Cannabis Use and Mania Symptoms: A Systematic Review and Meta-analysis

Running Title: Can Cannabis Trigger Mania?

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Background: Whilst cannabis use appears to be a causal risk factor for the development of schizophrenia-related psychosis, associations with mania remain relatively unknown. This review aimed to examine the impact of cannabis use on the incidence of manic symptoms and on their occurrence in those with pre-existing bipolar disorder

Methods: A systematic review of the scientific literature using the PRISMA guidelines. PsychINFO, Cochrane, Scopus, Embase and MEDLINE databases were searched for prospective studies.

Results: Six articles met inclusion criteria. These sampled 2,391 individuals who had experienced mania symptoms. The mean length of follow up was 3.9 years.

Studies support an association between cannabis use and the exacerbation of manic symptoms in those with previously diagnosed bipolar disorder. Furthermore, a meta-analysis of two studies suggests that cannabis use is associated with an approximately 3-fold (Odds Ratio: 2.97; 95% CI: 1.80 to 4.90) increased risk for the new onset of manic symptoms.

Limitations: We were only able to identify a small number of studies of variable quality, thus our conclusions remain preliminary.

Conclusions: Our findings whilst tentative, suggest that cannabis use may worsen the occurrence of manic symptoms in those diagnosed with bipolar disorder, and may also act as a causal risk factor in the incidence of manic symptoms. This underscores the importance of discouraging cannabis use among youth and those with bipolar disorder to help prevent chronic psychiatric morbidity. More high quality prospective studies are required to fully elucidate how cannabis use may contribute to the development of mania over time.

(Word count: 250)

Keywords: *Mania, bipolar, cannabis, systematic review, meta-analysis*

1. Introduction

Cannabis is the most commonly used illegal substance in many countries, including the UK (British Crime Survey, 2012) and the USA (NSDUH, 2011). Cannabis use has been shown to produce transient, usually mild, psychotic and affective experiences in healthy individuals (D'Souza et al., 2004). Symptoms which persist beyond, or occur independently of, intoxication effects are of greater concern (Moore et al., 2007). There is strong evidence that cannabis use contributes to the development of psychosis and results in a poorer prognosis for those with a pre-existing vulnerability to psychosis (Arseneault et al., 2004, Van Os et al., 2002, Large et al., 2011, Smit et al., 2004). What is less clear is whether cannabis use may also play a causal role in the development of manic affective symptoms and manic episodes specifically (Van Laar et al., 2007, Gruber et al., 2012). Although co-morbid cannabis use is more common in people experiencing bipolar disorder, the association between cannabis use and mania has not received the same degree of attention as that of cannabis use and schizophrenia (Henquet et al., 2006).

Bipolar disorder has the highest rate of substance use co-morbidity of any Axis I disorder (Leweke and Koethe, 2008) and a complex and somewhat reciprocal association between cannabis use and bipolar disorder has been noted (Duffy et al., 2012, Salloum and Thase, 2000). Anecdotal evidence suggests that bipolar patients may engage in 'self-medication' by using cannabis to moderate the symptoms of their illness (Grinspoon and Bakalar, 1998). Other studies indicate that cannabis use predates the advent of bipolar disorder and the reoccurrence of manic episodes (Strakowski et al., 1998, Strakowski and DelBello, 2000), which would suggest a potential causal association.

Bipolar disorder is a complex disease with extensive and diverse symptom clusters (van Rossum et al., 2009) including manic and depressive phases. In terms of cannabis use, associations with manic phases appear especially likely (Strakowski and DelBello, 2000, Sarkar et al., 2003). Manic symptoms are common in patients diagnosed with schizophrenia,

and psychotic symptoms often occur in those with bipolar disorder (Dunayevich and Keck Jr, 2000, Henquet et al., 2006). It has been suggested that mania and psychosis may share aetiological influences (e.g., cannabis use, neuroticism) potentially underpinned by similar physiological mechanisms (Murray et al., 2004). For example, 'sensitisation' of the dopamine system may not only increase the risk of schizophrenia but also mania (Henquet et al., 2006); whether risk eventuates in psychotic or manic disorder is likely to depend on interactions between genetic vulnerability and environmental risk factors (Murray et al., 2004).

Due to the potentially overlapping aetiology between disorders, it is important to distinguish mania from co-occurring psychotic symptoms when assessing associations between cannabis use and mania symptoms. The aim of this review is to assess the prospective associations between cannabis use and mania symptoms as distinct from psychosis symptoms. Specifically we consider:

(1) Does cannabis use lead to increased occurrence of mania symptoms or manic episodes in individuals with pre-existing bipolar disorder?

(2) Does cannabis use increase the risk of onset of mania symptoms in those without pre-existing bipolar disorder?

2. Method

2.1. Search strategy

We used the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Moher et al., 2009) as a framework for our review and reporting procedures. An extensive search of papers in the English language catalogued in PsychINFO, Cochrane, Scopus, Embase and MEDLINE data bases was conducted in June 2014. Search terms were used in three groups and included: cannabis, marijuana, delta-9-

tetrahydrocannabinal, cannabinoids, cannabidiol, cannabinol, tetrahydrocannabivarin (group 1) AND bipolar disorder, manic depressive disorder, mania, hypomania, manic depression, bipolar spectrum (group 2) AND onset, trigger, induce,* course (group 3). All MeSH terms (terms related to individual words) were also included within the search. In addition we examined the first 20 pages in Google Scholar using the terms 'cannabis AND cause AND mania.'

