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Evidence-Based Report

Childhood Sexual Abuse and Bipolar Disorder

Reviewer	Associate Professor Ian Lambie
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Date Draft Report Completed	27 October 2015
Date Final Report Completed	20 June 2016

Important Note:

- The purpose of this brief report is to summarise the evidence for the association between childhood sexual abuse and the development of bipolar disorder.
- It is not intended to replace clinical judgement, or be used as a clinical protocol.
- A reasonable attempt has been made to find and review papers relevant to the focus of this report; however, it does not claim to be exhaustive.
- This report is based upon information supplied up to October 2015.

1. Executive Summary

- Childhood sexual abuse can have significant short- and long-term effects, including the subsequent development of bipolar disorder.
- The purpose of this report is to provide an evidence-based guide on the association between childhood sexual abuse and bipolar disorder as a teenager/adult. These findings will be used to assist in the decision making process regarding cover and entitlements of those who have experienced childhood sexual abuse and later developed bipolar disorder.
- A literature search was conducted in October 2015 using Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Cochrane Database of Systematic Reviews, PsycINFO, and the Worldwide Web. Further literature was also located through reading the reference list of review articles.
- Findings from the three systematic reviews identified in this report showed that:
    - A history of childhood sexual abuse is more likely to be present in those with bipolar disorder than in non-psychiatric controls. However, rates of child sexual abuse among those with bipolar disorder are similar or lower compared to those with other mental disorders.
    - There is fair quality evidence that childhood sexual abuse is likely an indirect and direct risk factor for a more severe presentation of bipolar disorder, including early onset of bipolar disorder (OR = 2.91) and suicidal attempts among adults (OR = 3.33), as well as longer duration of bipolar disorder among youth (OR = 1.2).
    - Limitations of the current research examining the association between childhood sexual abuse and bipolar disorder include abuse being reported retrospectively, differing study methods and definitions of abuse, and the presence of a number of confounding variables. Furthermore, there is a significant lack of literature examining the relationship between childhood sexual abuse and bipolar disorder. Due to these limitations, any findings should be interpreted with caution.
- There is a lack of research investigating the mechanisms underlying the relationship between childhood sexual abuse and the subsequent development of bipolar disorder. Further research in this area is required.
- Given the identified limitations of the current literature, the lack of research in this area, and that there are likely to be many causes and risk factors for bipolar disorder, it is difficult to draw conclusions as to whether childhood sexual abuse is a direct and sufficient cause of bipolar disorder. Based on the current literature, we can only

conclude that childhood sexual abuse is more frequent among people with bipolar disorder than the general population, and that childhood sexual abuse is associated with an exacerbated course and form of bipolar disorder. However, experience of childhood sexual abuse is similar or less frequent among those with bipolar disorder compared to those with other mental disorders.

2. Introduction

The estimated lifetime prevalence of bipolar disorder in the general population is approximately 4% (Kessler et al., 2005), with the highest prevalence found among the 18 to 29 year age group. Bipolar disorder can be a severe and chronic illness, affecting an individual's quality of life and in some cases resulting in considerable suffering, morbidity, and difficulties with occupational and social functioning (Maniglio, 2013b).

The estimated prevalence of childhood sexual abuse for females is between 8 to 31%, and between 3 to 17% for males; the wide estimate ranges reflecting the heterogeneity of studies (Barth, Bermetz, Heim, Trelle, & Tonia, 2013). Despite the methodological challenges inherent in conducting international systematic reviews and meta-analyses, most studies have consistently shown that worldwide more than 1 out of 5 women, and 1 out of 10 men experience childhood sexual abuse (Pereda, Guilera, Forns, & Gómez-Benito, 2009). However, underreporting of childhood sexual abuse is a well-documented phenomena and likely impacts the prevalence rates (Leclerc & Wortley, 2015).

For victims of childhood sexual abuse, the effects can be devastating both in the short- and long-term. Frequently reported short-term effects include fear, anxiety, depression, aggression, anger and hostility, and sexually inappropriate behaviour. Long-term effects include ongoing depression and anxiety, poor self-esteem, difficulty in trusting others, self-harm and suicide, a tendency toward revictimisation, feelings of isolation and stigma, substance abuse, and a host other mental health problems (Browne & Finkelhor, 1986; Fergusson, McLeod, & Horwood, 2013; Paolucci, Genuis, & Violato, 2001). One such group of mental health disorders which has been linked to childhood sexual abuse is bipolar disorder, which is the focus of this report.

3. Background

ACC Research subcontracted Associate Professor Ian Lambie to conduct an evidence-based review to investigate the association between childhood sexual abuse and the subsequent development of bipolar disorder as a teenager/adult.

This evidence-based report will be used to provide ACC clinical advisors, claims management staff and service providers with an evidence-based guide on the relationship between childhood sexual abuse and the development of bipolar disorder. In addition, this report will be used to assist in the development of an approach to deciding cover and entitlements for people who experienced childhood sexual abuse and develop bipolar disorder at an older age.

4. Investigation

A search was conducted in October 2015 in the following databases: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Cochrane Database of Systematic Reviews, and PsycINFO. Further literature was also located through searching the Worldwide Web and reading the reference list of review articles. Only articles in English and published between 2000 and 2015 were included.

Search terms used included: Bipolar, bipolar disorder, bipolar affective disorder, manic depressive illness, childhood sexual abuse, child sexual abuse, sexual abuse.

Inclusion criteria: Systematic reviews and meta-analyses looking at the relationship between childhood sexual abuse and bipolar disorder.

