

Cannabis and Bipolar Manic Episodes

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Abbreviations

AUD Alcohol use disorder
BD Bipolar disorder
fMRI Functional magnetic resonance imaging
MDD Major depressive disorder
SUD Substance use disorder

SUBSTANCE USE AND BIPOLAR DISORDER

Among mood spectrum disorders, bipolar disorder bears the highest rate of substance abuse, with about 50% of subjects having a lifetime comorbidity of an alcohol use disorder and 41% having any other substance use disorder (Regier et al., 1990; Strakowski et al., 2007). The association between cannabis use and mood disorders is well recognized and cannabis is the most commonly used illegal drug among patients with bipolar disorders. Around one-third of bipolar patients have a diagnosis of cannabis abuse or dependence and lifetime prevalence rates from 26% to 46% have been reported (Agrawal, Nurnberger, & Lynskey, 2011; Cerullo & Strakowski, 2007; Leweke & Koethe, 2008).

Substance abuse and increased symptom severity have also been shown (Lagerberg et al., 2011).

CHILDHOOD TRAUMA, CANNABIS, AND BIPOLAR DISORDERS

A link has been reported between childhood trauma and increased risk of substance abuse in adulthood (Fergusson, Boden, & Horwood, 2008; Shin, Edwards, Heeren, & Amodeo, 2009). In a 2014 study exploring the influence of childhood trauma and substance abuse on the clinical picture of 587 patients with bipolar disorder (BD), Aas et al. (2014) showed significant additive effects between childhood abuse and cannabis abuse on increased clinical expression of BD.

IMPACT OF CANNABIS USE ON MANIA PHENOMENOLOGY

It has been proposed that manic episodes can be classified as predominantly euphoric, which is usually called “classic” or “pure” mania, or dysphoric mania, characterized by inner tension,

irritability, and anger with verbal and/or physical aggressiveness (Dilsaver, Chen, Shoaib, & Swann, 1999; Swann et al., 2013).

Higher rates of substance use disorders (SUDs) have been reported in patients with dysphoric mania compared with euphoric mania (Feinman & Dunner, 1996). In a 2015 study with bipolar hospitalized manic patients, Güclü, Senormanci, Aydin, Erkiran, and Kokturk (2015) evaluated distinct clusters of subtypes and the relationship between the clinical features such as SUDs and the various clusters. They found that 39% of the patients in the psychomotor elevation cluster (with features such as increased motor activity, enhanced rate of speech, disruptive behavior, elevated mood, increased sexual interest, and diminished sleep) had an alcohol use disorder. In the dysphoric–psychotic cluster, 31.6% presented an alcohol and a cannabis use comorbidity. The authors raise the hypothesis that patients with classical or pure mania may use the sedative effect of alcohol as a self-medication. They also point to a causal relationship between cannabis and psychosis (Güclü et al., 2015).

Moreover, in the dysphoric–psychotic cluster, 47% of patients had made one suicide attempt during their lifetime. This result is in agreement with previous studies showing that dysphoria is associated with suicide attempts (Dalton, Cate-Carter, Mundo, Parikh, & Kennedy, 2003).

In one study, the duration of cannabis abuse was closely related with the duration of manic episodes (Cerullo & Strakowski, 2007). The impact of cannabis on mania phenomenology is summarized in Table 1.

IMPACT OF CANNABIS USE ON BIPOLAR DISORDER OUTCOME

In the field of mood disorders, the association of cannabis use and BDs has been less investigated than the association with unipolar depression (Feingold, Weiser, Rehm, & Lev-Ran, 2015). Nevertheless, several studies have reported an association between cannabis use and BD (Cerullo & Strakowski, 2007; Etain et al., 2013). As pointed out by Feingold et al. (2015), longitudinal studies have suggested a relationship between baseline cannabis use and the diagnosis of BD at follow-up (Baethge et al., 2008; Tjijssen et al., 2010). However, methodological limitations imply that these findings must be taken with caution.

TABLE 1 Impact of Cannabis on Mania Phenomenology

- Psychotic symptoms
- Dysphoric mania
- More lifetime suicide attempts
- Longer episodes

The characteristics listed above have been linked to cannabis use.

