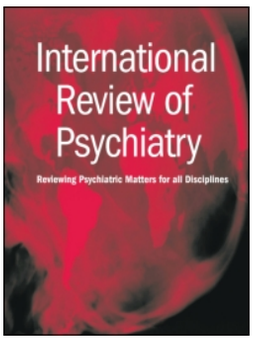

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REVIEW

Psychiatric comorbidity in Wilson's disease

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ABSTRACT

Wilson's disease (WD) is a relatively rare autosomal recessive inherited disorder causing copper accumulation in different organs, mainly the liver and brain. Psychiatric disturbances represent a diagnostic and therapeutic issue in WD. A search for relevant articles was carried out on PubMed/Medline, Scopus, and Google Scholar, for papers focused on psychiatric disorders in WD published between 1985–2016. Ninety-two articles were included in this review, showing the findings from 35 observational and case-control studies and 57 case reports. This study discussed the findings on the prevalence of psychiatric symptoms in WD, their impact on the life of those diagnosed, and the efficacy of available treatments on the psychiatric outcomes of WD. Psychiatric disorders are confirmed frequent in WD, with a high prevalence of mood disorders, and contribute to worse Quality-of-Life and psychosocial outcomes. Because specific therapies for WD lead to a good life expectancy, adherence to medicaments and clinical monitoring should be warranted by a multidisciplinary approach, including a hepathologic, neurologic, and psychiatric careful evaluation and education of those affected and their relatives.

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KEYWORDS
Wilson's disease; psychiatric comorbidity; quality-of-life; mood disorders; burden of disease

Introduction

Wilson's disease (WD), or hepatolenticular degeneration, is a relatively rare autosomal recessive inherited disorder (Bearn, 1959) that causes a reduction in copper excretion and the accumulation of copper mainly in the liver, central nervous system, and kidneys, and other organs, such as the cornea, joints, and heart (Ala, Walker, Ashkan, Dooley, & Schilsky, 2007; Scheinberg, Sternlieb, Schilsky, & Stockert, 1987). If untreated, WD leads to the death of those affected.

The worldwide prevalence of WD ranges from ~1:30 000 to 1:100 000, and the rate of carrier, previously estimated in ~1:90 (El-Youssef, 2003), according to recent research could be higher than 1:50 (Coffey et al., 2013). WD is more frequent in communities isolated and characterized by high rates of consanguinity (i.e. 'founder effect'), such as in the island of Sardinia, where an incidence of 1:7000 live births has been found (Loudianos et al., 1999), and the highest prevalence has been reported in a mountainous village in the island of Crete, with six cases of WD in 90 births from 1978–2005 (Dedoussis et al., 2005). Most of the WD cases become symptomatic in childhood and young age, usually between the ages of 5–35 (Patil, Sheth, Krishnamurthy, & Devarbhavi, 2013), although the possibility of a late or very-late onset WD beyond the seventh decade has been described (Weitzman et al., 2014).

WD is caused by over 500 different mutations in a gene located on chromosome 13q14 (Coffey et al., 2013; Rodriguez-Castro, Hevia-Urrutia, & Sturniolo, 2015), the ATP7B, which encodes a P-type adenosine triphosphatase (named Wilson's disease ATPase), involved in both the copper transportation across cell membranes for the incorporation of copper into ceruloplasmin, and in the biliary excretion of copper (Wu, Wang, Pu, Qiao, & Jiang, 2015). If ATP7B is muted, the level of ceruloplasmin decreased, and Cu^{2+} is stored in the liver and released in plasma as non-ceruloplasmin-bound copper. In the liver, the massive accumulation of Cu^{2+} in hepatocyte lysosomes accelerates the formation of reactive oxygen species that cause cellular damage; through the plasma, Cu^{2+} reaches other organs and gradually tends to accumulate, determining tissue damage and impaired functions (Kodama, Fujisawa, & Bhadhprasit, 2012).