Exclusion criteria: Non-English studies, animal or laboratory studies, narrative reviews, letters or editorials; study designs other than systematic review or meta-analysis.

This resulted in identifying 27 articles, of which three systematic reviews were used in this report.

Evidence tables were created for each systematic review, and they can be found in Appendix 1. A table of the excluded studies can be found in Appendix 2.

Any relevant papers were assessed for their methodological quality using the following SIGN* criteria:

Levels of evidence (LOE)	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

* Scottish Intercollegiate Guidelines Network http://www.sign.ac.uk/

5. Findings

Systematic Reviews

Three systematic reviews are included in this report: Maniglio (2013a)[1], Maniglio (2013b)[2], and Mauritz (2013)[3]. Maniglio reports that prior to these publications, no systematic reviews have focused exclusively on the relationship between childhood sexual abuse and bipolar disorder, and therefore "very little" is known about this relationship (2013a, p. 561)[1]. This statement fits with the literature search conducted for this report, which found no meta-analyses and only the abovementioned three systematic reviews published in this area[Ψ].

The first systematic review by Maniglio (2013a)[1] investigated prevalence rates of childhood sexual abuse among adults and youths with bipolar disorder. The authors included 20 studies with a total of 3407 adults and youths with a diagnosis of bipolar disorder.

The overall prevalence of childhood sexual abuse among individuals with bipolar disorder was 24%, with adults with bipolar disorder reporting higher rates of childhood sexual abuse than youth (26% versus 13%, respectively). However, the author stated that such prevalence rates might be underestimated, because many studies restricted definitions of childhood sexual abuse to the most severe forms of abuse.

Compared to healthy individuals, patients with bipolar disorder reported higher rates of child sexual abuse (19% versus 31%, respectively). In the only study that employed a comparison group matched for age, gender, ethnicity, and family constellation (Rucklidge, 2006), youths with bipolar disorder reported significantly higher rates of child sexual abuse compared to community adolescents without bipolar disorder (29% versus 0%, respectively). By contrast, Maniglio (2013a) found that compared to populations with other mental disorders, participants with bipolar disorder reported similar or lower rates of such abuse.

Overall, the author concluded that individuals with bipolar disorder are at risk of having a history of child sexual abuse, although such risk seems to be neither more specific to nor stronger for these individuals compared to people with other psychiatric disorders.

This systematic review was of fair methodological quality (1-). Due to the methodological limitations present in the studies reviewed, no statistical analyses or meta-analysis were able to be conducted. Additional limitations of this systematic review include abuse among subjects being reported retrospectively in all studies; small samples that risked sampling

[Ψ] Another identified systematic review by Carr et al. (2013) examined studies investigating early life stress (e.g., sexual abuse) and their association with psychiatric disorders in adulthood, including bipolar disorder. However, identification and discussion of studies specifically investigating bipolar disorder was very limited. Therefore, this study was not reported on in this evidence-based report. An overview of the systematic review by Carr et al. (2013) can be found in the evidence-based report for Depressive Disorders.

bias; temporality; differing study methods, measures, and definitions; and failing to control for the overlap with comorbid disorders and/or other traumatic events. The author stated that due to these limitations, conclusions regarding causality are unable to be made; therefore, extreme caution is required when interpreting these findings. However, it can be hypothesised that experience of childhood sexual abuse may be more prevalent among people with bipolar disorder than the general population.

The second systematic review by Maniglio (2013b)[2] was of fair methodological quality (1-) and looked at the influence of childhood sexual abuse on the course of bipolar disorder in adults and youths. The authors included 18 studies with a total of 2996 adults and youths with a diagnosis of bipolar disorder.

Childhood sexual abuse was found to be directly or indirectly associated with clinical features that represent a more severe form of bipolar disorder. At a univariate level, a history of sexual abuse in youths with bipolar disorder was significantly associated with lifetime alcohol and/or drug abuse or dependence. Among adults with bipolar disorder who had experienced childhood sexual abuse, childhood sexual abuse was significantly related to a variety of clinical variables, such as younger age at onset of bipolar disorder, severity of manic and depressive episodes, rapid cycling, suicide attempts, lifetime psychotic symptoms, lifetime alcohol and／or drug abuse, lifetime posttraumatic stress disorder, lifetime panic disorder, comorbid personality disorders, a family history of bipolar disorder, alcohol and／or drug abuse, and other psychiatric illnesses.

At a multivariate level, a history of sexual abuse in youths was independently associated with a longer duration of bipolar disorder (OR[†]= 1.2), lifetime posttraumatic stress disorder (OR = 5.1), and lifetime conduct disorder (OR = 3.8). A history of childhood sexual abuse in adults independently predicted early onset of bipolar disorder (OR = 2.91), suicide attempts (OR = 3.33), lifetime posttraumatic stress disorder (OR = 4.932), a family history of other psychiatric illnesses (OR = 1.94), lifetime alcohol abuse or dependence (OR = 3.04), and fewer side effects from psychiatric medications (OR = 0.80).

Overall, the results of this systematic review indicate that a childhood sexual abuse is associated with clinical phenomenon that represent a more severe form of bipolar disorder.

Limitations of this systematic review include abuse among subjects being reported retrospectively in all studies; small samples that risked sampling bias; temporality; differing study methods, measures, and definitions; and failing to control for confounding concurrent third variables that may mediate the relationship between childhood sexual abuse and increased severity of bipolar disorder. Similar to the systematic review above (Maniglio,

[†] odds ratio

2013a)[1], the author stated that due to these methodological limitations, findings should be interpreted with extreme caution. It can only be speculated from these findings that childhood sexual abuse exacerbates the course and form of bipolar disorder.