In a longitudinal investigation drawn from the National Epidemiology Survey on Alcohol and Related Conditions, [Feingold et al. \(2015\)](#) explored the association between cannabis use and major depressive disorder (MDD) and BD over a 3-year prospective study. For unipolar disorder, they found that there was no difference in the incidence of MDD between cannabis users compared to nonusers, which is in agreement with several previous studies. For BD, their results suggest that the association between cannabis use and increased incidence of BD was not confirmed after adjusting for very frequent (daily or almost daily) users as well as for subjects using cannabis on a less-than-weekly basis. The authors hypothesize that additional factors may mediate the association between cannabis use and BD ([Feingold et al., 2015](#)).

Some studies have shown a poorer medication adherence and a more severe course of illness for BD individuals with cannabis use ([Agrawal et al., 2011](#)). It has also been reported that bipolar patients with cannabis use spend more time in affective episodes ([Strakowski et al., 2007](#)) and that the number of manic or depressive episodes is higher ([De Hert et al., 2011](#); [Lev-Ran, Le Foll, McKenzie, George, & Rehm, 2013a](#)).

A study that did not differentiate between cannabis use alone or cannabis plus other substances reported a higher rate of substance abuse for BD type I than BD type II ([Regier et al., 1990](#)). However, when types I and II BD were compared for the rate of cannabis abuse comorbidity and the course of illness, no significant difference was found ([Bega, Schaffer, Goldstein, & Levitt, 2012](#)). [Stone et al. \(2014\)](#) also showed that cannabis users who diminished or stopped the use of cannabis after a first hospitalization had a greater improvement in symptomatology at 1-year follow-up compared to subjects who continued to use cannabis at the same frequency. Based on data from a 2-year prospective observational study in individuals with a manic or mixed episode (EMBLEM), [Zorrilla et al. \(2015\)](#) reported that patients who stopped using cannabis during a manic/mixed episode had similar functional outcome compared to patients who never used cannabis. In contrast, continuous use was associated with poorer functioning and a higher risk of recurrence ([Zorrilla et al., 2015](#)).

[Agrawal et al. \(2011\)](#) have reported more frequent mixed episodes in patients with cannabis use disorders. [Lev-Ran, Le Foll, McKenzie, George, and Rehm \(2013b\)](#) showed a more severe course of illness and poorer treatment outcomes in BD patients with cannabis abuse.

In 2015, [Kvitland et al. \(2015\)](#) examined the association between recent onset BD type I and course of illness with cannabis use. They reported that continuous cannabis use was significantly associated with elevated mood and diminished global functioning at follow-up. Moreover, inferior global functioning was linked to elevated mood.

CANNABIS USE AND ONSET MANIC EPISODE

There are sufficient data showing that the risk of psychotic disorders increases with the frequency and intensity of cannabis use ([Bally, Zullino, & Aubry, 2014](#)). The question of whether cannabis also increases the risk of developing BD has been less investigated.

Using a retrospective design, [Agrawal et al. \(2011\)](#) reported that around half of bipolar patients identified their mood disorders prior to cannabis use. Some studies have also suggested that people with BD may use cannabis as self-medication for their (hypo) manic and/or depressive mood episodes ([Bizzarri et al., 2009, 2007](#)) and that BD increases the risk of developing any future substance abuse ([Merikangas et al., 2008](#)).

However, there is now accumulating evidence suggesting that the age of onset of first manic or depressive episode is younger when there is co-occurring cannabis abuse ([Duffy et al., 2012](#); [Lagerberg et al., 2011](#)). In a study with 101 subjects with first-treatment BD type I, [Kvitland et al. \(2014\)](#) reported that recent cannabis use was significantly associated with lower age at onset of first manic and psychotic episode.

In contrast, there was no association with first depressive episode.

In an 8-year prospective study with 705 young subjects ages 14–24 years, [Tijssen et al. \(2010\)](#) found that cannabis use was significantly associated with onset of (hypo)manic symptoms. In this study, subjects who reported past cannabis use were clearly more likely to develop manic symptomatology.

