subsequent figures. Decisions regarding free color illustrations will be made at the time of acceptance of the article. Authors required to pay for color must complete a color work agreement form and send it by POST ONLY to the production editor at the address below as soon as the manuscript has been accepted. Colour Work Agreement Forms sent by any method other than post cannot be accepted.

Amanda Hunter
Wiley-Blackwell
101 George Street, 3rd Floor
Edinburgh EH2 3ES
UK

Legends
Legends should be typed double-spaced in consecutive order on a separate page. They should be brief and specific. If micrographs are used, information about staining methods and magnification should be given.

Abbreviations, symbols and nomenclature
They should be standardized and in accordance with ELLIS G (ed.). Units, symbols and abbreviations. The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE, 1975.

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Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables and legends by Arabic numerals (in parentheses). All references cited, and only these, must be listed at the end of the paper. References should be according to the style used in Index Medicus and International list of periodical title word abbreviations (ISO 833).

Examples:
1. International Steering Committee. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336: 309.
2. Gershon S, Soares JC. Current therapeutic profile of lithium. Arch Gen Psychiatry 1997; 54:16-20.
3. Soares JC, Mann JJ. The anatomy of mood disorders--review of structural neuroimaging studies. Biol Psychiatry 1997; 41: 86-106.
4. Post RM, Weiss SRB. Kindling and stress sensitization. In: Young LT, Joffe RT ed. Bipolar Disorder - Biological Models and Their Clinical Application. New York: Marcel Dekker, Inc., 1997: 93-126.

References in Articles
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CHECKLIST FOR AUTHORS

Complete this checklist before sending your manuscript:

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Title page: Title (short title of less than 40 spaces), Author(s) and affiliation(s), Address, telephone and fax numbers and e-mail address of corresponding author, Word count

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- Discussion
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Authors must make sure that their article is written in idiomatic English and that typing errors have been carefully eliminated.

NHS

National Research Ethics Service

[redacted] Research Ethics Committee [redacted]

Telephone: [redacted]
Facsimile: [redacted]

09 March 2010

Prof Christine Barrowclough
Room S28
2nd Floor Zochonis Building
Brunswick Street
The University of Manchester
M13 9PL

Dear Prof Barrowclough

Study Title:	**Investigating co-morbid Bipolar Disorder and Substance Use: Service User Experiences.**
REC reference number:	**10/H1002/12**
Protocol number:	**2.0**

Thank you for your letter of 04 March 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		28 January 2010
REC application	1.0	28 January 2010
Protocol	2.0	04 March 2010
Investigator CV		28 January 2010
Participant Information Sheet	2.0	04 March 2010
Participant Consent Form: Part 1	2.0	04 March 2010
Participant Consent Form: Part 2	2.0	04 March 2010
Participant Consent Form: Consent for storage of contact detail for future research	1.0	04 January 2010
Letter of invitation to participant	1.0 - *2	15 January 2010
GP/Consultant Information Sheets	1.0	01 December 2009
Letter from Sponsor		27 January 2010
Letter from Statistician		08 December 2009
Referees or other scientific critique report		01 January 2010
Questionnaire: Validated Questionnaire - Adapted SCID		01 January 2010
Questionnaire: Validated Questionnaire - PHQ-9		01 January 2010
Questionnaire: Validated Questionnaire - Internal State Scale		01 January 2010
Questionnaire: Validated Questionnaire - BIS/BAS Scale		01 January 2010
Questionnaire: Non-Validated Questionnaire - Sociodemographic Information	1.0	07 December 2009
Advertisement	1.0	01 December 2009
Letter from Funder		01 January 2010
Instructions for Part 1		01 December 2009
Q Study Items (part 1)	1.0	01 December 2009
ESM Booklet (part 2)		01 December 2009
ESM Booklet (part 2)		01 December 2009
Questionnaire: Non-Validated Questionnaire - Pre Screen	1.0	01 December 2009
Summary CV for Researcher NB		28 January 2010
Summary CV for Researcher ET		28 January 2010
Response to Request for Further Information		04 March 2010
Referrer Information Sheet	2.0	05 March 2010