The third systematic review by Mauritz et al., 2013[3] was of fair methodological quality (1-) and investigated the prevalence of interpersonal trauma exposure and trauma-related disorders in severe mental illness. The authors included 33 studies, defining severe mental illness as schizophrenia spectrum disorders, bipolar disorder, major depression/depressive disorders, anxiety disorders, eating disorders, and personality disorders. Six of these studies specifically assessed the relationship between bipolar disorder and sexual abuse; however only one study separated the prevalence of sexual abuse into rates for childhood and adulthood abuse (Goldberg et al., 2005).

No prevalence rates were clearly reported in the text or tables of the review; instead rates were presented on a graph with an imprecise x axis (see Appendix A). From this graph, the prevalence of childhood sexual abuse in those with bipolar disorder in the Goldberg et al. study was estimated to be around 30 percent. Overall, lower rates of trauma (physical abuse, sexual abuse) were found for bipolar and major depressive disorder, and higher rates found for schizophrenia, borderline personality disorder and groups labelled as severely mentally ill.

Two studies separated the lifetime prevalence rate of sexual abuse into male and female rates. The graph displaying these rates (Appendix A) indicates that women with bipolar disorder have approximately 2.5 to 3.5 times higher prevalence of lifetime sexual abuse than men.

Limitations of this systematic review include differing study methods, measures, and definitions; a very restrictive literature search that may have led to the loss of important information; and the design of many studies that combined rates of childhood and adult sexual abuse, in addition to being retrospective.

Although this systematic review demonstrates an association between sexual abuse and severe mental illness, a causal relationship between childhood sexual abuse and the development of bipolar disorder cannot be established through its findings.

6. Additional Information

Other Risk Factors of Bipolar Disorder

Although not the focus of this report, other risk factors for the development of bipolar disorder will help provide context to the evidence about childhood sexual abuse. One source was used (with no formal methodological appraisal): *DynaMed*™***.

DynaMed™

Likely risk factors:

- First-degree relatives of patients with bipolar disorder have increased risk
  - parental bipolar disorder associated with increased risk of bipolar disorder in offspring
    - based on cohort study of 388 children of 233 parents with bipolar disorder
- Genetic risk factors
  - increased risk of bipolar disorder in relatives of persons with schizophrenia; increased risk of bipolar disorder in relatives of persons with bipolar disorder
    - based on cohort study of 76,472 persons discharged from psychiatric hospital in Sweden with diagnosis of schizophrenia, bipolar disorder, or both
    - estimated heritability 59% for bipolar disorder
- Specific single-nucleotide polymorphisms associated with increased risk of neuropsychiatric disorders
  - based on case-control study of 33,332 patients with autism spectrum disorders, attention deficit hyperactivity disorder, bipolar disorder, major depressive disorder, or schizophrenia
- Diagnosis of depression
    - based on prospective cohort study of 74 patients hospitalized for unipolar major depression (mean age 23 years), followed for 15 years
- Decreased gray matter volume in left rostral anterior cingulate cortex and right fronto-insular cortex associated with bipolar disorder
  - based on systematic review of 21 studies

*** a clinical reference resource tool created by physicians for physicians and other health care professionals with conclusions based on the best available clinical evidence which has been consistently and systematically identified, evaluated and selected

Possible risk factors:

- *MTHFR* gene C677T variant may be associated with bipolar disorder
  - based on systematic review of observational studies
- Advanced paternal age associated with increased incidence of bipolar disorder
  - based on case-control study of 13,428 patients with bipolar disorder diagnosed on ≥ 2 hospital admissions
- Environmental risk factors
  - life events and chronic stress may precipitate and/or perpetuate mood episodes
  - familial death during childhood associated with small increase in risk of nonaffective or affective psychosis
    - based on retrospective cohort study of 1,045,336 individuals in Sweden

Mediators of the Association between Childhood Sexual Abuse and Bipolar Disorder

Understanding of possible mediators can help provide further understanding into the association between childhood sexual abuse and bipolar disorder. Here, one source was used (with no formal methodological appraisal): a review by Alloy et al., (2006). This is followed by a brief discussion of the current literature exploring mechanisms underlying the relationship between childhood sexual abuse and bipolar disorder.

Alloy et al., (2006)

This review looked at the role of parenting and maltreatment histories in unipolar and bipolar mood disorders, and whether this is mediated by cognitive vulnerability to depression. The evidence suggests that the development of cognitive vulnerabilities such as rumination, hopelessness, dysfunctional attitudes, and negative attributional style, may provide one mechanism through which childhood sexual abuse and maltreatment contribute to the development of mood disorders. Although the studies referenced in the review have methodological limitations, such as retrospective design and lack of a control group, the review has possible implications for treatment for those with bipolar disorder in terms of targeting these negative cognitive styles.

Theories

In their reviews of bipolar disorder, Maniglio (2013a,b) outlined a number of theories that have been proposed to help explain the mechanisms underlying the relationship between childhood sexual abuse and bipolar disorder. However, upon further inspection of the

research cited by Maniglio (2013a,b) in support of these theories, it appears that these studies have not examined bipolar disorder specifically, and have instead investigated mental health disorders in general (e.g., Maniglio, 2009), schizophrenia (e.g., Brekke, Prindle, Bae & Long, 2001), or mood and anxiety disorders (e.g., Heim & Nemeroff, 2001). It is therefore apparent that there is a considerable need for research to explore the mediators of the relationship between childhood sexual abuse and bipolar disorder specifically.