The diagnosis of WD should include the following elements: (1) levels of serum ceruloplasmin decreased by 50% of the lower normal value (i.e. <0.2 g/L); (2) elevated 24 h urinary copper excretion, >1.6 µmol/24 h in adults and >0.64 µmol/24 h in children; (3) serum 'free' copper >1.6 µmol/L; (4) hepatic copper >4 µmol/

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g dry weight; and (5) the presence of Kayser-Fleischer rings on slit-lamp examination observed by an experienced ophthalmologist (European Association for the Study of the Liver, 2012).

Early manifestations of the disease can be prevalently hepatic (~50% of cases), neurological (40%), or psychiatric (20%), and more rarely can be haematologic, renal, cardiologic, osteoarticular, endocrinological, and ocular (Hassan & Masood, 2004).

The hepatic form of WD usually begins in late childhood or adolescence, with a widely varying degree of involvement of the liver, from an asymptomatic slight increase of transaminases, to the acute hepatic failure, or a chronic progressive liver disease with liver cirrhosis of the macronodular type (Devarbhavi, et al., 2012; Patil et al., 2013).

A neurological presentation of WD tends to occur later, mainly in the third decade of life (Rosencrantz & Schilsky, 2011). The most common neurological features of WD include postural and intentional tremors (80% of the cases), a Parkinsonian-like extrapyramidal syndrome (40%), and focal or generalized dystonia (10–30%) (Ferenci, Litwin, Seniow, & Czlonkowska, 2015). Besides the pure neurological presentation, in WD, can occur a hepatic encephalopathy due to the liver failure and the porto-systemic shunts. Such a condition, particularly if in an initial, mild form of hepatic encephalopathy, could be difficult to distinguish from the neurological form of WD and could overlap (Ferenci et al., 2015).

About 50–70% of people with WD experienced psychiatric symptoms, ranging from behavioural disorders to affective disorders, psychotic symptoms, and cognitive impairment. Psychiatric symptoms can either represent the onset of WD, or manifest during the course of a hepatic, neurological or mixed WD form, or be a side-effect of a treatment, or represent a psychological dysfunctional response to a chronic organic disease (Carta, Mura, Sorbello, Farina, & Demelia, 2012; European Association for the Study of the Liver, 2012; Svetel, et al., 2009; Zimbrean & Schilsky, 2014). Whether the occurrence of such symptoms had been recognized before the earlier description of the disease by Samuel Alexander Kinnier Wilson (Wilson, 1912) is unsure; however, psychiatric disturbances, particularly if they manifest in undiagnosed subjects, continue to nowadays be a diagnostic and therapeutic issue in WD.

Aiming to provide an overview to psychiatrists on psychiatric comorbidity in WD, a systematic review was carried out to synthetize the findings of studies published over the last three decades on the prevalence of psychiatric symptoms in patients with WD, to determine the relevance of these symptoms, their impact on the life of those diagnosed, and the efficacy of available treatments on the psychiatric outcomes of WD.