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating

Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H1002/12	**Please quote this number on all correspondence**

Yours sincerely

[redacted]

Email: [redacted]

Enclosures: "After ethical review – guidance for researchers" *[SL-AR1 for CTIMPs, SL- AR2 for other studies]*

Copy to: *R Hopkins, R&D, MMHSC NHS Trust*
Karen Shaw, University of Manchester
Nancy Black, University of Manchester

[redacted]

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NHS

Research & Development Office

[redacted]

Submission Point for Electronic Approval of Research

22nd March 2010

Prof. Christine Barrowclough
Room S28
2nd Floor, Zochonis Bldng
Brunswick Street
University of Manchester
M13 9PL

Information for ID Badge if required:
Research Project Ref No: 0929
Expiry Date: 31/07/2011
You must take this letter with you.

Dear *Christine,*

Re: Research Governance Decision Letter

Project Reference: 0929 (CSP: 37662/GM)
Unique SPEAR Identifier: *0929*
Project Title : *Investigating co morbid Bipolar Disorder and Substance Use: Service User Experiences.*

Further to your request for research governance approval, we are pleased to inform you that this Trust has approved the study. Please note when contacting the R&D office about your study you must always provide the project reference numbers provided above.

Trust R&D approval covers all locations within the Trust, however, you should ensure you have liaised with and obtained the agreement of individual service/ward managers/medical records departments before commencing your research.

Please take the time to read the attached 'Information for Researchers – Conditions of Research Governance Approval' leaflet, which give the conditions that apply when research governance approval has been granted. Please contact the R&D Office should you require any further information. You may need this letter as proof of your approval.

[redacted]

POSITIVE ABOUT DISABLED PEOPLE

May I wish you every success with your research.

Yours sincerely

[redacted]

cc : Research Governance Sponsor: University of Manchester
Day to Day Contact for study : Nancy Black

Enc: Approval Conditions Leaflet
Induction & ID Badge Information, TrustTECH Leaflet

APPENDIX D

Experiences of Substance Use in Bipolar Disorder

Participant Information Sheet

Bipolar Disorder and Substance Use: Service User Experiences

We would like to invite you to take part in a service user defined research study. Before you decide whether you would like to take part, it is important that you understand why this research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is unclear or that you would like more information about. Take time to decide whether or not you wish to take part.

What is the research project about?

This research aims to find out more about peoples' experiences of substance use in bipolar disorder, what positive and negative effects substances may have on the course of the illness and if and how substance use is related to Bipolar symptoms.

The research is related to another study we conducted last year using Q methodology involving participants with Bipolar Disorder who regularly use alcohol and/or cannabis (sorting cards relating to reasons for substance use). This study has now finished.

Who is organising the research?

This project is being organised by a team of researchers, academics and health professionals from Manchester Mental Health and Social Care Trust, the Universities of Manchester and Lancaster and a Service User Reference Group comprising of service users from across the North West.

The research will focus specifically on Cannabis use in Bipolar Disorder and will ask that participants wear a watch for 6 days which will beep at random times throughout the day to prompt completion of a brief diary.

Who will be taking part?

We will recruit up to 40 participants with Bipolar Disorder who regularly use Cannabis.

The criteria for cannabis use is: use at least two times per week in at least half the weeks in the 3 months prior to assessment.

Participants will be recruited from the North West and East Midlands. Participants' minimum age will be 18.

Why have I been asked to take part?

Sharing your experiences with us will help to increase our understanding of substance use in bipolar disorder. We think that you could make a valuable contribution to this research project

Do I have to take part?

It is completely up to you to decide whether or not you would like to take part. If you do decide to take part you will be given a copy of this information sheet and be asked to sign a consent form. If you do decide to take part but change your mind later you are free to withdraw at any time and do not need to give us a reason. If you do decide not to take part, or to withdraw at any time, we will not use any of the data we may already have collected from you. Decision to withdraw will not affect the standard of care you receive.