7. Conclusions

The three systematic reviews included in this report found:

- Fair quality evidence (i.e., the review was of fair methodological quality (1+/1-)) from two systematic reviews that people with bipolar disorder are more likely to have experienced childhood sexual abuse than those in the general population. However, rates of child sexual abuse among those with bipolar disorder are similar or lower compared to those with other mental disorders[1,3].
- Fair quality evidence from one systematic review that childhood sexual abuse is both indirectly and directly associated with clinical features that represent a more severe presentation of bipolar disorder, including early onset of bipolar disorder (OR = 2.91) and suicidal attempts among adults (OR = 3.33), as well as a longer duration of bipolar disorder among youth (OR = 1.2)[2].

Using Bradford Hill's guide to causation (Appendix 3), the strength of association between childhood sexual abuse and having a more severe presentation of bipolar disorder is in the order of 1 to 5 increased odds for each clinical feature, and this appears relatively consistent[2]. Temporality (i.e. that the abuse occurs before the development of bipolar disorder) is not able to be established due to retrospective study designs. The biological gradient or dose-response (i.e. more exposure results in greater risk of developing bipolar disorder) has not been directly investigated in this report.

In relation to plausibility, there may be evidence for cognitive vulnerabilities acting as a mediator of the link between childhood sexual abuse and the development of bipolar disorder. However, overall there is a lack of research examining the mechanisms underlying the relationship between childhood sexual abuse and the subsequent development of bipolar disorder. Further research in this area is required.

Limitations of the current research examining the association between childhood sexual abuse and bipolar disorder include abuse being reported retrospectively, differing study methods and definitions of abuse, and the presence of a number of confounding variables. Furthermore, there is a significant lack of literature examining the relationship between childhood sexual abuse and bipolar disorder. Due to these limitations, any findings should be interpreted with caution.

Given the identified limitations of the current literature, the lack of research in this area, and that there are likely to be many causes and risk factors for bipolar disorder, it is difficult to draw conclusions as to whether childhood sexual abuse is a direct and sufficient cause of bipolar disorder. Based on the current literature, we can only conclude that childhood sexual

abuse is more frequent among people with bipolar disorder than the general population, and that childhood sexual abuse is associated with an exacerbated course and form of bipolar disorder. However, experience of childhood sexual abuse is similar or less frequent among those with bipolar disorder compared to those with other mental disorders.

8. Limitations of this report

As only English language articles were included, the presence of publication bias in this report is a possibility. In addition, only focusing on systematic reviews and meta-analyses may have missed more recent research.

9. Appendix 1: Evidence Tables

Reference and study design	Studies	Exposure	Outcome measure	Results/effect size	Conclusions
Maniglio (2013) "Prevalence of child sexual abuse among adults and youth with bipolar disorder: A systematic review". Clinical Psychology Review, **33(4)**, 561-573. Italy. Included studies: Alvarez et al. 2011; Bauer et al. 1997; Brown et al. 2005 ; Darves-Bornoz et al. 1995; Dienes et al. 2006; Etain et al., 2010; Gao et al. 2009; Garno et al. 2005; Gellar et al., 2000; Hammersley et al. 2003; Hlastala et al., 2005; Hyun et al., 2000; Leverich et al. 2003; Levitan, 1998; Maguire, 2008; Marchand, 2005; McIntyre et al. 2008; Romero et al. 2009, Rucklidge, 2006; Sullivan, 1995. (Only studies with	Number of studies: N=20 Total number of patients in the studies: n= 3407 Inclusion criteria: Studies needed to have been published in journals, sampled human subjects, had primary and sufficient data derived from longitudinal, cross-sectional, case-control, or cohort studies; and reported explicitly rates of prevalence for childhood sexual abuse for individuals with bipolar disorder. Exclusion criteria: Literature reviews, dissertation papers,	Childhood sexual abuse	Prevalence rates of CSA in BD participants and controls (%), P value (p) for significant correlates of childhood sexual abuse in those with bipolar disorder	Adults with bipolar disorder Brown et al., 2005, n = 330 BD participants with CSA: 95 (29%) Correlates of CSA: CSA without CPA: gender (p = 0.001). Etain et al. 2010, n = 206 BD participants with CSA: 64 (31%) Controls with CSA: 34 (18%) Correlates of CSA: gender (p < .01), CEN (p < 0.01), CEA (p < 0.001), CPN (p < 0.01), CPA (p < 0.001). Garno et al. 2005, n = 100 BD participants with CSA: 21 (21%) Correlates of CSA: CEN, CEA, CPN, CPA (p value not provided). Hyun et al. 2000, n = 142 BD participants with CSA: 41 (29%) Controls with CSA: 34 (18%) Correlates of CSA: diagnosis (p < 0.02), diagnosis x gender (p < 0.005). McIntyre et al. 2008, n = 381 BD participants with CSA: 36 (9%)	Author's conclusions: The prevalence of CSA in those with BD was 24%. Those with BD report higher rates of CSA than in the general population/control groups. Causality between CSA and BD cannot be determined due to methodological limitations of the individual studies. Results should be interpreted with extreme caution given methodological limitations. Reviewer's conclusions: This systematic review presents evidence suggesting that those with bipolar disorder are at risk of having a history of CSA.