Methods

Search strategy and articles selection

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, Altman, & Prisma Group, 2009), a search for relevant articles was carried out on PubMed/Medline, Scopus, and Google Scholar, combining free-text and MeSH terms using a broad range of synonyms and related terms, such as the following: (‘mental disorders’[MeSH Terms] OR (‘mental’[All Fields] AND ‘disorders’[All Fields]) OR ‘mental disorders’[All Fields] OR (‘psychiatric’[All Fields] AND ‘disorders’[All Fields]) OR ‘psychiatric disorders’[All Fields]) OR (‘depressive disorder, major’[MeSH Terms] OR (‘depressive’[All Fields] AND ‘disorder’[All Fields] AND ‘major’[All Fields]) OR ‘major depressive disorder’[All Fields] OR (‘major’[All Fields] AND ‘depressive’[All Fields] AND ‘disorder’[All Fields]) OR ‘major depressive disorder’[All Fields] OR ‘depressive disorder’[MeSH Terms] OR (‘depressive’[All Fields] AND ‘disorder’[All Fields]) OR ‘depressive disorder’[All Fields] OR (‘major’[All Fields] AND ‘depressive’[All Fields] AND ‘disorder’[All Fields])) OR (‘bipolar disorder’[MeSH Terms] OR (‘bipolar’[All Fields] AND ‘disorder’[All Fields]) OR ‘bipolar disorder’[All Fields]) OR (‘mania’[All Fields]) OR (‘psychotic disorders’[MeSH Terms] OR (‘psychotic’[All Fields] AND ‘disorders’[All Fields]) OR ‘psychotic disorders’[All Fields] OR (‘psychotic’[All Fields] AND ‘disorder’[All Fields]) OR ‘psychotic disorder’[All Fields]) OR (‘schizophrenia’[MeSH Terms] OR ‘schizophrenia’[All Fields]) OR (‘anxiety disorders’[MeSH Terms] OR (‘anxiety’[All Fields] AND ‘disorders’[All Fields]) OR ‘anxiety disorders’[All Fields]) AND (‘hepatolenticular degeneration’[MeSH Terms] OR (‘hepatolenticular’[All Fields] AND ‘degeneration’[All Fields]) OR ‘hepatolenticular degeneration’[All Fields] OR (‘wilson’s’ [All Fields] AND ‘disease’[All Fields]) OR ‘Wilson’s disease’[All Fields]). To avoid the risk of missing relevant articles, additional papers were searched on the grey literature (i.e. generic web search) and throughout the bibliography of previous reviews. One author (GM) ran the

search and screened the initial 484 titles after duplicates were removed.

Two authors (GM and MGC) independently examined potential relevant articles in depth, using the following criteria: only papers published in peer-review journals were included, if written in English, with any type of design, focused on psychiatric comorbidity in WD. Unpublished papers, abstracts, and conference/symposium papers/posters were excluded. The interval set for the research was from 1985–2016. First author's name and year of publication, sample size, design of the study, assessment, and results of the selected articles were recorded through an electronic spreadsheet. Disagreements between reviewers were solved by discussion, or by a third reviewer's opinion (PZ).

The search was carried out from May 2016 until September 2016.

Results

From 673 titles originally identified through database searching, and 33 additional titles identified by searching the bibliography of previous reviews, we were able to assess for eligibility 220 full-text papers. The process of inclusion of the studies for qualitative review through PRISMA statement (Moher et al., 2009) is shown in Figure 1.

Ninety-two articles were retrieved from the search that fulfilled our criteria of inclusion: 35 observational and case-control studies and 57 case reports. Synthetic results from selected observational and case-control studies are shown in Tables 1–3. A brief summary of selected case reports is shown in Table 4.

Psychiatric comorbidity in Wilson's disease: epidemiological aspects and burden of psychiatric disorders

The first author who described psychopathological symptoms in WD was Wilson himself, who detailed psychiatric manifestations in eight out of his 12 original cases. These presentations included schizophrenia-like states, emotional lability, and progressive cognitive decline. Although Wilson recognized the importance of these psychiatric symptoms, he did not attribute them in totality to WD, stating that they