What will taking part involve for me?

If you do decide to take part, a research assistant will arrange a time to come and meet you, either at home or at another place where you feel comfortable. We will ask you some questions first about your mood and substance use, just to confirm that you meet the criteria for the study. We will also take some details about prescribed medications you currently take. These questions will take 60-90 minutes.

We will then arrange another appointment to conduct the study.

The study uses a method called Experience Sampling. This is a structured diary method where you will wear a watch for 6 days which beeps randomly at 10 different times throughout the day. Immediately following the beep you will be asked to fill out a booklet containing questions on your current situation, mood, bipolar symptoms and cannabis use. You can continue with your usual routine whilst wearing the watch.

Appointments will be audio taped. This is so that researchers can reflect on what is discussed and accurately record any extra details you provide.

Is the study confidential?

All the information that you give will be strictly confidential. Any data taken from you during the study will be held by the immediate research team. The research team may access your medical notes to help us clarify diagnostic issues however this is optional so you can refuse this access if you wish.

Data and material may be looked at by relevant individuals from the University of Manchester, regulatory authorities or the NHS Trust, for monitoring and auditing purposes. In these situations, strict confidentiality will be maintained.

The information (data) collected will be anonymised, any tapes will be destroyed at the end of the study and any direct quotes used in the write up of the study will be done so in such a way as not to identify individuals.

If at any point during your involvement with the study, the research team are concerned for you in any way, they may wish to contact someone involved in your care. If this is the case, they will speak to you about it first and explain what they plan to do.

What are the advantages and disadvantages of taking part?

The study will give you a chance to reflect on your experiences of substance use in bipolar disorder. We hope that your experiences will help to inform the development of an intervention specifically for people who use substances in bipolar disorder, which will hopefully influence the practice of mental health professionals in delivering treatment and interventions to yourself and other service users.

Participants who complete the study will receive £10 towards expenses. This will be given at the end of the 6 day period, once booklets are completed and watches are returned.

It is possible that talking about your personal experiences may result in some distress. The people interviewing you will be sensitive to this. You will have the opportunity to discuss any concerns at the end of the interview and you are free to withdraw from the process at any point. We will check if there are any concerns you wish to raise and, if necessary, you will be able to talk to one of the clinical psychologists on the research team.

What do I do if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, then in the first instance please contact:

Professor Christine Barrowclough, Professor of Clinical Psychology, The University of Manchester, Manchester, M13 9PL

Telephone: [redacted] Email: [redacted] or

Professor Steven Jones, Professor of Psychology and Clinical Psychologist, Spectrum Centre for Mental Health Research, Lancaster University, Lancaster, LA1 4WY.

Telephone: [redacted] Email: [redacted]

What will happen to the results of the research?

If you participate in the above study you will be informed of the results. The findings will also be presented to a range of mental health professionals and service users with the aim of increasing the understanding substance use in bipolar disorder. It is hoped that the findings will also help to improve services and validate the experiences of other service users. The findings will be published in mental health journals and other publications with the aim of reaching a range of mental health professionals and service users.

The findings will be used to inform subsequent phases of the PARADES programme: a treatment development phase involving consultation with service users and health professionals to develop an intervention for substance use in bipolar disorder. What we learn from this study will be key in helping us to do this.

If you want any further information or have any questions, please contact the research assistants on this project:

Nancy Black – Research Assistant

[redacted]

Lizzie Tyler – Trainee Clinical Psychologist

[redacted]

Telephone: [redacted]

APPENDIX E

Experiences of Substance Use in Bipolar Disorder

Bipolar Disorder and Substance Use: Service User Experiences

Referrer Information Sheet

Who we are

We are a team of researchers based in the North West. The Primary Investigator of the PARADES programme is Professor Steven Jones based at the Spectrum Centre for Mental Health Research at Lancaster University and the Chief Investigator for the Substance Misuse in Bipolar Disorder stream is Professor Christine Barrowclough based at the University of Manchester. Dr Lisa Riste is the Programme Manager, and there are two researchers working on this study: Nancy Black (Research Assistant) and Lizzie Tyler (Trainee Clinical Psychologist). They will be assisted with recruitment by members of the Mental Health Research Network team.