significant findings reported in results column).	conference proceedings, editorials, case reports, case series, commentaries. <u>Databases used:</u> EBSCO, ERIC, MEDLINE (PubMed and PubMed Central), PsycINFO, ScienceDirect + reference list search. <u>Description of the methodological assessment of studies:</u> Study reporting assessed by Newcastle-Ottawa Scale, blind assessments of study eligibility and quality. <u>Fixed or variable effects:</u> Not applicable. <u>Heterogeneity:</u> Not discussed.			Correlates of CSA: CPA ($p < 0.01$) Sullivan, 1995, n = 14 BD participants with CSA: 11 (79%) Controls with CSA: 27 (37%) Correlates of CSA: BD diagnosis ($p = 0.04$). <u>Youths with bipolar disorder</u> Romero et al. 2009, n = 446 BD participants with CSA: 52 (12%) Correlates of CSA: CSA with CPA: age ($p < 0.05$), living situation ($p < 0.05$). Rucklidge, 2006, n = 24 BD participants with CSA: 7 (29%) Controls with CSA: 0 (0%) Correlates of CSA: Diagnosis ($p < 0.001$). <u>Total average prevalence of CSA in participants with BD with high/low outliers included:</u> 24% (with outliers removed: 23%) <u>Average prevalence of CSA in participants with BD vs control in the 9 studies using a control group</u>: Total: 32%, 51%; adult BD vs control: 39%, 62%; youth BD vs control: 8%, 10%.	

BD = bipolar disorder; CEA = child emotional abuse; CEN = child emotional neglect; CPA = child physical abuse; CPN = child physical neglect; CSA = child sexual abuse.
Study type: Systematic review **Quality: 1-** **Comments:** Adequately conducted systematic review with appropriately no meta-analysis. Systematic search of multiple databases. Methodological assessment adequate. Methodological limitations of individual studies mean causal inferences are not feasible.

Reference and study design	Studies	Exposure	Outcome measure	Results/effect size	Conclusions
Maniglio (2013) "The impact of child sexual abuse on the course of bipolar disorder: A systematic review". Bipolar Disorders, **15(4)**, 341-358. Italy. Included studies: Alvarez et al. 2011; Bauer et al. 1997; Brown et al. 2005 ; De Pradier et al. 2010 ; Dienes et al. 2006; Gao et al. 2009; Garno et al. 2005; Garno et al. 2005; Goldberg and Garno, 2005; Hammersley et al. 2003; Leverich et al. 2002; Leverich et al. 2003; McIntyre et al. 2008; Mowlds et al. 2010; Savitz et al. 2009; Goldstein et al. 2008; Marchand et al. 2005; and Romero et al. 2009. (Only studies with significant findings reported in results column).	Number of studies: N=18 Total number of patients in the studies: n= 2996 Inclusion criteria: Studies needed to have been published in journals, sampled human subjects, had primary and sufficient data derived from longitudinal, cross-sectional, case-control, or cohort studies; and investigated the relationship between one or more clinical phenomena occurring after the onset of bipolar disorders and a history of child sexual abuse specifically. Exclusion criteria: Literature reviews,	Childhood sexual abuse	Odds ratio (OR), p value (p) for significant correlates of childhood sexual abuse in those with bipolar disorder	Adults with bipolar disorder Alvarez et al., 2011, n = 40 Univariate correlate: SA (p = 0.03). Brown et al., 2005, n = 330 Multivariate correlates: CSA without CPA: current AAD (OR = 3.04, p = 0.014), fewer side effects from medications (OR = 0.80, p = 0.04). CSA with CPA: current PTSD (OR = 4.34, p < 0.001), past AAD (OR = 2.24, p = 0.023). Dienes et al., 2006, n = 57 Univariate correlate: Younger age of onset (p = 0.002). Garno et al., 2005, n = 100 Multivariate correlate: SA (OR = 3.327, p = 0.045). Goldberg & Garno, 2005, n = 100 Multivariate correlates: Past or current PTSD after controlling for age, gender, race, D severity, childhood PA/EA/PN/EN (OR = 4.932, p = 0.023). Past or current PTSD after controlling for gender, adult SA, death of close person (OR = 5.294, p = 0.005). Hammersley et al. 2003, n = 96	Author's conclusions: Childhood sexual abuse is associated either directly or indirectly with some clinical phenomena that represent a more severe form of bipolar disorder. Across studies, in those with bipolar disorder, childhood sexual abuse was strongly and perhaps directly associated with PTSD. Childhood sexual abuse was less strongly and perhaps indirectly associated with suicide attempts, alcohol/drug abuse/dependence, psychotic symptoms and early age of onset. Results should be interpreted with extreme caution given methodological limitations. Reviewer's conclusions: This systematic review presents evidence