These data are in agreement with [De Hert et al. \(2011\)](#) and [Strakowski et al. \(1998, 2007\)](#), suggesting that substance abuse including cannabis can trigger the onset of BD and the occurrence of new manic episodes ([Strakowski, DelBello, Fleck, & Arndt, 2000](#)). They also support the hypothesis that cannabis may increase the risk of manic and psychotic episodes through an interaction with genetic vulnerability and other environmental stressors ([Kvitland et al., 2014](#); [Lev-Ran et al., 2013a](#)). Major factors increasing the risk of bipolar onset episodes or psychosis in subjects using cannabis are shown ([Figure 1](#)).

In view of the published evidence and as stated in a 2014 review on cannabis and first manic episode ([Bally et al., 2014](#)), a causal relationship between cannabis use and onset (hypo) mania is building up. Nevertheless, further investigations are still needed to confirm the association between cannabis use and onset of BD.

CANNABIS USE AND PSYCHOSIS

A large enough body of data has now accumulated to point to a causal relationship between cannabis use and onset of psychosis ([Burns, 2013](#)). For example, the age at onset of positive symptoms in schizophrenia was younger for subjects using cannabis ([Donoghue et al., 2014](#)). [Koskinen, Lohonen, Koponen, Isohanni, and Miettunen \(2010\)](#) reported in a meta-analysis that young male subjects with first psychotic episode used cannabis more often. Moreover, in bipolar patients, cannabis use was shown to be associated with a higher risk of psychotic symptoms ([van Rossum, Boomsma, Tenback, Reed, & van Os, 2009](#)).

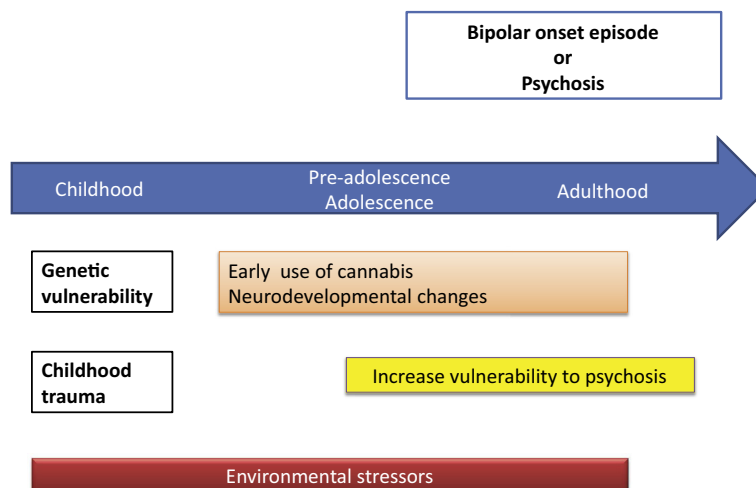


FIGURE 1 Longitudinal overview of cannabis use and bipolar onset episode or psychosis. Major factors increasing the risk of bipolar onset episodes or psychosis in subjects using cannabis are shown.

MECHANISMS UNDERLYING CANNABIS USE AND MANIC SYMPTOMS

Burns (2013) proposed two major pathways from cannabis use to psychosis. One pathway refers to the hypothesis that early use of cannabis during adolescence as well as lifetime use in people genetically vulnerable leads to neurodevelopmental changes. This in turn would end up in disruptions of normal endocannabinoid, γ -aminobutyric acid-ergic, and dopaminergic systems. Individuals would thus become more vulnerable to psychosis.

The second pathway applies to subjects without a lifetime history of cannabis use but who start cannabis use a short time before the onset of psychosis. Burns proposes that although cannabis use is starting only shortly before the episode, these subjects are already genetically and developmentally vulnerable to psychosis.

The neurobiological mechanisms underlying the relationship between cannabis use and mania are still unknown but some common factors with the above hypothesis could partially explain the pathway from cannabis to mania.

Interestingly, in a functional magnetic resonance imaging study comparing adolescents with BD, adolescents with cannabis use, adolescents with co-occurring cannabis use and BD, and healthy adolescents, Bitter et al. (2014) found that adolescents with comorbid BD and cannabis use do not show the same overactivation of the regions involved in emotional processing as seen in adolescents with BD alone. The authors propose that these results suggest that subjects with comorbid BD and cannabis use may have a unique endophenotype of BD. Alternatively, brain activation may be altered specifically in BD subjects who use cannabis (Bitter et al., 2014).