2.2. Inclusion and exclusion criteria

Studies were included if they were primary experimental, prospective, cohort, or longitudinal and if participants were diagnosed with bipolar disorder I or II (i.e., to explore prospective associations between cannabis use and mania in those with pre-existing bipolar disorder) or described as experiencing mania during the follow-up period (i.e., to explore whether cannabis use precedes the onset of mania in those without pre-existing illness). We included studies reporting on both sub-clinical mania symptoms and manic episodes (i.e., meeting criteria for a full manic episode).We selected *prospective* studies only so we could be more confident regarding the temporal ordering of exposure and outcome variables (Schünemann et al., 2011). Studies with participants primarily diagnosed with a psychotic disorder (e.g., schizophrenia, schizoaffective disorder) were excluded in order to help delineate potential causal associations between cannabis use and incident mania or mania symptoms/episodes in bipolar disorder specifically (i.e., if participants had a psychotic disorder, associations between cannabis use and mania independent of psychotic symptoms could not be assessed). Non-English papers and articles published before 1980 were also excluded.

2.3. Data extraction

Following the initial search, the reference lists of review papers were scrutinised for further relevant studies and a hand search was carried out of articles published over the last five years from six journals *(Acta Psychiatrica Scandinavica, Bipolar Disorders, Journal of Affective Disorders, The British Medical Journal, British Journal of Psychiatry and Psychological Medicine)* previously found to contain a substantial quantity of relevant papers or particularly significant ones. Search results were downloaded into *EndNote X5*. Titles of papers were inspected and excluded if irrelevant. M.G and E.G independently coded 100% of the remaining abstracts applying the inclusion criteria for full text retrieval. Percentage agreement between raters was very high (99%). The researchers met to review discrepancies regarding three papers, which were related to whether the study design met criteria for full text retrieval. If there was doubt over whether an abstract should be included for full text retrieval, the decision was made to include. All papers were read, and if suitable, data was extracted on sample size, study design, sampling frame, length of follow up period, prevalence of cannabis use, other drug use, prevalence of mania / manic symptoms, diagnostic tools used and effect sizes of associations between cannabis and mania / manic symptoms. The main reasons for study exclusion subsequent to full text retrieval were: the mania sample was not clearly defined or outcome was conflated with psychosis, schizophrenia or other mood disorders; cannabis use alone was not clearly defined or was conflated with other drug and alcohol use; or the study design was not prospective.

2.4 Quality assessment

The Cochrane collaborations guidelines to assessing risk of bias were used to determine the quality of the studies (Higgins and Altman, 2008). This is a two part tool addressing the seven specific domains of: sequence generation, allocation concealment, blinding of

participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues.' Each domain in the tool includes one or more specific entries in a 'risk of bias' table. Within each entry, the first part of the tool describes what was reported to have happened in the study in sufficient detail to support a judgment relating to the risk of bias. The second part of the tool assigns a judgment relating to the risk of bias for that entry. This is achieved by assigning a judgment of 'Low risk', 'High risk' or 'Unclear risk' of bias.

2.5. Data synthesis

In line with the nature of the data extracted, we utilised two methods to synthesise results. Studies regarding aim one (i.e., does cannabis use lead to increased mania symptoms or manic episodes in individuals with pre-existing bipolar disorder?) were synthesised narratively as they did not yield quantitative summary statistics which could be meaningfully combined. Two (of the three) studies pertaining to aim two (i.e., does cannabis use increase the risk of onset of mania symptoms in those without pre-existing bipolar disorder?) yielded odds ratios, which could be combined using meta-analysis. Due to the heterogeneity of the studies we decided to use a random effects model (Field and Gillett, 2010) and data was analysed using the –*metan*- command in STATA 12 (for MAC).

3. Results

3.1. Description of studies

Our initial search identified 781 abstracts. After repeats were excluded, 431 abstracts remained. Three further relevant articles were identified by hand search. All abstracts were read, 33 of which were selected for full text retrieval. Overall, 6 studies met full criteria for inclusion and final data extraction. A PRISMA flowchart describing the results of the search is shown in **Figure 1.** The mean length of follow up was 3.9 years. Attrition rates in the included studies ranged from 4% to 49% (2 of the studies (Strakowski et al., 2000, Duffy et al., 2012) did not state attrition rates). Details of the included studies are shown in **Table 1.** The 6 identified studies comprised a mix of large community (Henquet et al., 2006) (N = 4,815) and clinical (van Rossum et al., 2009) (N= 1,612) populations; moderate community (Tijssen et al., 2010) (N = 705) and clinical (2008) (N = 166) populations; one small clinical sample (Strakowski et al., 2000) (N = 50); and one moderate sample of a high risk population (Duffy et al., 2012) (N = 211). In total, 14, 918 participants were included in the 6 studies.