	dissertation papers, conference proceedings, editorials, case reports, case series, commentaries. <u>Databases used:</u> EBSCO, ERIC, MEDLINE (PubMed and PubMed Central), PsycINFO, ScienceDirect + reference list search. <u>Description of the methodological assessment of studies:</u> Study reporting assessed by Newcastle-Ottawa Scale, blind assessments of study eligibility and quality. <u>Fixed or variable effects:</u> Not applicable. <u>Heterogeneity:</u> Not discussed.			Univariate correlates: Past or current H ($p < 0.005$), past or current VC ($p < 0.002$). Leverich et al. 2002, n = 631 Univariate correlates: Younger age of onset (OR = 2.91, $p = 0.0001$), SA (OR = 2.04, $p = 0.0092$), other FH (OR = 1.94, $p = 0.024$). Multivariate correlates: Past or current DA ($p = 0.000$) and AA ($p = 0.15$), PTSD: past ($p = 0.000$), current ($p = 0.005$), past or current Axis I disorders ($p = 0.000$), cluster A PD ($p < 0.001$), cluster B PD ($p < 0.001$), cluster C PD ($p = 0.003$), total PD ($p < 0.001$), personality ($p < 0.001$), M severity ($p = 0.002$), D severity ($p = 0.024$), past RC ($p = 0.034$), past ultra RC ($p = 0.043$), younger age of onset ($p < 0.001$), SA($p < 0.001$), SI when M ($p = 0.034$), SI when D ($p = 0.008$), BD FH ($p = 0.034$), AA FH ($p < 0.001$), DA FH ($p = 0.003$), other FH ($p < 0.001$), current medical conditions ($p <0.001$), longer M duration ($p < 0.001$), longer D duration($p < 0.005$). Leverich et al, 2003, n = 648. Univariate correlate: SA ($p < 0.000$) Multivariate correlate: SA (OR = 2.27, $p < 0.05$).	suggesting that a history of childhood sexual abuse should be considered a strong, although nonspecific, risk factor for PTSD in those with bipolar disorder. This is consistent with the findings of other reviews. The clinical features found to be indirectly associated with childhood sexual abuse in those with bipolar disorder remain merely hypothesis generating, due to methodological limitations of the individual studies.

				Mowlds et al. 2005, n = 52. Univariate correlate: Current inter-episode D (p = 0.007). Saviz et al. 2009, n = 49 Univariate correlate: Past or current PS (p = 0.0062). <u>Youths with bipolar disorder</u> Goldstein et al. 2008. n = 249 Univariate correlate: Past or current ADAD (p < 0.001). Romero et al. 2009, n = 446 Multivariate correlates: CSA without CPA: Past or current PTSD (OR = 7.8, p = 0.003). CSA with CPA: BD duration (OR = 1.2, p < 0.05), past or current PTSD (OR = 3.8, p < 0.05), past or current CD (OR = 3.8, p < 0.05).	
AA = alcohol abuse; AAD = alcohol abuse/dependence; AD = anxiety disorders; ADAD = alcohol/drug abuse/dependence; ASA = adult sexual abuse; BD = bipolar disorder; CD = conduct disorder; CEA = childhood emotional abuse; CEN = childhood emotional neglect; CPA = childhood physical abuse; CPN = childhood physical neglect; CSA = childhood sexual abuse; D = depression; DA = drug abuse; DAD = drug abuse/dependence; FH = family history; H = hallucinations; M = mania; OR = odds ratio; PD = personality disorders;; PH = psychiatric hospitalizations;; PTSD = posttraumatic stress disorder; QOL = quality of life; RC = rapid cycling; SA = suicide attempts.					
Study type: Systematic review **Quality: 1-** **Comments:** Adequately conducted systematic review with appropriately no meta-analysis. Systematic search of multiple databases. Methodological assessment adequate. Methodological limitations of individual studies mean causal inferences are not feasible.					

Reference and study design	Studies	Exposure	Outcome measure	Results/effect size	Conclusions
Mauritz et al. (2013) "Prevalence of interpersonal trauma exposure and trauma-related disorders in severe mental illness". European Journal of Psychotraumatology **4**. The Netherlands. Included studies (those related to bipolar disorder only): Assion et al., 2009; Goldberg and Garno, 2005; Kauer et al., 2007; Leverich et al., 2002ab; Maguire et al., 2008; Meade et al., 2009; Neria et al., 2005; Neria et al., 2008).	Number of studies: N=33 (studies related to bipolar disorder n=8). Inclusion criteria: Studies needed to have been published in peer reviewed journals, used adult subjects (≥ 18 years). In addition, the following criteria were applied: (1) SMI was labelled as such or one of the following mental disorders was mentioned: schizophrenia spectrum disorders, bipolar disorders, major depression/ depressive disorders, anxiety disorders, eating disorders, or personality disorders (a) Classified in DSM-III, DSM-IV or DSMIV-TR (b) SMI determined on the basis of both dimensions: (i) Duration of illness and/or treatment (2 years) (ii) Obvious dysfunction (GAF 560 or clear description of minimum of three impairments according the NIMH definition) and (2) Report of prevalence of interpersonal trauma exposure with specific description: (a) Type of abuse, reference period (childhood,	Interpersonal trauma	Prevalence rate of interpersonal trauma and trauma-related disorders	Prevalence rate for sexual abuse in those with severe mental illness compared to general population: 37%, 23%. See graphs below for population-weighted mean prevalence rates for sexual abuse in those with bipolar disorder specifically, and prevalence rates for sexual abuse in those with bipolar disorder by gender (no raw figures supplied).	Author's conclusions: Prevalence rates of interpersonal trauma were higher in those with severe mental illness than in the general population. Lower rates of trauma (physical abuse, sexual abuse) are found for bipolar and major depressive disorder, high rates found for schizophrenia, borderline personality disorder and groups labelled as severely mentally ill. Women with BD had higher rates of sexual abuse than men. Reviewer's conclusions: The authors present evidence suggesting an