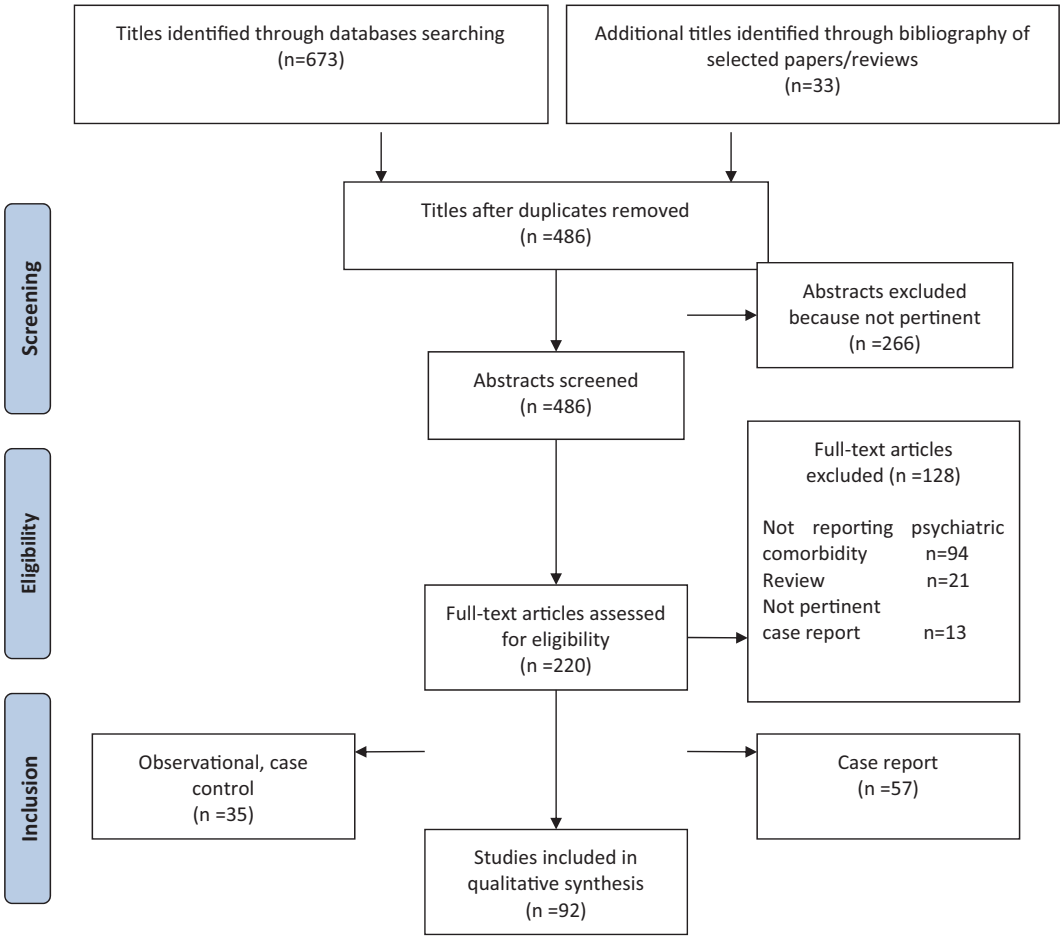

Figure 1. Process of inclusion of the studies for qualitative review according to the PRISMA statement.

might represent 'not an integral part' of the disease (Wilson, 1912). Few latter studies emphasized psychiatric aspects as core clinical features of WD (see Dening (1985) for a comprehensive review of the literature from 1959–1982). The lack of diagnostic rigorous assessment, the misuse of terminology, and the fact that most of the clinicians were not psychiatrists, did not allow any univocal conclusions from these early researches, thus we focused our review on papers published over the last 30 years.

WD presenting as a psychiatric disorder

One of the most confounding characteristics of the onset of WD is the occurrence of psychiatric manifestations without neurological or hepatic signs. Table 1 shows synthetic findings from retrospective studies on WD presenting with psychiatric symptoms (Akil, Schwartz, Dutchak, Yuzbasiyan-Gurkan, & Brewer, 1991; Dening & Berrios, 1989a; Huang & Chu, 1992; Kumar, Datta, Jayaseelan, Gnanmuthu, & Kuruvilla, 1996; Lowette et al., 2010; Medici et al., 2006; Prashanth, Taly, Sinha, Arunodaya, & Swamy, 2004; Shanmugiah et al., 2008; Soltanzadeh et al., 2007; Srinivas et al., 2008; Taly, Meenakshi-Sundaram, Sinha, Swamy, & Arunodaya, 2007; Walshe & Yealland, 1992).