APPLICATIONS TO OTHER ADDICTIONS AND SUBSTANCES MISUSE

In healthy subjects, cannabis can induce a variety of experiences. They are usually temporary and include euphoric and mild psychotic experiences (D'Souza et al., 2004). However, there is now sufficient evidence that heavy cannabis use can participate in the

development of a psychotic disorder (see review in Gibbs et al., 2015). Longitudinal studies suggest a causal link between cannabis use and onset of psychosis (Burns, 2013). For example, the age at onset of positive symptoms in schizophrenia was younger for subjects using cannabis (Donoghue et al., 2014).

Regarding other substances misuse, cocaine and amphetamines are well-known inducers of manic episodes (Table 2).

DEFINITION OF TERMS

Manic episode The main feature of a manic episode is an elevated mood associated with increased energy and physical as well as mental activity. Other features are also part of the clinical picture such as diminished need for sleep, increased libido, and increased risk taking. Delusions and hallucinations can be present in the severe forms of mania.

It must last at least several days to satisfy diagnosis criteria but can last for weeks or even for months before mood and behavior go back to normality. Manic episodes are usually followed by a depressive episode.

Onset mania About half of BDs start with a manic episode. The peak of onset episode is between 15 and 25 years of age.

Euphoric and dysphoric mania Euphoric, or classical, mania refers to a manic episode with elated mood and exaggerated optimism. This is in contrast to dysphoric mania, which manifests itself with inner tension, anxiety, and aggressive verbal and physical behaviors.

KEY FACTS OF MANIA AND BIPOLAR DISORDERS

- BD has a prevalence of around 2–3% worldwide.
- BD type I is characterized by manic and depressive episodes.
- Manic episodes can be triggered mainly by acute or chronic stress, substance abuse, antidepressants, and various somatic treatments.
- A manic episode can last from several days to several months and is usually followed by a depressive episode.
- The number of manic episodes is highly variable from one subject suffering from BD to another.

TABLE 2 Medications and Substances That May Induce Mania**Medication Category****Cardiology**

Angiotensin converting enzyme inhibitors

Psychotropic medications

All antidepressants

Antidepressant discontinuation

Antiepileptic drugs

Anti-infectives

Various antibiotics

Metabolism

Anabolic steroids

Corticosteroids

Thyroid hormones

Varia

Antihistamines

Caffeine

Cyclosporin

Immunomodulators

Sympathomimetics (phenylpropanolamine)

Substance of Abuse

Amphetamine

Alcohol

Cocaine

Heroin

Morphine

Cannabis

Medications and substances of abuse that have been reported to induce manic symptomatology. For a complete description, see Aubry, Ferrero, and Schaad (2013).

SUMMARY POINTS

- Among mood spectrum disorders, BD bears the highest rate of substance abuse.
- Cannabis is the most commonly used illegal drug among patients with BD.
- The age of onset of first manic or depressive episode is younger when there is co-occurring cannabis abuse. There is a poorer medication adherence, a more severe course of illness, and a higher number of manic or depressive episodes with cannabis use.
- Mania phenomenology seems to be influenced by cannabis, found more frequently in dysphoric than in euphoric manic patients.
- Data published as of this writing suggest that there may be a causal relationship of cannabis use to onset mania and also to the occurrence of new manic episodes. However, further investigations are still necessary to confirm this causal link.