3.2. Quality assessment of studies

Using the Cochrane guidelines to assess risk of bias, no studies were deemed to be low risk of bias in all 7 domains (see **Table 2** for risk allocations). A detailed table showing supporting arguments for each of these judgements is available from the authors on request. In Henquet et al. (2006) high risk of bias was evident in selection (inadequate randomisation and concealment of allocation), performance, detection and attrition domains. From an initial 7,076 participants, 4,815 were included in the final analysis, though the sensitivity analyses suggested that drop-out did not bias study findings. Similarly, Strakowski and DelBello (2000) was deemed high risk of bias in selection (random generation and allocation concealment), performance, detection and attrition (rates of attrition not reported) domains. Tijssen et al. (2010) was high risk of bias in selection, attrition and 'other' domains. From an

initial 1, 395 participants, only 705 remained at 8 year follow-up. Exclusion of participants with manic and depressive symptoms at baseline resulted in a loss of power, which could have led to an underestimation of associations ('other' bias). van Rossum et al. (2009) was high risk of bias in selection (random generation and allocation concealment), performance and detection domains. Baethge et al. (2008) was classified as high risk in the domains of selection (random generation and allocation concealment) and attrition bias. Duffy et al. (2012) was also found to be high risk of bias in selection (random generation and allocation concealment) and attrition domains.

3.3. Does cannabis use worsen mania symptoms in individuals with pre-existing bipolar disorder?

Using a small clinical sample of 50 new-onset bipolar patients aged 16-45 years, Strakowski et al. (2000) considered the impact of cannabis use on the course of bipolar disorder over 2 years. At one month, then 4 monthly intervals mania symptoms (full syndrome or significant symptoms) were assessed using the Young Mania Rating Scale (YMRS), while cannabis use was assessed using the Structured Clinical Interview for DSM-IV-Patient version (SCID-P). For each assessment interval the investigators made week-by-week ratings of the severity of substance abuse and mania symptoms. From these assessments the percentage of weeks with full (i.e., full syndrome, severe; full syndrome) or significant (i.e., marked symptoms; partial remission) substance abuse and mania symptoms was calculated. Regression analysis revealed that the duration of time with active cannabis use syndrome/symptoms (i.e., as defined by the percentage of weeks with full or significant symptoms) was significantly associated with the duration of time with mania syndrome/ symptoms ($R = .42$, $p < 01$).

In a larger clinical study, Baethge et al. (2008) prospectively followed-up (mean length 4.7 years) 166 first episode DSM-IV bipolar I patients with a median intake age of 28 (range 18-72) years to assess the association between cannabis use (exceeding sporadic) and mania (major episode or hypomania according to DSM-IV). Using generalised estimating equation regression modelling the authors found that by quarters (i.e., 3 month periods) cannabis use strongly and selectively predicted (RC = 0.111; 95% CI = 0.054–0.168; z-score = 3.80, $p < 0.001$) manic symptoms or episodes. Conversely, substance use was not preceded by mood states in the previous quarter. Associations with manic symptoms were reported to be specific. Cannabis use did not predict depression symptoms and alcohol use did not predict mania symptoms. While the authors concluded that these findings suggest potential 'causal' associations between cannabis use and mania, it should be borne in mind that cannabis use also coincided with manic symptoms during the same quarter (RC = 0.116; 95% CI = 0.053–0.178; z-score = 3.63, $p < 0.001$), indicating the possibility of reverse causality (i.e., cannabis use could have occurred in the context of existing mania symptoms).

van Rossum et al. (2009) explored the association between cannabis use and mania symptoms over the course of a year in a very large sample (N=3,426) of bipolar in-and out-patients. Mania symptoms were assessed using the Clinical Global Impression Bipolar (CGB-BP) mania scale and rated for severity on a seven point index (yielding a total mania symptom score) at baseline, 12 weeks, 6 months and 1 year. Cannabis use was dichotomised into 'any cannabis use,' incorporating any instances of use, abuse or dependence, versus 'no use.' As each assessment pertained to the preceding 3 months, any cannabis use referred to reported use at least once over the 15 month period. After controlling for baseline mania symptoms, sex, treatment compliance, age, age of onset (i.e., first symptoms of bipolar disorder) and use of alcohol and other drugs, multi-level random regression analyses revealed that any cannabis use was significantly associated with CGI-BP mania score (B = 0.15, CI:

0.06, 0.24; $p < 0.001$). The authors assessed 'any cannabis use' regardless of level of dependency or duration of use. Therefore, reported associations likely lacked precision, due to heterogeneity between individuals in terms of dependency, volume, frequency and duration of cannabis use. As has been observed for the course of psychosis (Moore et al., 2007), it is likely that the effects of chronic cannabis use on mania may be markedly different from those of short-term or occasional use.