Up to 20% of people with WD reported having seen a psychiatrist prior to the diagnosis (Dening & Berrios, 1989a). Results from retrospective studies showed that psychiatric symptoms occurred as onset of WD in a wide varying percentage of subjects, ranging from 1.1% (Srinivas et al., 2008) to 20% (Dening & Berrios, 1989a) in the larger cohorts, and from 16% (Shanmugiah et al., 2008) to 24% (Soltanzadeh et al., 2007) in smaller samples drawn from neurologic units.

Psychiatric presentation of WD generally occurs in the second decade of life, similarly to the pure neurologic form of the disease. The most common psychopathological features with which WD tended to present at onset were: a decrease in scholastic performance (Kumar et al., 1996; Prashanth et al., 2004; Soltanzadeh et al., 2007), behavioural problems (Dening & Berrios, 1989a; Kumar et al., 1996; Medici et al., 2006; Prashanth et al., 2004; Soltanzadeh et al., 2007), affective disorders (Akil et al., 1991; Kumar et al., 1996; Lowette et al., 2010; Medici et al., 2006; Prashanth et al., 2004; Srinivas et al., 2008; Walshe & Yealland, 1992), and psychosis (Akil et al., 1991; Huang & Chu, 1992; Prashanth et al., 2004; Srinivas et al., 2008; Walshe & Yealland, 1992).

Findings from both early case reports (Dening, 1985; Jayaswal, Lal, Nepal, & Wig, 1984) and the

Table 1. Psychiatric onset of WD in retrospective studies (ordered by sample size).

Reference	Sample size	Number of patients with psychiatric onset (%)	Age at diagnosis, years (mean ± SD) or median	Age at onset, years (mean ± SD)	Delay from diagnosis
Srinivas et al. (2008)	350	4 (1.1%)	19.8 ± 5.8	16.9 ± 5.4	from 0.02–14 years
Prashanth et al. (2004)	307	12 (8.9%)	15.6 ± 7.3	13.5 ± 6.9	2.0 ± 3.0 years
Taly et al. (2007)	282	7 (2.4%)	24.1 (median, psychiatric WD)	15.93 ± 8.10	3.5 years
Dening and Berrios (1989a)	195	39 (20%)	19.7 ± 9.7	NR	NR
Walshe and Yealland (1992)	136 (neurologic WD)	32 (23.5%)	NR	16.2 (median, neurologic WD)	12.8 months (mean delay neurologic WD)
Huang and Chu (1992)	71	8 (11.3%)	21.0 ± 6.3	18.1 ± 6.5 (total sample) 25.3 ± 2.4 (psychiatric WD)	NR
Shanmugiah et al. (2008)	50 (neurologic WD)	8 (16%)	16.3 ± 7.0	14.2 ± 6.4	NR
Kumar et al. (1996)	31 (neurologic WD)	6 (19.4%)	17.3 ± 9.4	15.2 ± 9	NR
Soltanzadeh et al. (2007)	50 (neurologic WD)	10 (20%)	17.30 (median, neurologic WD)	16 (median, neurologic WD)	17 months (median delay)
Akil et al. (1991)	42	24 (64.8%)	15 patients <20 22 patients between 20–30 5 patients >30	10–44 years (range), with 89% in the 2nd or 3rd decade of life	NR
Medici et al. (2006)	35	11 (31.4%)	NR	15.5 ± 7.2	3 ± 4.5 years
Lowette et al. (2010)	24	5 (21%)	23.2 ± 8.11	20.79 ± 7.91	NR

NR: not reported; WD: Wilson's disease.

Table 2. Psychiatric comorbidity in the course of WD: cohort studies (ordered by the sample size).