REFERENCES

- Aas, M., Etain, B., Bellivier, F., Henry, C., Lagerberg, T., Ringen, A., ... Melle, I. (2014). Additive effects of childhood abuse and cannabis abuse on clinical expressions of bipolar disorders. *Psychological Medicine*, 44(8), 1653–1662. <http://dx.doi.org/10.1017/S0033291713002316>.
- Agrawal, A., Nurnberger, J. I., Jr., & Lynskey, M. T. (2011). Cannabis involvement in individuals with bipolar disorder. *Psychiatry Research*, 185(3), 459–461. <http://dx.doi.org/10.1016/j.psychres.2010.07.007>.
- Aubry, J. M., Ferrero, F., & Schaad, N. (2013). *Psychopharmacologie des troubles bipolaires*. Chêne-Bourg (GE): Médecine et Hygiène.
- Baethge, C., Hennen, J., Khalsa, H. M., Salvatore, P., Tohen, M., & Baldessarini, R. J. (2008). Sequencing of substance use and affective morbidity in 166 first-episode bipolar I disorder patients. *Bipolar Disorders*, 10(6), 738–741. <http://dx.doi.org/10.1111/j.1399-5618.2007.00575.x>.
- Bally, N., Zullino, D., & Aubry, J. M. (2014). Cannabis use and first manic episode. *Journal of Affective Disorders*, 165, 103–108. <http://dx.doi.org/10.1016/j.jad.2014.04.038>.
- Bega, S., Schaffer, A., Goldstein, B., & Levitt, A. (2012). Differentiating between Bipolar Disorder Types I and II: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Journal of Affective Disorders*, 138(1–2), 46–53. <http://dx.doi.org/10.1016/j.jad.2011.12.032>.
- Bitter, S. M., Adler, C. M., Eliassen, J. C., Weber, W. A., Welge, J. A., Burciaga, J., ... DelBello, M. P. (2014). Neurofunctional changes in adolescent cannabis users with and without bipolar disorder. *Addiction*, 109(11), 1901–1909. <http://dx.doi.org/10.1111/add.12668>.
- Bizzarri, J. V., Rucci, P., Sbrana, A., Miniati, M., Raimondi, F., Ravani, L., ... Cassano, G. B. (2009). Substance use in severe mental illness: self-medication and vulnerability factors. *Psychiatry Research*, 165(1–2), 88–95. <http://dx.doi.org/10.1016/j.psychres.2007.10.009>.
- Bizzarri, J. V., Sbrana, A., Rucci, P., Ravani, L., Massei, G. J., Gonnelli, C., ... Cassano, G. B. (2007). The spectrum of substance abuse in bipolar disorder: reasons for use, sensation seeking and substance sensitivity. *Bipolar Disorders*, 9(3), 213–220. <http://dx.doi.org/10.1111/j.1399-5618.2007.00383.x>.
- Burns, J. K. (2013). Pathways from cannabis to psychosis: a review of the evidence. *Frontiers in Psychiatry*, 4, 128. <http://dx.doi.org/10.3389/fpsy.2013.00128>.
- Cerullo, M. A., & Strakowski, S. M. (2007). The prevalence and significance of substance use disorders in bipolar type I and II disorder. *Substance Abuse Treatment, Prevention, and Policy*, 2, 29. <http://dx.doi.org/10.1186/1747-597X-2-29>.
- Dalton, E. J., Cate-Carter, T. D., Mundo, E., Parikh, S. V., & Kennedy, J. L. (2003). Suicide risk in bipolar patients: the role of co-morbid substance use disorders. *Bipolar Disorders*, 5(1), 58–61. <http://dx.doi.org/10.1034/j.1399-5618.2003.00017.x>.
- De Hert, M., Wampers, M., Jendricko, T., Franck, T., Vidovic, D., De Vriendt, N., ... van Winkel, R. (2011). Effects of cannabis use on age at onset in schizophrenia and bipolar disorder. *Schizophrenia Research*, 126(1–3), 270–276. <http://dx.doi.org/10.1016/j.schres.2010.07.003>.
- Dilsaver, S. C., Chen, Y. R., Shoaib, A. M., & Swann, A. C. (1999). Phenomenology of mania: evidence for distinct depressed, dysphoric, and euphoric presentations. *The American Journal of Psychiatry*, 156(3), 426–430.