Study aims

This study endeavours to understand more about the experiences of Substance Use for patients with Bipolar Disorder. This phase of the project will have 2 parts:

Part 1 employs Q methodology which involves participants sorting through a deck of cards which have individual statements written on them and placing the cards in their chosen order onto a response grid which identifies on a continuum which of the statements apply to them and which do not. The order in which the cards are placed will be recorded and later compared with other people's answers to investigate whether any themes or patterns emerge. There are 2 separate decks of cards to sort through – the first will describe immediate experiences of substance use in Bipolar Disorder and the second will describe delayed experiences of substance use in bipolar disorder. We will ask participants to complete both card sorts.

Part 2 uses a method called Experience Sampling. This is a structured diary method where participants will wear a watch for 6 days which will beep 10 times throughout the day. Immediately following the beep participants will be asked to fill out a booklet containing questions about their current situation, mood, bipolar symptoms and cannabis use.

Participants who use cannabis regularly will have the option of being involved in both parts, but they can decide to take part in only 1 if they wish.

Those who use alcohol will be suitable for part 1.

The results of both studies will then be used to inform subsequent phases of the project, a treatment development phase which will involve consultation with service users and health professionals to develop an intervention specifically for substance use in bipolar disorder. This will then be trialled in Phase 3 of the project with participants who experience substance use in bipolar disorder and we will measure this in terms of effectiveness and feasibility. We will be recruiting for phases 2 and 3 at a later date.

Rationale

There is a high level of substance use (SU) in individuals with Bipolar Disorder (BD). Some studies have reported levels up to 60%; this level is higher than any other Axis 1 psychiatric disorder. Many studies have shown that outcomes of having both disorders concurrently can be far worse than managing one of these disorders alone, for example with higher levels of treatment non-compliance, higher rates of suicide and increased periods of depression.

Despite the growing concern for patients living with dual diagnosis, there has been very little research into specific treatments for this co morbidity. Some trials testing psychological treatments for BD and SUD have shown some improvements in Substance Use but not necessarily in symptoms of BD. Research to date suggests that people with Bipolar Disorder use substances for different reasons – some give the same reasons as people without a co-morbid mental health problem; but some suggest that they use to help treat symptoms of BD.

The planned studies aim to explore the relationships between Bipolar Disorder and Substance use more closely, asking participants with both diagnoses how it really is for them.

Start date

We will be recruiting from March 2010. Recruitment will continue through until July 2011.

Criteria

We are looking for approx 40 people to take part in each study. Participants will meet the following criteria:

Study 1:

- Have a diagnosis of Bipolar disorder I or II
- Age 18+
- Alcohol use per week exceeding **28 units** for males/ **21 units** for females
- **OR** use of Cannabis at least **two times** per week

Study 2:

- Have a diagnosis of Bipolar disorder I or II
- Age 18+
- Use of Cannabis at least **two times** per week

Get involved!

We would like you to consider anyone you are currently working with who may have bipolar disorder and regularly use cannabis or alcohol, and tell them about the research. Then if they are interested, ask them if it would be ok for one of us to contact them with more information.

We will provide extra details and answer any questions people may have. If they wish to take part, we will gain their written consent. This is an exciting time for service users to get involved in research into their own health problems and to be involved in change and development.