Reference	Sample size	Number of patients with psychiatric comorbidity (%)	Psychiatric assessment	Number of patients with diagnosis/symptoms (where available)
Litwin et al. (2012)	627	71 (14%)	Clinical, retrospective	NR
Srinivas et al. (2008)	350	15 (4.2%)	Clinical, retrospective	9 (2.5%) BD 5 (1.4%) PSYCHOTIC DISORDERS 1 (0.2%) COGNITIVE IMPAIRMENT
Prashanth et al. (2004)	307 (delay diagnoses)	12 (8.9%)	Clinical, retrospective	SCHIZOPHRENIA, BIPOLAR DISORDER, DEPRESSION, MANIA, ANXIETY DISORDER, PARANOID PSYCHOSIS
Taly et al. (2007)	282	43 (15.2%)	Clinical, prospective	MANIA, SCHIZOPHRENIA-LIKE SYNDROME, BEHAVIOuRAL DISORDERS
Beinhardt et al. (2014)	229	16 (7.2%)	Clinical, prospective	1 (0.4%) SUICIDE
Dening and Berrios (1989a)	195	99 (50.7%)	Retrospective (AMDP System)	25 (12.8%) IRRITABILITY 25 (12.8%) INCONGRUOUS BEHAVIOuR 17 (8.7%) AGGRESSION 16 (8.2%) PERSONALITY CHANGE 11 (5.6%) COGNITIVE IMPAIRMENT 10 (5%) ELATION 8 (4%) DEPRESSION 7 (3.6%) DISORIENTATION 7 (3.6%) FORENSIC HISTORY 6 (3%) SUICIDAL BEHAVIOuR 5 (2.5%) BD 4 (2%) OVERACTIVITY 4 (2%) ANXIETY 3 (1.5%) ALCOHOL ABUSE 2 (1%) DELUSIONS 1 (0.5%) HALLUCINATIONS 1 (0.5%) DRUG ABUSE
Członkowska et al. (2005)	20 (deaths) on 164	4 (20%)	Clinical, retrospective	3 (15%) MANIC PSYCHOSIS 1 (5%) DEPRESSION, SUICIDE
Svetel et al. (2009)	142	NR	Clinical, prospective	4 (2.8%) SUICIDE 2 (1.4%) SEVERE DEPRESSION
Lin et al. (2014)	133	7 (5.3%)	Clinical, retrospective	2 (1.5%) DEPRESSION 2 (1.5%) HALLUCINATIONS 2 (1.5%) PERSONALITY CHANGE 1 (0.7%) ANXIETY 1 (0.7%) DELUSION
Machado et al. (2006)	118 (neurologic WD)	65 (67%)	Clinical	65 WITH MILD PSYCHIATRIC SYMPTOMS (DEPRESSION, EMOTIONAL LABILITY, IRRITABILITY, DISINHIBITION); 9 WITH SEVERE PSYCHIATRIC SYMPTOMS: CATATONIA, AGITATION, AGGRESSION, DELUSIONS, MANIA
Soltanzadeh et al. (2007)	50 (neurologic WD)	12 (24%)	Clinical, retrospective	5 IRRITABILITY 3 HALLUCINATIONS 2 DEPRESSION 2 INAPPROPRIATE LAUGHING
Oder et al. (1991)	45	15 (33.3%)	Clinical, prospective	12 (26.6%) MOOD DISTURBANCES 7 (15.5%) SUICIDE ATTEMPTS 3 (6.3%) DELUSION
Medici et al. (2005)	37 (liver transplantation WD)	7 (18.9%)	Clinical, retrospective	PARANOID PSYCHOSIS, HYSTERICAL NEUROSIS, DEPRESSION, INSOMNIA, DRUG DEPENDENCE
Bem et al. (2011)	36	6 (16.6%)	Clinical, retrospective	BIPOLAR DISORDER, ATTENTION DEFICIT DISORDER, PERSONALITY ALTERATIONS, BODY NEGLIGENCE, IRRITABILITY, HYPERSOMNIA
Kumar et al. (1996)	31 (neurologic WD)	18 (58%)	Clinical, retrospective	14 (45.2%) COGNITIVE IMPAIRMENT 9 (29%) INAPPROPRIATE AFFECT 5 (16.1%) IRRITABILITY 5 (16.1%) POOR SCHOLASTIC PERFORMANCE 4 (12.9%) DEPRESSION 4 (12.9%) OVERACTIVITY 3 (9.7%) AGGRESSION 2 (6.5%) DISORIENTATION 2 (6.5%) HALLUCINATIONS 1 (3.2%) DELUSIONS 1 (3.2%) MANIA/HYPOMANIA 1 (3.2%) INCONGRUOUS BEHAVIOuR
Pellecchia et al. (2003)	30	2 (6.6%)	Clinical, retrospective	2 (6.6%) BEHAVIuORAL DISTURBANCES
Tatsumi et al. (2010)	30	NR	Clinical, prospective	2 (6.6%) SUICIDE