- Donoghue, K., Doody, G. A., Murray, R. M., Jones, P. B., Morgan, C., Dazzan, P., ... Maccabe, J. H. (2014). Cannabis use, gender and age of onset of schizophrenia: data from the AESOP study. *Psychiatry Research*, 215(3), 528–532. <http://dx.doi.org/10.1016/j.psychres.2013.12.038>.
- D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y. T., ... Krystal, J. H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology*, 29(8), 1558–1572. <http://dx.doi.org/10.1038/sj.npp.1300496>.
- Duffy, A., Horrocks, J., Milin, R., Doucette, S., Persson, G., & Grof, P. (2012). Adolescent substance use disorder during the early stages of bipolar disorder: a prospective high-risk study. *Journal of Affective Disorders*, 142(1–3), 57–64. <http://dx.doi.org/10.1016/j.jad.2012.04.010>.
- Etain, B., Mathieu, F., Lique, S., Raust, A., Cochet, B., Richard, J. R., ... Bellivier, F. (2013). Clinical features associated with trait-impulsiveness in euthymic bipolar disorder patients. *Journal of Affective Disorders*, 144(3), 240–247. <http://dx.doi.org/10.1016/j.jad.2012.07.005>.
- Feingold, D., Weiser, M., Rehm, J., & Lev-Ran, S. (2015). The association between cannabis use and mood disorders: a longitudinal study. *Journal of Affective Disorders*, 172, 211–218. <http://dx.doi.org/10.1016/j.jad.2014.10.006>.
- Feinman, J. A., & Dunner, D. L. (1996). The effect of alcohol and substance abuse on the course of bipolar affective disorder. *Journal of Affective Disorders*, 37(1), 43–49. [http://dx.doi.org/10.1016/0165-0327\(95\)00080-1](http://dx.doi.org/10.1016/0165-0327(95)00080-1).
- Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2008). Exposure to childhood sexual and physical abuse and adjustment in early adulthood. *Child Abuse and Neglect*, 32(6), 607–619. <http://dx.doi.org/10.1016/j.chiabu.2006.12.018>.
- Gibbs, M., Winsper, C., Marwaha, S., Gilbert, E., Broome, M., & Singh, S. P. (2015). Cannabis use and mania symptoms: a systematic review and meta-analysis. *Journal of Affective Disorders*, 171, 39–47. <http://dx.doi.org/10.1016/j.jad.2014.09.016>.
- Güclü, O., Senormanci, O., Aydin, E., Erkiran, M., & Kokturk, F. (2015). Phenomenological subtypes of mania and their relationships with substance use disorders. *Journal of Affective Disorders*, 174, 569–573. <http://dx.doi.org/10.1016/j.jad.2014.11.016>.
- Koskinen, J., Lohonen, J., Koponen, H., Isohanni, M., & Miettinen, J. (2010). Rate of cannabis use disorders in clinical samples of patients with schizophrenia: a meta-analysis. *Schizophrenia Bulletin*, 36(6), 1115–1130. <http://dx.doi.org/10.1093/schbul/sbp031>.
- Kvitland, L. R., Melle, I., Aminoff, S. R., Demmo, C., Lagerberg, T. V., Andreassen, O. A., & Ringen, P. A. (2015). Continued cannabis use at one year follow up is associated with elevated mood and lower global functioning in bipolar I disorder. *BMC Psychiatry*, 15, 11. <http://dx.doi.org/10.1186/s12888-015-0389-x>.
- Kvitland, L. R., Melle, I., Aminoff, S. R., Lagerberg, T. V., Andreassen, O. A., & Ringen, P. A. (2014). Cannabis use in first-treatment bipolar I disorder: relations to clinical characteristics. *Early Intervention in Psychiatry*. <http://dx.doi.org/10.1111/eip.12138>.
- Lagerberg, T. V., Sundet, K., Aminoff, S. R., Berg, A. O., Ringen, P. A., Andreassen, O. A., & Melle, I. (2011). Excessive cannabis use is associated with earlier age at onset in bipolar disorder. *European Archives of Psychiatry and Clinical Neuroscience*, 261(6), 397–405. <http://dx.doi.org/10.1007/s00406-011-0188-4>.
- Lev-Ran, S., Le Foll, B., McKenzie, K., George, T. P., & Rehm, J. (2013a). Bipolar disorder and co-occurring cannabis use disorders: characteristics, co-morbidities and clinical correlates. *Psychiatry Research*, 209(3), 459–465. <http://dx.doi.org/10.1016/j.psychres.2012.12.014>.