3.4. Does cannabis use increase the risk of onset of mania symptoms in those without pre-existing bipolar disorder?

Tijssen et al. (2010) conducted an 8 year prospective, community study of 705 youth aged 14-24 years. Participants completed baseline, and three follow-up assessments. Lifetime cannabis use was defined as having used cannabis five or more times. Hypo (manic) symptoms were assessed using mania section of the Composite International Diagnostic Interview (CIDI). Items were rated as absent or present, thus a sum score of 0-11 was possible (dichotomised into 0 to 3=no mania symptoms; >3 = mania symptoms). The association between cannabis use and onset of manic symptoms was calculated as the strength of association between cannabis use at baseline and follow-up manic symptoms in the absence of manic symptoms at baseline. Onset of (hypo) manic symptoms was significantly associated with cannabis use, i.e., those reporting past cannabis use were approximately four times more likely to develop mania symptoms (OR: 4.26; 95% CI 1.42, 12.76, P < 0.01).

In a larger general population study of 4,185 individuals aged 18-64 years Henquet et al. (2006) explored the prospective association between cannabis use and sub-threshold mania symptoms. Cannabis use (any and frequency) and manic symptoms were assessed

using the CIDI. In unadjusted analysis, cannabis use was associated with a 5 times increased risk of mania symptoms (i.e., at least one positive rating on any of the 11 items of the CIDI) at follow-up. While attenuated following control for sociodemographic variables, neuroticism, use of other drugs and alcohol, baseline mania and psychosis symptoms, the association between cannabis use and mania remained significant. Furthermore, a dose response association was observed. The strength of association between cannabis use and mania symptoms was nearly double for cannabis use on 3-4 days per week (OR: 6.94; 95% CI: 2.00 to 24.06) in comparison to 1-2 days per week (OR: 3.78; 95% CI: 1.59, 8.97).

In a recent study, Duffy et al. (2012) used a high-risk offspring cohort of 211 adolescents aged 12 years and older to assess the association between lifetime substance use disorder (SUD) and bipolar disorder (NOS, BDI, BDII). All offspring were assessed annually using the Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime (KSADS-PL) interview. Lifetime substance use disorder (23.7%) was classified according to DSM-IV criteria, with cannabis use being the most common disorder (70% of SUDs). Bipolar disorder showed a bidirectional relationship with SUD. Cox Proportional Hazards (CPH) analysis revealed that having an a priori SUD predicted the subsequent development of bipolar disorder (Hazard Ratio: 3.403; $p < 0.01$). Conversely, bipolar disorder increased the risk of subsequent substance use disorder (Hazard Ratio: 3.066; $p < 0.01$). When appraising these results it should be noted that while cannabis use was the first drug of abuse in 70% of the SUD cases, some individuals reported alcohol abuse disorder with subsequent cannabis use, and a very small proportion reported poly substance abuse. This heterogeneity could have confounded the reported associations between cannabis use and bipolar disorder, though studies have indicated that alcohol abuse may be associated with depression rather than mania symptoms in bipolar disorder (Baethge et al. 2008; Strakowski et al., 2005).

Meta-analysis results

Two community studies (Henquet et al., 2006, Tijssen et al., 2010) provided information suitable for synthesis using meta-analytical techniques (i.e., they provided a cannabis-mania association value which could be meaningfully pooled and converted into a common effect size (Field and Gillett, 2010)). There was a low, non-significant degree of heterogeneity between studies (I squared=0.00, p=0.469). The pooled effect size (displayed in figure 2) for the association between cannabis use and mania symptoms was: Odds Ratio = 2.97 (95% Confidence Intervals: 1.80, 4.90).

4. Discussion

We completed a comprehensive systematic review of the extant literature in an attempt to establish whether cannabis use may worsen mania symptoms in those formerly diagnosed with bipolar disorder, and also trigger onset of manic symptoms in those without prior diagnosis. Specifically, we were interested in the independent associations between cannabis use and subsequent mania as distinct from psychotic symptoms. Collectively, the findings from the systematic review and meta-analysis suggest that there is a significant relationship between cannabis use and subsequent exacerbation and onset of mania symptoms. Results from the meta-analysis demonstrated that cannabis use was associated with an almost three-fold increase in the odds of mania symptoms in non-clinical populations, indicating a moderate association (Ferguson, 2009).

4.1. Does cannabis use increase the occurrence of manic symptoms or mania in those with pre-existing bipolar disorder?

Collating results from studies utilising clinical populations, it can be concluded that cannabis use may worsen the course of bipolar disorder by increasing the likelihood, severity or duration of manic phases (van Rossum et al., 2009, Strakowski et al., 2000, Baethge et al., 2008). Previously, it has been unclear whether cannabis use predates manic episodes, represents a symptom of bipolar disorder or an attempt to self-medicate, or that both disorders share common risk factors (Strakowski and DelBello, 2000). Evidence here mainly supports the contention that cannabis use precedes the presence/re-occurrence of manic symptoms in at least a proportion of the population previously diagnosed with bipolar disorder. For example, Baethge et al. (2008) reported that while cannabis use preceded mania symptoms, there was no reciprocal pattern, i.e., mania did not precede cannabis use. Further, van Rossum et al. (2009) reported an association between cannabis use and mania after controlling for baseline mania symptoms, supporting that cannabis use is associated with new manic symptoms. While these findings are suggestive, it should be acknowledged that both Baethge and van Rossum studied patients with an existing diagnosis of bipolar disorder, thus it is possible that low level (i.e., below the study threshold) mania symptoms could have exacerbated the likelihood of subsequent cannabis use. The clinical studies reviewed here also indicate a degree of *specificity* regarding the associations between cannabis use and mania symptoms in bipolar populations. In two studies, the duration of cannabis abuse was significantly associated with the duration of mania (Strakowski et al., 2000, van Rossum et al., 2009). Furthermore, while cannabis use appears to selectively precede mania symptoms, it has not been found to be similarly associated with depression symptoms (Baethge et al., 2008).