Any questions, queries or referrals, please contact us any time on:

Nancy Black ( ) or
Lizzie Tyler ( )
Or Telephone:
Mobile:

APPENDIX F

CONSENT FORM – Part 2

Bipolar Disorder and Substance Use: Service User Experiences
Part 2 (Bipolar Disorder and the use of Cannabis: An Experience Sampling Study)

REC ref: _____
Name of Researcher: _____
Name of Participant: _____ **Please initial box**

Participant Number ☐☐☐☐

1. I confirm that I have read and understand the information sheet version number …V4…. dated …13/06/10……for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. ☐

3. I give my consent for my appointments with the research team to be audio-taped so that the researchers can reflect on what was discussed and record accurately any extra information I provide. ☐

4. I give my consent for the research team to access my medical records should they need to clarify diagnostic information or update risk assessments. ☐

5. I understand that any data collected during the study may be looked at by individuals from regulatory authorities or from the NHS trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

6. I agree to my GP (and care co-ordinator where appropriate) being informed of my participation in this study and being informed should the researchers have concerns about my mental health while I'm in the study. ☐

7. Please indicate if you would like to be informed of the results. ☐

8. I agree to take part in the above study. ☐

9. I give permission for my direct quotations to be recorded and used if required in published format, and understand that this information will be kept anonymous. ☐

10. I agree for my details to be available to other researchers within the PARADES Programme and for them to contact me should I be considered appropriate for related studies. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent (If different from Principal Investigator)	Date	Signature

APPENDIX G

What was I thinking (just before the beep went off)……
……

This thought was…	Not				Moderately	
▪ pleasant	1	2	3	4	5	6
▪ clear	1	2	3	4	5	6
▪ normal	1	2	3	4	5	6
I have trouble concentrating	1	2	3	4	5	6

Please describe your mood just before the beep went off:

I feel...	Not				Moderately	
▪ cheerful	1	2	3	4	5	6
▪ excited	1	2	3	4	5	6
▪ lonely	1	2	3	4	5	6
▪ relaxed	1	2	3	4	5	6
▪ anxious	1	2	3	4	5	6
▪ satisfied	1	2	3	4	5	6
▪ Irritated	1	2	3	4	5	6
▪ sad	1	2	3	4	5	6
▪ guilty	1	2	3	4	5	6
Overall, I'm feeling happy	1	2	3	4	5	6

Right now.....	Not				Moderately	
▪ I like myself	1	2	3	4	5	6
▪ I am ashamed of myself	1	2	3	4	5	6
▪ I am a failure	1	2	3	4	5	6
▪ I am a good person	1	2	3	4	5	6

Right now I am...	Not				Moderately	
▪ full of energy	1	2	3	4	5	6
▪ restless and fidgety	1	2	3	4	5	6
▪ high	1	2	3	4	5	6
▪ full of good ideas	1	2	3	4	5	6

Right now I feel…						
▪ slowed down	1	2	3	4	5	6
▪ low	1	2	3	4	5	6
▪ bad about myself	1	2	3	4	5	6
▪ fearful	1	2	3	4	5	6

Right now…						
▪ I am suspicious	1	2	3	4	5	6
▪ I hear voices	1	2	3	4	5	6

Right now…

▪ I want to try something new	12	3	4	5	6	7
▪ Nothing can stand in my way	12	3	4	5	6	7
▪ I'm craving excitement	12	3	4	5	6	7

Where am I? ……
Am I alone? Yes / No
If not, with whom? ……..…..……..
How many men?.....women?.....children?.....

With these people, I feel…..

	Not						Very
Comfortable	1	2	3	4	5	6	7
Threatened	1	2	3	4	5	6	7
Accepted	1	2	3	4	5	6	7
Frightened	1	2	3	4	5	6	7

What was I doing (just before the beep went off)……...
……

	Not				Moderate		Very
I would prefer to be doing something else	1	2	3	4	5	6	7
I'm active	1	2	3	4	5	6	7
I takes a lot of effort	1	2	3	4	5	6	7
I am skilled to do it	1	2	3	4	5	6	7
I was challenged by it	1	2	3	4	5	6	7

Since the last beep, the most important event that happened to me was: ……....
……..…….

