**Comorbidity of ADHD and adult bipolar disorder: A systematic review and meta-analysis**

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**Highlights**

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We conducted a meta-analysis of comorbidity between [ADHD](https://www.sciencedirect.com/topics/neuroscience/attention-deficit-hyperactivity-disorder) and adult [BD](https://www.sciencedirect.com/topics/psychology/bipolar-disorder).

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Up to 1 in 13 patients with [ADHD](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/attention-deficit-disorder) has comorbid [BD](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/bipolar-disorder) and up to 1 in 6 patients with [BD](https://www.sciencedirect.com/topics/psychology/bipolar-disorder) has comorbid [ADHD](https://www.sciencedirect.com/topics/psychology/attention-deficit-hyperactivity-disorder).

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Comorbidity rates are heterogeneous and differ per continent and diagnostic system.

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[BD](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/bipolar-disorder) age of onset was nearly 4 years earlier in patients with comorbid [ADHD](https://www.sciencedirect.com/topics/neuroscience/attention-deficit-hyperactivity-disorder).

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Careful [differential diagnosis](https://www.sciencedirect.com/topics/neuroscience/differential-diagnosis) of both disorders is necessary.

**Abstract**

Attention-deficit / hyperactivity disorder (ADHD) and Bipolar Disorder (BD) are common mental disorders with a high degree of comorbidity. However, no systematic review with meta-analysis has aimed to quantify the degree of comorbidity between both disorders. To this end we performed a systematic search of the literature in October 2020. In a meta-analysis of 71 studies with 646,766 participants from 18 countries, it was found that about one in thirteen adults with [ADHD](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/attention-deficit-disorder) was also diagnosed with BD (7.95 %; 95 % CI: 5.31–11.06), and nearly one in six adults with BD had [ADHD](https://www.sciencedirect.com/topics/psychology/attention-deficit-hyperactivity-disorder) (17.11 %; 95 % CI: 13.05–21.59 %). Substantial heterogeneity of comorbidity rates was present, highlighting the importance of contextual factors: Heterogeneity could partially be explained by diagnostic system, sample size and geographical location. Age of BD onset occurred earlier in patients with comorbid ADHD (3.96 years; 95 % CI: 2.65–5.26, p < 0.001). Cultural and methodological differences deserve attention for evaluating diagnostic criteria and clinicians should be aware of the high comorbidity rates to prevent misdiagnosis and provide optimal care for both disorders.

**Introduction**

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder with a worldwide prevalence between 5 and 8% in children (Asherson et al., 2016; Polanczyk et al., 2007). Up to 65 % of patients (Faraone et al., 2006a) continue to experience impairing symptoms into adulthood (adult ADHD, aADHD), although symptoms change over time; hyperactivity seems to diminish, while inattention and emotional problems prevail or even become more important (Chang et al., 2013; Larsson et al., 2011). The prototypic symptom complex that can be observed in aADHD (Asherson et al., 2016) comprises concentration problems and inattention, mind wandering, problems staying on task or keeping deadlines, and also impulsive behaviour, restlessness, and difficulty regulating emotions triggered by external stimuli. The trajectory of ADHD over the life span is characterized by a high degree of comorbidity (Franke et al., 2018) that, at least partially, could be tracked back to shared genetic vulnerability which is especially pronounced for major depressive disorder (MDD) (Demontis et al., 2019). Among the disorders shown to occur more often in aADHD than chance predicts, is bipolar disorder (BD) (Torres et al., 2015).

Like ADHD, BD is a common mental disorder with a prevalence of 1%–3%, depending on how narrowly diagnostic criteria are applied (Merikangas et al., 2007, 2011). The core feature of BD is the lifespan occurrence of depressive as well as manic episodes, the latter of which are defined by increased energy and drive, psychomotor hyperactivity, restlessness, euphoria or irritability, and increased impulsivity in a state-like manner. In between mood episodes, patients are mostly euthymic and free of disease symptoms, although up to 40 % of patients continue to suffer from a varying degree of cognitive deficits (Volkert et al., 2015). Especially in bipolar-II disorder (BD-II), which is characterized by the exclusive presence of hypomania, the differential diagnosis between aADHD and BD can be challenging when not considering the trait-like nature of aADHD in contrast to the state-like features of BD. This is further complicated by the inter-episode cognitive deficits in BD as well as common sub-syndromal mood states and phenomena such as mixed episodes and rapid cycling, i.e., high-frequency mood swings, both occurring more often in BD-II. Thus, there is considerable overlap in the diagnostic criteria and associated features between BD and aADHD. Since diagnostic criterion overlap may not entirely explain the comorbidity of both (Milberger et al., 1995), it is possible that other shared clinical features are due to shared genetic or environmental risk factors.