4.2. Does cannabis use induce mania symptoms specifically?

While results from clinical populations can inform us regarding the course and severity of bipolar disorder as a result of cannabis use, non-clinical population studies (which assess cannabis use *prior* to the *onset* of the disorder) are required in order to understand whether a consistent and strong signal emerges with regards to possible causality. High-risk offspring population studies and community cohorts of adolescents and young people prospectively followed over time suggest that cannabis use is associated with bipolar disorder (i.e., NOS, BDI, BDII) (Duffy et al., 2012) and mania symptoms (Henquet et al., 2006). Importantly, Henquet et al. (2006) found that baseline cannabis use predicted sub-threshold mania symptoms during follow-up once baseline mania symptoms and a number of important confounders such as psychotic symptoms were statistically accounted for, supporting that cannabis use may contribute to the development of non-psychotic mania symptoms specifically (Van Laar et al., 2007). While population studies are suggestive of a causal association between cannabis use and the onset of mania, it should be borne in mind that mania symptoms are considered in terms of sub-threshold levels in these studies (Henquet et al., 2006, Tijssen et al., 2010). Thus, the clinical relevance of these findings remains uncertain. Nevertheless, as has been described for sub-threshold psychosis symptoms (Van Os et al., 2009), research suggests that expressions of mania outside the realm of clinical disorder have a distribution in the general population (Akiskal, 2003, Krabbendam et al., 2004) and that sub-threshold expressions of mania show continuity with clinical diagnoses of mania and thus bipolar disorder (Regeer et al., 2006, Thomas, 2004).

4.3. Potential mechanisms underlying the association between cannabis use and manic symptoms

Pharmacological and brain imaging studies suggest that dopaminergic hyperactivity may underlie both psychosis and mania. Both disorders share a genetic predisposition towards dysregulation of the dopamine system, which may be exacerbated by social or pharmacological stress (Murray et al., 2004). An increase in positive psychotic symptoms in response to cannabis use has been linked to its main psychoactive component tetrahydrocannabinol (THC), which appears to enhance mesolimbic dopaminergic activity (D'Souza et al., 2005). Additionally, cannabinoid receptors, such as CB1, appear to decrease the uptake of dopamine, potentiating its actions (D'Souza et al., 2005). Therefore, as has been described for schizophrenia, cannabis use may contribute to the development of mania symptoms by leading to a sensitisation of the dopaminergic system (Sarkar et al., 2003). 'Sensitisation' in this case refers to a process by which intermittent cannabis exposure produces a permanent change in dopaminergic responses (Wolf et al., 1993). Thus, regular cannabis use may render individuals gradually more sensitive to dopamine- induced perceptual and cognitive abnormalities (De Hert et al., 2011), Indeed, Henquet et al. (2006) reported that while baseline cannabis use was significantly associated with mania symptoms at follow-up, a similar association between *follow-up* cannabis use and mania was not observed. This supports that the effects of cannabis use on manic symptoms may result from long term rather than acute exposure

4.4. Limitations

Although we were comprehensive in the data sources reviewed, we were able to identify only a relatively small number of studies on which to base our conclusions. The scarcity of available studies, and variations in assessment tools and statistical approaches, limited our ability to present a full quantitative synthesis of the data (e.g., meta-regression techniques to

explore associations independent of confounding study factors). Furthermore, all studies demonstrated risk of bias in at least 3 (and usually more) out of 7 domains, and our findings should also be seen in this light.

Studies were variable in terms of the precision of assessment of cannabis use. For example, some studies indicated cannabis use according to 'any cannabis use,' regardless of severity or frequency of use (van Rossum et al., 2009; Baethge et al., 2008). Duffy and colleagues (2012) did not differentiate cannabis users from other substance users, though the majority of participants primarily used cannabis. There were also wide variations in the assessment of mania symptoms. Duffy et al. (2012) considered associations with bipolar disorder (BPI, BPII, NOS) rather than mania symptoms per se. While BPI diagnosis necessitates only a single manic episode, BPII requires both hypomanic and depressive episodes(APA, 2000). Therefore, associations in this study may have lacked specificity. Other studies conflated sub-clinical with clinical levels of mania (Strakowski et al., 2000) or used a low threshold for the presence of mania symptoms (Henquet et al., 2006).