	Very Unpleasant			Moderate			Very Pleasant
This was:	-3	-2	-1	0	1	2	3

I am LYING DOWN / SITTING/ STANDING/ WALKING (Please circle your choice)

Since the last beep I've used: (Please tick)
Nothing □
Alcohol □ Type (e.g bottle of beer, small glass of wine).....……How many?…...
Cannabis□ Number of joints / bongs.....……

Other drug 1 □ Name..... How much?.....
Other drug 2 □ Name..... How much?.....
Other drug 3 □ Name..... How much?.....

It is now exactly……hrs……..minutes……

PARADES
Psychoeducation, Anxiety, Relapse, Advance Directive Evaluation and Suicidality

MANCHESTER 1824

Manchester Mental Health and Social Care Trust

APPENDIX H **BIS/BAS scale**

Name of Researcher: _____
Name of Participant: _____ **Date:**

Participant Number ☐☐☐☐

Each item of this questionnaire is a statement that a person may either **agree** with or **disagree** with.
For each item, indicate how much you **agree** or **disagree** with what the item says.
Please respond to all the items; do not leave any blank.
Choose only **one** response to each statement.
Please be as **accurate** and **honest** as you can be.
Respond to each item as if it were the **only item**. That is, don't worry about being "consistent" in your responses.
Choose **one** from the following **four response** options:

	Very true for me	**Somewhat true for me**	**Somewhat false for me**	**Very false for me**
1. A person's family is the most important thing in life.				
2. Even if something bad is about to happen to me, I rarely experience fear or nervousness.				
3. I go out of my way to get things I want.				
4. When I'm doing well at something I love to keep at it.				
5. I'm always willing to try something new if I think it will be fun.				
6. How I dress is important to me.				
7. When I get something I want, I feel excited and energized.				
8. Criticism or scolding hurts me quite a bit.				
9. When I want something I usually go all-out to get it.				
10. I will often do things for no other reason than that they might be fun.				
11. It's hard for me to find the time to do things such as get a haircut.				
12. If I see a chance to get something I want I move on it right away.				

13. I feel pretty worried or upset when I think or know somebody is angry at me.				
14. When I see an opportunity for something I like I get excited right away.				
15. I often act on the spur of the moment.				
16. If I think something unpleasant is going to happen I usually get pretty "worked up."				
17. I often wonder why people act the way they do.				
18. When good things happen to me, it affects me strongly.				
19. I feel worried when I think I have done poorly at something important.				
20. I crave excitement and new sensations.				
21. When I go after something I use a "no holds barred" approach.				
22. I have very few fears compared to my friends.				
23. It would excite me to win a contest.				
24. I worry about making mistakes.				

Carver, C. S., & White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS scales. *Journal of Personality and Social Psychology*, 67, 319-333.

APPENDIX I

FACTOR ANALYSES

Mood scales

A principle components analysis revealed two distinct mood scales

	1	2
Cheerful	.874	
Excited	.785	
Relaxed	.656	
Satisfied	.762	
Happy	.778	
Lonely		.569
Anxious		.793
Irritated		.626
Sad		.853
Guilty		.796
% variance explained	32.9	31.2
Cronbachs Alpha	α 0.85	α 0.82
Mean score (S.D)	3.88 (1.30)	2.00 (1.26)

Bipolar symptom scales

A principle component analysis revealed two separate scales, however 'restless and fidgety' (originally mania) loaded onto both factors (higher onto depression), therefore was excluded.

	1	2
I feel slowed down	.573	
I feel low	.880	
I feel bad about myself	.900	
I feel fearful	.839	
I am full of energy		.808
I am full of good ideas		.837
I am high		.785
% variance explained	40.2	29.2
Cronbachs Alpha	α 0.82	α 0.75
Mean score (S.D)	2.10 (1.33)	2.71 (1.38)

APPENDIX J

```
correlate pos neg man dep

(obs=909)

             |      pos      neg      man      dep
-------------+------------------------------------
         pos |   1.0000
         neg |  -0.4616   1.0000
         man |   0.5809  -0.0359   1.0000
         dep |  -0.3936   0.8180  -0.0649   1.0000
```