

Review article

Antibiotics and mania: A systematic review

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ARTICLE INFO

Keywords:

Antibiotics
Bipolar disorder
Antibiomania
Review

ABSTRACT

Objectives: Mania can occur secondary to a medical condition and can be elicited by various pharmacological treatments, both in patients with or without a history of affective disorder. Antibiotic-induced mania or antibiomania is suggested to be a rare phenomenon. We reviewed the literature in order to collect published reports of antibiomania and to summarize new insights about its mechanism and management.

Methods: We performed a MEDLINE-search and used manual cross-referencing for reports of antibiotic-induced mania and included cases in which a (hypo)manic episode was diagnosed in close temporal relationship with the prescription of an antibiotic.

Results: 47 cases were published. Patients' ages ranged from 3 to 77 years (mean 40). Two-thirds of the cases were male. Twelve different anti-bacterial agents were implicated, with antitubercular agents, macrolides and quinolones being the most common causative groups.

Conclusions: Antibiotic treatment can be associated with (hypo)mania. The paucity of reported cases precludes statements regarding incidence or antibiotic-specific warnings. In the event of an antibiotic-induced mania, the suspicious drug should be discontinued and manic symptoms can be treated *lege artis*. The pathophysiological mechanism of antibiomania remains elusive.

1. Introduction

Mania can emerge in the context of a variety of somatic conditions and pharmacological treatments, both in patients with or without a history of affective disorder. These cases are best considered secondary manias (Krauthammer and Klerman, 1978), and classified as 'substance/medication induced bipolar and related disorder' in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM). One of the possible precipitating factors causing secondary mania is the use of antibiotics.

Antibiomania is a term introduced by Abouesh et al. (2002). The authors reported 21 published cases in an extensive literature review, including 143 unpublished cases from the adverse drug monitoring programs of the World Health Organization (WHO) and the Food and Drug Administration (FDA). Clarithromycin, ciprofloxacin and ofloxacin seemed to be the most common causative agents. Several hypotheses about the underlying mechanism, including pharmacokinetics and interactions with neurotransmitters in the central nervous system (CNS), were put forward.

In this paper we aim to update this endeavor, collecting published

reports of antibiomania and summarizing new insights about its mechanism and management.

2. Methods

We performed a MEDLINE-search using "(anti-bacterial agents OR antibiotics) AND (mania* OR manic* OR bipolar* OR psychosis* OR psychotic*)", from 1900 until February 2017. No language restrictions were applied. The reference lists of the papers thus retrieved were hand-searched for other relevant papers. All papers describing well documented cases of hypomania or mania, occurring in close temporal relation with the prescription of an antibiotic agent were included.

3. Results

Of 992 papers retrieved with the above-mentioned search strategy, 26 papers were included, describing 28 cases of antibiotic-induced mania. Eleven reports (containing 19 cases) were added by manual cross-referencing (Fig. 1).

Characteristics of the 47 published cases are presented in Table 1.

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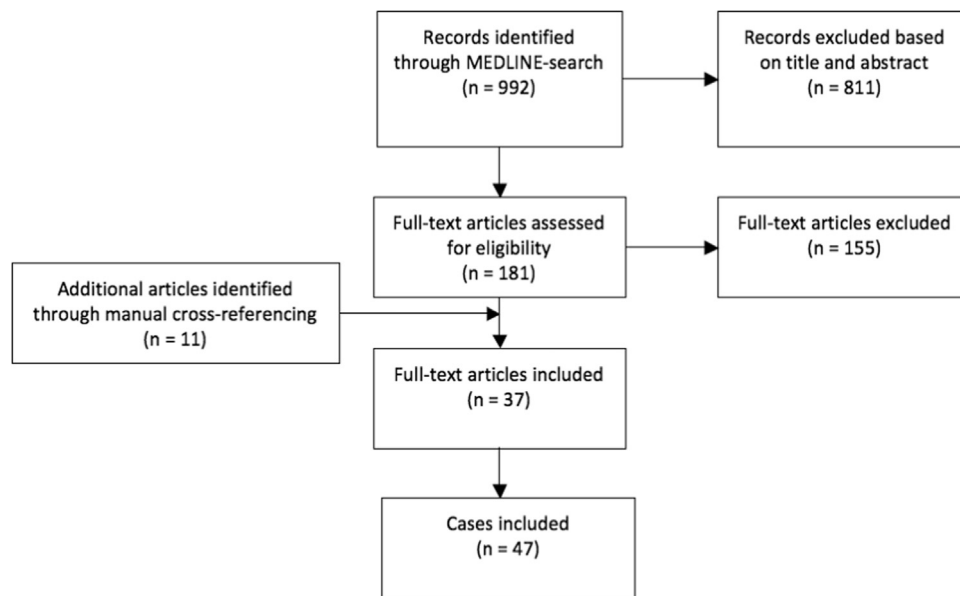


Fig. 1. Flow diagram.