To establish whether cannabis use triggers manic affective symptoms specifically, we sought to exclude all studies which included patients with a psychotic disorder. In some of the included studies, however, participants were experiencing a degree of psychotic symptoms (van Rossum et al., 2009; Duffy et al., 2012; Henquet et al., 2006), which were significantly associated with cannabis use. Unfortunately, only one of these studies, as far as we can discern, simultaneously controlled for psychotic symptoms when assessing the association between cannabis use and mania symptoms (Henquet et al., 2006). Other studies did not assess psychotic symptoms (Baethge et al. 2008; Strakowski et al. 2000; Tijssen et al. 2010), precluding assessment of mania-cannabis associations while concurrently adjusting for psychotic symptoms. In the absence of further studies in this vein, the observation of an

independent (of psychosis symptoms) association between cannabis use and mania remains tentative.

Our inclusion of prospective studies only, while necessary to tease out the directionality of effect, also reduced the number of available studies, highlighting the need for more well-designed epidemiologic prospective studies in order to trace the pathways from cannabis use to mania symptoms (Castle and Murray, 2004). Also even in our selection of prospective studies, it was not always clear that manic symptoms were being assessed in the absence of continued cannabis use (Strakowski et al. 2000, Baethge et al. 2008) raising the possibility that at least some manic symptomatology could be explained by intoxication effects or reverse causality. Finally, due to the observational nature of the identified review papers, we remain tentative in our conclusions regarding the *causal* link between cannabis use and mania symptoms. While cannabis use appears to predate mania, it is always possible that the observed associations may be attributable to unidentified third variables (Castle and Murray, 2004). Insomnia (Bauer et al., 2006, Leibenluft et al., 1996, Colombo et al., 1999, Ashton et al., 2005) and childhood maltreatment (Bender and Alloy, 2011, Thornberry et al., 2010), for example, have both been associated with cannabis use and mania, however, these factors were not included as confounders in the reviewed articles.

4.5. Implications for clinical and research practice

In sum, the observed tendency for cannabis use to precede or coincide with rather than follow mania symptoms, and the more specific association between cannabis use and new onset manic symptoms, suggests potential causal influences from cannabis use to the development of mania (Baethge et al., 2008). The symptom overlap between mania and psychosis suggests that the reasons postulated to explain the cannabis-psychosis link may also be part of the explanation of the cannabis-mania association, though of course other mechanisms may exist.

It is also important, however, for future studies to consider specific pathways from cannabis use to mania and how these may be modulated by genetic vulnerability and environmental risk factors (Murray et al., 2004).

Bipolar patients with co-morbid substance abuse have more severe symptoms and an increased risk of relapse, though the extent to which severe symptoms are predictive, or a consequence, of increased cannabis use remains unclear. Regardless, such patients merit special clinical consideration (Richardson, 2013). Cannabis is the most prevalent drug used by the under-18s (National Treatment Agency., 2012) and during this critical period of development (Paus et al., 2008) services should be especially aware of and responsive to the problems that cannabis use can cause for adolescent populations (NTA., 2012).

It has been established that there are limited studies addressing the association of cannabis use and manic symptoms, which suggests that this is a relatively neglected clinical issue, possibly due to the methodological and practical difficulties inherent in bipolar disorder research (Murphy and Sahakian, 2001). However the reviewed evidence supports that cannabis use is a major clinical problem occurring early in the evolving course of bipolar disorder (Tijssen et al., 2010) highlighting the importance of substance abuse prevention programs for youth (Paglia and Room, 1999) and developing and utilising interventions for those with this type of dual diagnosis.

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Figure 1 PRISMA flow chart detailing selection of the individual studies