	adulthood, lifetime) (b) Description of the diagnostic instruments used and (3) Report of prevalence of trauma-related disorders: (a) PTSD, complex PTSD (PTSD with associated features or DESNOS), DID, and/or DDNOS (b) Relevant diagnostic instruments were described. <u>Exclusion criteria:</u> Substance use disorders as only diagnosis; developmental disorders; delirium, dementia, amnesia or other cognitive disorders with a physical origin; forensic and/or imprisoned populations. <u>Databases used:</u> Embase, CINAHL, MEDLINE, PsycINFO. <u>Description of the methodological assessment of studies:</u> Reviewed by three researchers independently. <u>Fixed or variable effects:</u> Not applicable. <u>Heterogeneity:</u> Not discussed.				association between interpersonal trauma, including sexual abuse, and severe mental illness. Due to the nature of the studies, this cannot be shown to be causal. Very restrictive literature search criteria may have led to a loss of relevant information from studies that addressed only trauma exposure or trauma related disorders.
BD = Bipolar disorder; DESNOS = Disorder of extreme stress not otherwise specified; DDNOS = Dissociative disorder not otherwise specified; DID = Dissociative Identity Disorder; MMD = Major depressive disorder; Personality disorders (AV= Avoidant; B= Borderline; OC = Obsessive compulsive; ST = Schizotypal); PTSD = Posttraumatic stress disorder; SMI = Severe mental illness; SSD = Schizophrenic spectrum disorder.					

Fig 1. Prevalence rates for sexual abuse in those with bipolar disorder

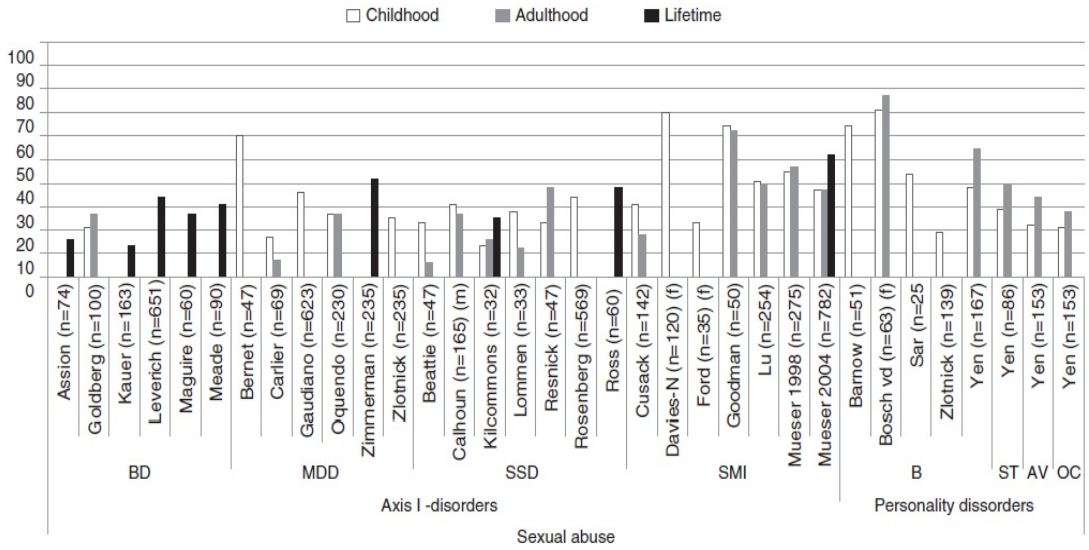
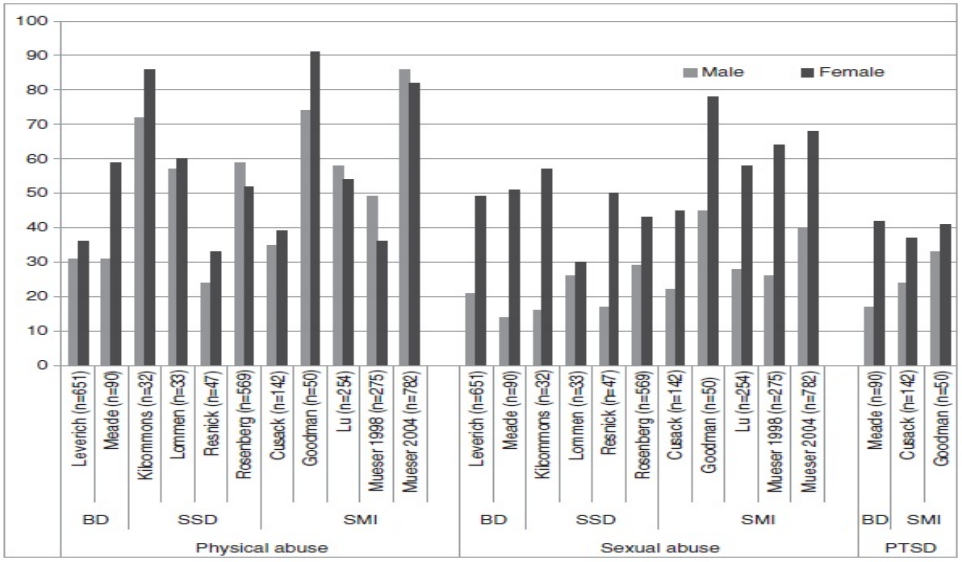


Fig 2. Prevalence rates for sexual abuse in those with bipolar disorder by gender



Study type: Systematic review

Quality: 1-

Comments: Adequately conducted systematic review with appropriately no meta-analysis. Systematic search of multiple databases. No formal methodological assessment.

10. Appendix 2: Excluded Study Table

The 24 studies excluded from this report are presented in the table below. These studies had the term “review”, “systematic review”, and/or “meta-analysis” stated in its abstract.