Mania was reported in 38 cases (81%) (Beal et al., 1986; Klain and Timmerman, 2015; Bhalerao et al., 2006; Abouesh and Hobbs, 1998; Fidan and Fidan, 2009; Brooks and Hoblyn, 2005; Fonseca et al., 2008; Lopes et al., 2011; Neff and Kuo, 2002; Nightingale et al., 1995; Ortiz-Dominguez et al., 2004; Przybylo et al., 2005; Rallis et al., 2009; Walrave et al., 2016; Bakhla et al., 2013; Carmichael and Paul, 1989; Gawkrödger, 1989; Manchia et al., 2013; Martin and Bowden, 2007; Narang, 1972; Brouet et al., 1965; Bloch et al., 1954; Crane, 1956; Chaturvedi and Upadhyaya, 1988; Duggal and Nizamie, 2000; Jackson, 1957; Kane and Taylor, 1963; Prasad et al., 1985; Hollweg et al., 1997; Pickles and Spelman, 1996), hypomania in 6 cases (13%) (Crane, 1956; Baranowski, 2010; Sarkar and Khandelwal, 2013; Zaudig et al., 1989; Hesslinger et al., 1996). In 3 cases (6%) (Cohen and Weitz, 1981; Cone et al., 1996; Mermelstein, 1998) the reported diagnosis was not (hypo) mania: one case (2%) (Mermelstein, 1998) was diagnosed as delirium, and in 2 cases (4%) (Cohen and Weitz, 1981; Cone et al., 1996) no diagnosis was mentioned. We chose to include these cases based on the description of the clinical picture, that is compatible with a diagnosis of (hypo)mania. Seven cases (Carmichael and Paul, 1989; Gawkrödger, 1989; Bloch et al., 1954; Pickles and Spelman, 1996; Zaudig et al., 1989; Hesslinger et al., 1996) were published prior to 2002, but were not included in the review of Abouesh et al. (2002). In Table 1, the unpublished WHO/FDA cases reported by Abouesh et al. (2002) are not included.

In all but 4 (Prasad et al., 1985; Hollweg et al., 1997) cases (91%), the symptoms and the clinical picture were carefully described, but in only 5 cases (11%) (Lopes et al., 2011; Baranowski, 2010; Sarkar and Khandelwal, 2013; Zaudig et al., 1989) diagnostic criteria (DSM/ICD) were used to establish the diagnosis. In only 4 cases (9%) (Walrave et al., 2016; Bakhla et al., 2013; Duggal and Nizamie, 2000) symptom severity was assessed using a standardized rating scale (Young Mania Rating Scale (YMRS) or Brief Psychiatric Rating Scale (BPRS)).

In 6 cases (13%), a previous manic episode secondary to either steroids (Lopes et al., 2011; Pickles and Spelman, 1996), cocaine (Brouet et al., 1965) or an antibiotic (Baranowski, 2010; Sarkar and Khandelwal, 2013) had occurred. One case (2%) had a history of a psychotic episode believed to be caused by erythromycin and codeine (Zaudig et al., 1989). In several other cases, a history of psychiatric illness was present (psychosis not further specified (one case (2%) (Hollweg et al., 1997)) or mood episode (6 cases (13%) (Fonseca et al., 2008; Bloch et al., 1954; Pickles and Spelman, 1996; Zaudig et al., 1989; Hesslinger et al., 1996))). Only 2 cases (4%) (5, 21) had

previously been diagnosed with bipolar disorder, both receiving lithium.

Gender was reported in all but 4 (Brouet et al., 1965; Bloch et al., 1954) cases (92%): 14 (30%) women and 29 (62%) men. In the cases reported by the WHO 42 out of 82 cases (51%) were men, whereas the FDA reported 25 (out of 61) (41%) male cases. Age, reported in 43 cases (91%), ranged from 3 to 77 years with a mean age of 40 years. In order to compare our findings with the results obtained from the adverse drug monitoring programs by Abouesh et al. (2002), we created 4 age groups: under 10 years (2 cases, 4%), 11–30 years (12 cases, 26%), 31–50 years (13 cases, 30%) and over 50 years of age (14 cases, 32%). The age distribution is shown in Fig. 2.

Figs. 3 and 4 show the number of cases per antimicrobial agent and per class of antibiotics, respectively. In 19 cases (40%) (Bhalerao et al., 2006; Lopes et al., 2011; Neff and Kuo, 2002; Nightingale et al., 1995; Przybylo et al., 2005; Bakhla et al., 2013; Martin and Bowden, 2007; Narang, 1972; Bloch et al., 1954; Chaturvedi and Upadhyaya, 1988; Duggal and Nizamie, 2000; Jackson, 1957; Kane and Taylor, 1963; Prasad et al., 1985; Pickles and Spelman, 1996; Cone et al., 1996), a combination of antimicrobial agents had been used.

Clarithromycin, ciprofloxacin and ofloxacin were the most common causative antibiotics in the WHO reports. In the published cases we reviewed, (hypo)mania was related to clarithromycin in 16 cases (34%), ciprofloxacin in 1 case (2%) and ofloxacin in 4 cases (9%). It must be noted that the 82 WHO reports, involving 18 antimicrobials, also included 8 cases of manic episodes caused by anti-fungal, anti-viral or anti-retroviral agents. Another important aspect is that the 61 FDA reports had been obtained by a request restricted to 7 antimicrobials.

In 18 cases (39%) (Nightingale et al., 1995; Przybylo et al., 2005; Rallis et al., 2009; Carmichael and Paul, 1989; Gawkrödger, 1989; Martin and Bowden, 2007; Narang, 1972; Bloch et al., 1954; Crane, 1956; Jackson, 1957; Prasad et al., 1985; Pickles and Spelman, 1996; Baranowski, 2010; Cohen and Weitz, 1981), manic symptoms subsided after discontinuing the antibiotic, without the addition of antimanic agents, supporting the hypothesis of the antibiotic being the causative agent. Several antimanic agents were used in the reported cases: lithium (2 cases (4%)) (Beal et al., 1986; Abouesh and Hobbs, 1998), antipsychotics (26 cases (55%)) (Beal et al., 1986; Bhalerao et al., 2006; Abouesh and Hobbs, 1998; Fidan and Fidan, 2009; Brooks and Hoblyn, 2005; Fonseca et al., 2008; Lopes et al., 2011; Neff and Kuo, 2002; Nightingale et al., 1995; Ortiz-Dominguez et al., 2004; Walrave et al., 2016; Bakhla et al., 2013; Manchia et al., 2013; Brouet et al., 1965;

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