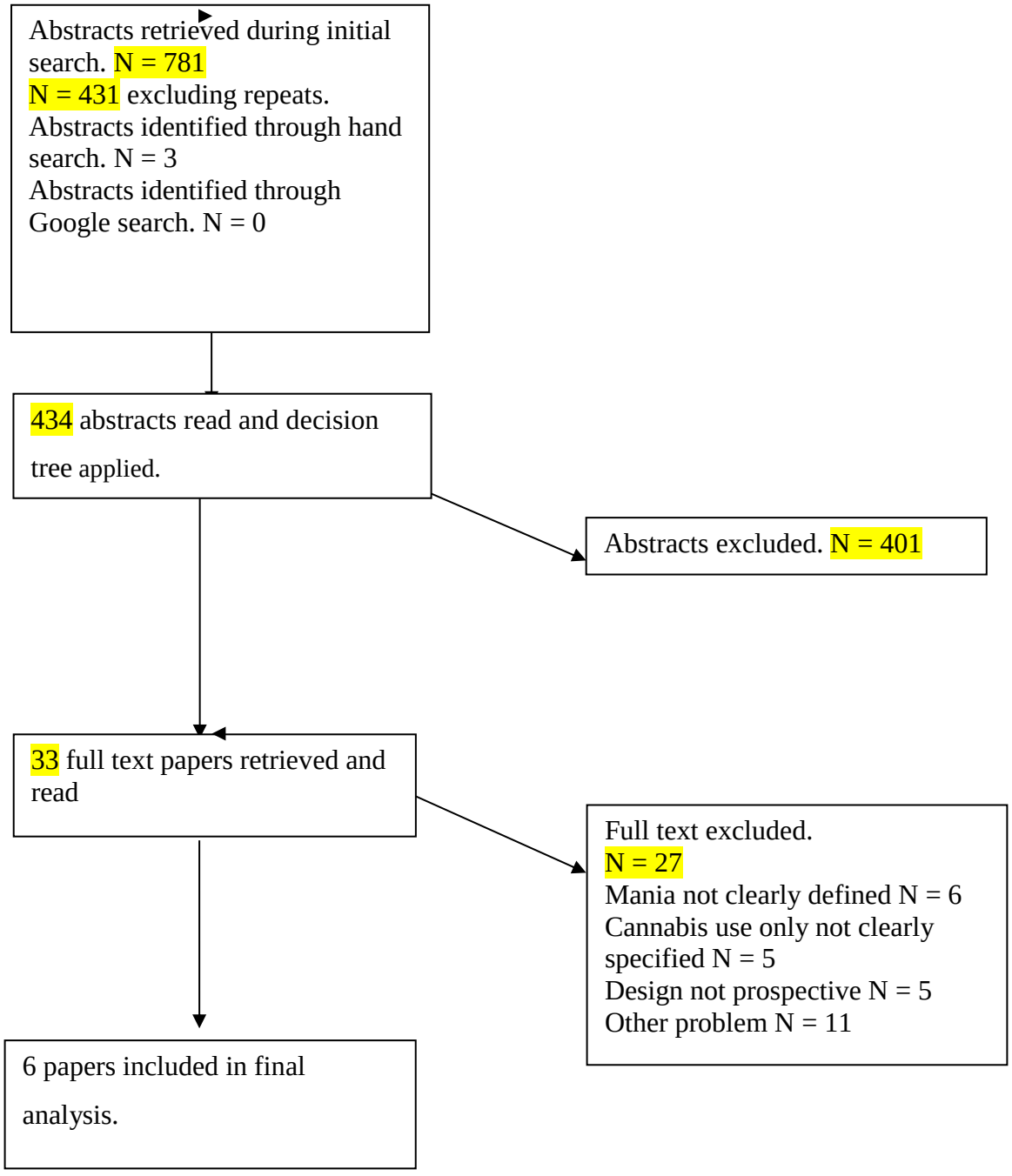

Figure 2: Cannabis and manic symptoms

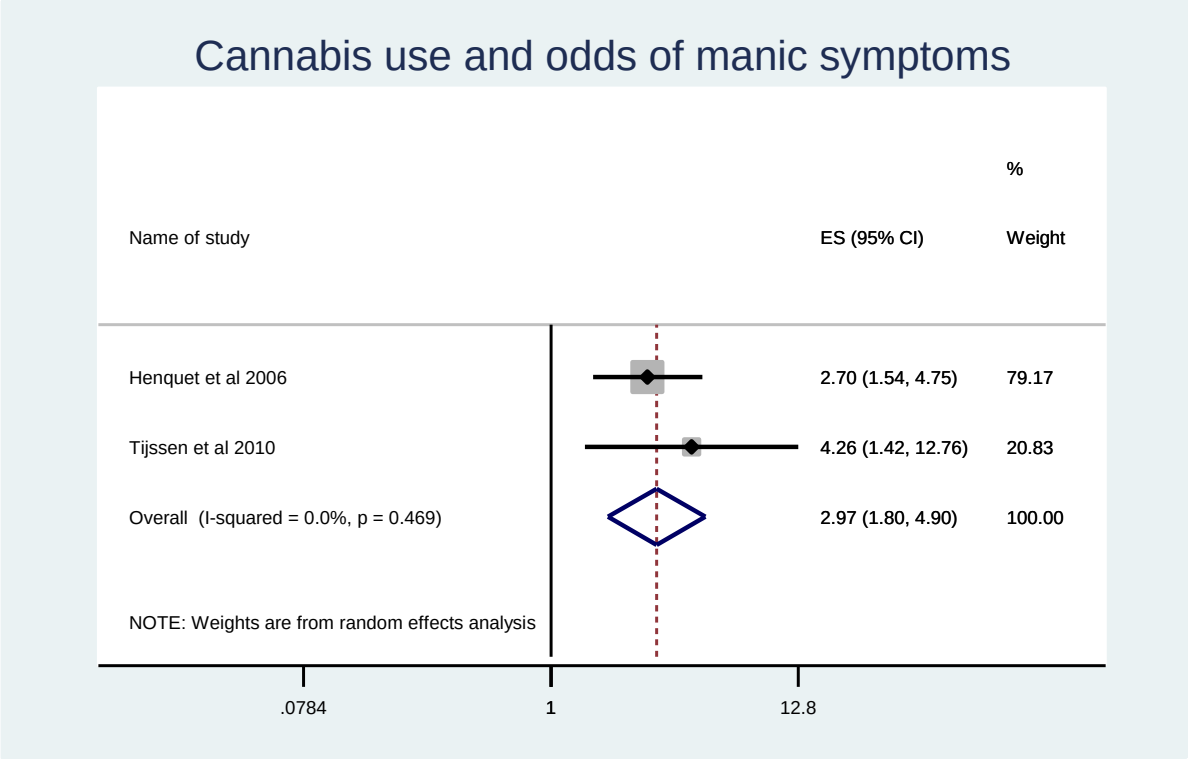

Table1 Details of Studies on Reporting on Cannabis Use and Mania Symptoms

Study	**Study design Year of enrolment**	**Participants**	**Follow-up**	**Outcome n (%)**	**Assessments**	**Diagnostic criteria/ instrument**	**Definition of cannabis use**	**Cannabis N (%)**	**Association between cannabis use and mania outcome**	**Confounding variables controlled for**	**Limitations of study**
Baethge *et al*. 2008	Prospective follow-up 1989-1996	166 first episode type I bipolar patients 18-72 years	4.7 years	Mania: Major episode or sub-syndromal	Every 3 months	DSM-IV/LIFE[1]	Exceeding sporadic usage according to patient	30 (18.1%)	Cannabis use during preceding quarter significantly associated with mania (11.1% excess risk)	Age, sex, years of total exposure time	Inclusion of hypomania (i.e., sub-threshold mania) may have reduced accuracy
Duffy *et al*. 2012	High-risk cohort	211 high-risk adolescents 12 + years	5.2 years (mean)	Bipolar Disorder 35 (16.6%)	Baseline and annually	DSM-IV/KSADS-PL[2]	DSM-IV criteria for substance use disorder (SUD)	35 (16.58%)	A priori SUD significantly predicted development of Bipolar Disorder (Hazard Ratio: 3.40)	Sex, socioeconomic status and familial correlation	Associations with SUD not cannabis use specifically
Henquet *et al*. 2006	Prospective population study	4815 individuals 18-64 years	3 years	hypo/sub- threshold mania symptoms (1≥ mania item) Rate of mania: Baseline: 192 (4%) Follow-up: 118 (25%)	Baseline, 1 year, 3 years	CIDI[3]	Lifetime and follow-up cannabis use -any -frequency	Baseline: 9.4% During follow-up: 3.9%	Baseline cannabis significantly predicted hypo/sub-threshold mania symptoms during follow-up (Odds Ratio: 2.51; 95% CI = 1.38 to 4.59)	Age, sex, education, ethnicity, marital status, other drugs, neuroticism, alcohol, baseline depression, mania and psychotic symptoms	Sub-threshold definition of manic-like symptoms applicability to clinical levels unclear
Strakowski *et al.* 2000	Prospective follow-up 1996	50 bipolar patients aged 16-45 years	Max 2 years	Full or significant symptoms Mania syndrome: - 10% of time with mania	Every month, then every 4 months	YMRS[4]	SCID-P [5] Full or significant	Exhibited cannabis abuse: 13% of time	Fraction of time with cannabis use associated with fraction of time with mania (Regression co-efficient: 0.42)	Age, gender, race, education, employment, affective state, age of bipolar disorder onset, duration of index episode, treatment noncompliance	Preliminary results as very small sample