An additional 100+ articles were identified by the literature searches conducted. However, these articles were not included in this report based on the exclusion criteria (i.e., non-English studies, animal or laboratory studies, narrative reviews, letters or editorials; study designs other than systematic review or meta-analysis).

Reference	Reason for Exclusion
Abreu et al. 2009	Focus not on causation
Barlow et al. 2014	Review; Focus not on bipolar
Bassett 2012	Review; Focus is on identifying similarities and differences between bipolar and borderline personality disorder
Bernardy et al. 2013	Review; Focus not on bipolar
Chen et al. 2010	Systematic review; Focus not on bipolar
Cox et al. 2011	Meta-analysis; Focus not on bipolar
Douglas et al. 2011	Review and case study
Ghaemi et al. 2014	Focus not on causation
Halfon et al. 2013	Focus not on childhood sexual abuse
Hauser et al. 2013	Review; Focus not on causation of bipolar
Hawton et al. 2014	Review; Focus not on bipolar and childhood sexual abuse
Hay et al. 2014	Review; Focus not on bipolar
Henken et al. 2007	Review; Focus not on bipolar
Hyun et al. 2000	Not a systematic review, meta-analysis, or review
Lima 2004	Literature review
Lopez et al. 2011	Review; Focus not on bipolar and childhood sexual abuse
McIntyre et al. 2008	Focus not on causation
Meekums et al. 2014	Focus not on bipolar
Perry et al. 2014	Review; Focus not on bipolar and childhood sexual abuse
Simkin 2002	Review; Focus not on bipolar
Sin et al. 2015	Review; Focus not on bipolar
Stoffers et al. 2013	Systematic review; Focus is on intervention not causation
Storebø et al. 2011	Review; Focus not on bipolar
Zhang et al. 2012	Review; Focus not on bipolar

11. Appendix 3: Bradford Hill's Criteria of Causation[6]

A suggested guide to assessing the likelihood of causation

- **Strength of the association**: A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.
- **Consistency of the association**: Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect.
- **Specificity**: Causation is likely if a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.
- **Temporality**: The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay).
- **Biological gradient**: Greater exposure should generally lead to greater incidence of the effect. However, in some cases, the mere presence of the factor can trigger the effect. In other cases, an inverse proportion is observed: greater exposure leads to lower incidence.
- **Plausibility:** A plausible mechanism between cause and effect is helpful (but Hill noted that knowledge of the mechanism is limited by current knowledge).
- **Coherence**: Coherence between epidemiological and laboratory findings increases the likelihood of an effect. However, Hill noted that "... lack of such [laboratory] evidence cannot nullify the epidemiological effect on associations".
- **Experiment**: "Occasionally it is possible to appeal to experimental evidence".
- **Analogy**: The effect of similar factors may be considered.

12. References

Alloy, L.B., Abramson, L.Y., Smith, J.M., Gibb, B.E., & Neeren, A.M. (2006). Role of parenting and maltreatment histories in unipolar and bipolar mood disorders: Medication by cognitive vulnerability to depression. *Clinical Child and Family Psychology Review, 9*, 23-64.

Barth, J., Bermetz, L., Heim, E., Trelle, S., & Tonia, T. (2013). The current prevalence of child sexual abuse worldwide: a systematic review and meta-analysis. *International journal of public health, 58*(3), 469-483.

Brekke, J.S., Prindle, C., Bae, S.W., & Long, J.D. (2001). Risks for individuals with schizophrenia who are living in the community. *Psychiatr Serv*, *52*, 1358–1366.

Browne, A., & Finkelhor, D. (1986). Impact of child sexual abuse: a review of the research. *Psychological bulletin, 99*, 66.

Fergusson, D. M., McLeod, G. F., & Horwood, L. J. (2013). Childhood sexual abuse and adult developmental outcomes: Findings from a 30-year longitudinal study in New Zealand. *Child abuse & neglect, 37*, 664-674.

DynaMed. 2014.

Heim, C., & Nemeroff, C.B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. *Biological Psychiatry, 49* 1023–1039.

Hill, A.B. (1965). The environment and disease: association or causation? *Proc R Soc Med, 58*, 295-300.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry, 62*, 593-602.

Leclerc, B., & Wortley, R. (2015). Predictors of victim disclosure in child sexual abuse: additional evidence from a sample of incarcerated adult sex offenders. *Child abuse & neglect, 43*, 104-111.

Maniglio R. (2009). Severe mental illness and criminal victimization: a systematic review. *Acta Psychiatr Scand*, *119*, 180–191.

[1]Maniglio, R. (2013a). Prevalence of child sexual abuse among adults and youths with bipolar disorder: A systematic review. *Clinical Psychology Review*, *33*, 561-573.

[2]Maniglio, R. (2013b). The impact of child sexual abuse on the course of bipolar disorder: A systematic review. *Bipolar Disorders*, *15*, 341–358.

[3]Mauritz, M.W., Goossens, P.J.J., Draijer, N., & van Achterberg, T. (2013). Prevalence of interpersonal trauma exposure and trauma-related disorders in severe mental illness. *European Journal of Psychotraumatology*, *4*.

Paolucci, E. O., Genuis, M. L., & Violato, C. (2001). A meta-analysis of the published research on the effects of child sexual abuse. *The Journal of psychology, 135*, 17-36.

Pereda, N., Guilera, G., Forns, M., & Gómez-Benito, J. (2009). The international epidemiology of child sexual abuse: A continuation of Finkelhor (1994). *Child abuse & neglect, 33*, 331-342.