- Lev-Ran, S., Le Foll, B., McKenzie, K., George, T. P., & Rehm, J. (2013b). Cannabis use and cannabis use disorders among individuals with mental illness. *Comprehensive Psychiatry*, 54(6), 589–598. <http://dx.doi.org/10.1016/j.comppsy.2012.12.021>.
- Leweke, F. M., & Koethe, D. (2008). Cannabis and psychiatric disorders: it is not only addiction. *Addiction Biology*, 13(2), 264–275. <http://dx.doi.org/10.1111/j.1369-1600.2008.00106.x>.
- Merikangas, K. R., Herrell, R., Swendsen, J., Rossler, W., Ajdacic-Gross, V., & Angst, J. (2008). Specificity of bipolar spectrum conditions in the comorbidity of mood and substance use disorders: results from the Zurich cohort study. *Archives of General Psychiatry*, 65(1), 47–52. <http://dx.doi.org/10.1001/archgenpsychiatry.2007.18>.
- Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L., & Goodwin, F. K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA*, 264(19), 2511–2518.
- Shin, S. H., Edwards, E., Heeren, T., & Amodeo, M. (2009). Relationship between multiple forms of maltreatment by a parent or guardian and adolescent alcohol use. *The American Journal on Addictions*, 18(3), 226–234. <http://dx.doi.org/10.1080/10550490902786959>.
- Stone, J. M., Fisher, H. L., Major, B., Chisholm, B., Woolley, J., Lawrence, J., ... MiData Consortium (2014). Cannabis use and first-episode psychosis: relationship with manic and psychotic symptoms, and with age at presentation. *Psychological Medicine*, 44(3), 499–506. <http://dx.doi.org/10.1017/S0033291713000883>.
- Strakowski, S. M., DelBello, M. P., Fleck, D. E., Adler, C. M., Anthenelli, R. M., Keck, P. E., Jr., ... Amicone, J. (2007). Effects of co-occurring cannabis use disorders on the course of bipolar disorder after a first hospitalization for mania. *Archives of General Psychiatry*, 64(1), 57–64. <http://dx.doi.org/10.1001/archpsyc.64.1.57>.
- Strakowski, S. M., DelBello, M. P., Fleck, D. E., & Arndt, S. (2000). The impact of substance abuse on the course of bipolar disorder. *Biological Psychiatry*, 48(6), 477–485. [http://dx.doi.org/10.1016/S0006-3223\(00\)00900-8](http://dx.doi.org/10.1016/S0006-3223(00)00900-8).
- Strakowski, S. M., Sax, K. W., McElroy, S. L., Keck, P. E., Jr., Hawkins, J. M., & West, S. A. (1998). Course of psychiatric and substance abuse syndromes co-occurring with bipolar disorder after a first psychiatric hospitalization. *The Journal of Clinical Psychiatry*, 59(9), 465–471.
- Swann, A. C., Suppes, T., Ostacher, M. J., Eudicone, J. M., McQuade, R., Forbes, A., & Carlson, B. X. (2013). Multivariate analysis of bipolar mania: retrospectively assessed structure of bipolar I manic and mixed episodes in randomized clinical trial participants. *Journal of Affective Disorders*, 144(1–2), 59–64. <http://dx.doi.org/10.1016/j.jad.2012.05.061>.
- Tijssen, M. J., Van Os, J., Wittchen, H. U., Lieb, R., Beesdo, K., & Wichers, M. (2010). Risk factors predicting onset and persistence of sub-threshold expression of bipolar psychopathology among youth from the community. *Acta Psychiatrica Scandinavica*, 122(3), 255–266. <http://dx.doi.org/10.1111/j.1600-0447.2010.01539.x>.
- van Rossum, I., Boomsma, M., Tenback, D., Reed, C., & van Os, J. (2009). Does cannabis use affect treatment outcome in bipolar disorder? A longitudinal analysis. *The Journal of Nervous and Mental Disease*, 197(1), 35–40. <http://dx.doi.org/10.1097/NMD.0b013e31819292a6>.
- Zorrilla, I., Aguado, J., Haro, J. M., Barbeito, S., Lopez Zurbano, S., Ortiz, A., ... Gonzalez-Pinto, A. (2015). Cannabis and bipolar disorder: does quitting cannabis use during manic/mixed episode improve clinical/functional outcomes? *Acta Psychiatrica Scandinavica*, 131(2), 100–110. <http://dx.doi.org/10.1111/acps.12366>.