Tijssen *et al.* 2010	Prospective cohort community study 1994	705 adolescents and young adults	8 years	Mania (hypomania) symptoms (11 item scale) Experienced manic symptoms: - follow-up: 79 (11.2%)	1.6, 3.4 and 8.3 years	DIA-X/M-CIDI [6]	Lifetime cannabis: used 5 times or more	4.4%	Baseline cannabis significantly predicted (hypo) mania symptoms during follow-up (Odds Ratio: 4.26;	Age, sex, socioeconomic status, family history of mood episodes, exposure to trauma, loss of a parent, alcohol use,	Sub-threshold outcome thus applicability to clinical levels unclear Those with

				Baseline and follow-up: 46 (6.5%)					95% CI 1.42–12.76)	personality style	baseline mania (or hypomania) excluded reducing power
Van Rossum *et al*. 2009	Prospective follow-up	3426 bipolar in- and out-patients Mean age 44.6 years	1 year	Mania symptoms on a 7-point index Mania mean (SD) -baseline: 4.8 (1.0) -3months: 2.2 (1.2) -6 months: 1.9 (1.2) -12 months: 1,9 (1.3)	Baseline, 12 weeks, 6 months, 1 year	CGI-BP mania	Abuse or dependence	436 (12.7%)	There was a significant association between any cannabis use and mania score during follow-up B = 0.15, CI: 0.06, 0.24; p = 0.001).	Country, sex, compliance, age of onset, use of alcohol and other drugs	Clinical sample with baseline rating of mania thus could only infer about the severity and persistence of symptoms (not causality)

Table 2 Quality assessment of the included studies based on risk of bias

Study	Selection bias- Random sequence generation	Selection bias- allocation concealment	Performance bias- blinding of participants and personnel	Detection bias- Blinding of outcome assessment (patient-reported outcomes)	Attrition bias- Incomplete outcome data	Reporting bias- Selective reporting	Other bias
Baethge et al (2008)	High	High	Low	Low	High	Low	Low
Tijssen et al (2010)	High	High	Low	Low	High	Low	High
Van Rossum et al (2009)	High	High	High	High	Low	Low	Low
Henquet et al (2006)	High	High	High	High	High	Low	Low
Duffy et al (2012)	High	High	Low	Low	High	Low	Low
Strakowski et al (2000)	High	High	High	High	High	Low	Low