Unsurprisingly so, aADHD and BD have been found to be comorbid in cross-sectional studies, with comorbidity rates ranging between 5 % (McGough et al., 2005) and 47 % (Wilens et al., 2003) when the primary sample was aADHD. Family-based studies suggest a relative risk of about 2% for the comorbid phenotype in first-degree relatives (Faraone et al., 2012). Also, longitudinal follow-ups - especially from a family-based Canadian study (Duffy et al., 2014)- argue for a trajectory from childhood ADHD to adult comorbid BD/ADHD. This is also supported by recent cross-disorder meta-analyses from genome-wide association studies which found an overlap in common genetic risk variants for ADHD and BD (Consortium et al., 2019).

To date, and to the best of our knowledge, no systematic review and meta-analysis has quantified the degree of comorbidity between ADHD and adult BD. The comorbidity of ADHD and BD is also a highly relevant and timely topic in paediatric psychiatry: Especially in the Americas, the number of children diagnosed with paediatric bipolar disorder has risen in the last years (Dickstein and Leibenluft, 2012). Since the reason for this increased diagnostic occurrence is still heavily debated and may be due to different American and European diagnostic traditions (Carlson, 2018; Goldstein et al., 2019; Parry et al., 2018), we here opted for the description of BD comorbidity occurring in adolescence and adulthood only. For an overview on comorbidity of ADHD in paediatric BD, see reference (Joshi and Wilens, 2009). Furthermore, we updated a previous meta-analysis on family-based studies (Faraone et al., 2012) on this topic and undertook a systematic review on large genetic studies investigating this comorbidity.

**Section snippets**

**Literature search**

To conduct the review, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015) were followed. The review protocol was registered on PROSPERO (ID: CRD42020179855). In- and exclusion criteria were discussed and approved by all authors. Databases were searched independently, and title, abstract and full text screening, as well as assessment of article eligibility were independently performed by authors CS and GAH. Disagreements as to eligibility

**Study characteristics**

After duplicate removal, 4812 titles and 1027 abstracts of unique articles were screened. Four hundred thirty-one full-text articles were assessed for eligibility. Three hundred fifty-eight articles were excluded, of which 6 were not available and 352 were excluded with reasons (Supplementary Information 1). In total, 71 studies involving 646,766 participants of 18 countries were included in the meta-analysis of ADHD and BD comorbidity (see PRISMA Flow diagram in Fig. 1). Thirty-eight of those

**Discussion**

In the here examined studies, 1 in 13 patients with ADHD had BD and nearly 1 in 6 patients with BD were diagnosed with ADHD. These numbers are strikingly high. Given the published lifetime prevalence for ADHD of 6.5 % and a lifetime BD prevalence of 1–2 % (these number however vary widely across studies and represent the rough median of published data) (Fayyad et al., 2017; Polanczyk et al., 2007, 2014), one could tentatively estimate that, based on the few population based studies included in

**Conclusion**

Our review found that the co-occurrence of ADHD and BD is much higher than expected by chance. We found important variations depending on geographic location (and/or cultural norms), the diagnostic system used (ICD vs DSM) and sample size and an earlier age of onset for BD with comorbid ADHD. Our study highlights that clinicians should be aware of this diagnostic co-occurrence, which can have important implications for diagnostic specification and potentially treatment.

**CRediT authorship contribution statement**

**Carmen Schiweck:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Gara Arteaga-Henriquez:** Conceptualization, Methodology, Validation, Investigation, Writing - original draft. **Mareike Aichholzer:** Conceptualization, Methodology, Validation, Investigation, Writing - original draft. **Sharmili Edwin Thanarajah:** Conceptualization, Methodology, Validation, Investigation, Writing -

**Declaration of Competing Interest**

Carmen Schiweck, Gara Arteaga-Henríquez, Mareike Aichholzer, Sharmili Edwin-Thanarajah, Sebastián Vargas-Cáceres and Silke Matura have no conflict of interest to declare. Oliver Grimm has received honoraria as speaker from Medice Arzneimittel Pütter & Co KG GmbH. Sarah Kittel-Schneider received speaker’s honoraria from Shire/Takeda and Medice Arzneimittel Pütter GmbH&Co KG.Josep Antoni Ramos-Quiroga reports grants and personal fees from Takeda, grants and personal fees from Janssen, grants and

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