AMDP: Association for Methodology and Documentation in Psychiatry; NR: not reported; WD: Wilson's disease.

Table 3. Psychiatric comorbidity in the course of WD: cross-sectional and case-control studies.

Reference	Sample size	Age	Assessment	Number of diagnoses (%)
Svetel et al. (2009)	50	35.5 ± 10.1 (EVALUATION)	SCID NPI	TOTAL: 13 (26%, SCID) ANXIETY: 31 (62%, NPI) IRRITABILITY: 13 (26%, NPI) MANIA/HYPOMANIA: 9 (18%, NPI) BD: 7 (14%, SCID) MDD: 3 (6%, SCID) DYSTIMIA: 2 (4%, SCID)
Shanmugiah et al. (2008)	50	14.2 ± 6.4 (ONSET) 16.3 ± 7.0 (DIAGNOSIS)	SCID	TOTAL: 12 (24%) BD: 9 (18%) MDD: 2 (4%) DYSTIMIA: 1 (2%)
Carta et al. (2015)	38	42.2 ± 11.8 (EXAMINATION) 28.2 ± 17.3 (ONSET)	ANTAS-SCID MDQ	TOTAL: 17 (44.7%) BD: 9 (23.7%) MDD: 8 (21.05)
Carta, Sorbello, et al. (2012)	23 WD 92 CTRL	42.02 ± 12.52 (EXAMINATION) 30.19 ± 18.28 (DIAGNOSIS)	ANTAS-SCID MDQ	TOTAL: 19 (82.6%) MDD: 11 (47.8%) BD: 7 (30.4%, SCID), 9 (39.1%, MDQ) TOT ANXIETY DISORDERS: 4 (17.3%) PANIC DISORDER: 2 (8.7%)
Piga et al. (2008)	25 WD 25 CTRL	30.6 ± 9.4	Clinical	TOTAL: 2 (8%) DEPRESSION AND ANXIETY: 1 (4%) HALLUCINATORY PSYCHOSIS: 1 (4%)
Lang et al. (1990)	17 WD 17 CTRL	29.29 ± 9.20 (WD) 32.82 ± 10.01 (CTRL) 20 (MEAN AGE ONSET)	Standardized psychiatric history and mental status documentation	TOTAL: 8 (47.5%) DEPRESSION: 3 (17.6%) MANIA/HYPOMANIA: 2 (11.7%) DELUSION: 2 (11.7%) IRRITABILITY: 1 (5.8%) AGGRESSIVITY: 1 (5.8%) SUICIDAL BEHAVIOuR: 1 (5.8%)

ANTAS: Advanced Neuropsychiatric Tools and Assessment Schedule; BD: Bipolar Disorder; CTRL: controls; MDD: Major Depressive Disorder; MDQ: Mood Disorders Questionnaire; NPI: Neuropsychiatric Inventory; SCID: Structured Clinical Interview for Axis-I Psychiatric Disorders; WD: individuals with Wilson's disease.

recent ones (for case reports synthesis, see Table 4) emphasized the occurrence of WD with major psychiatric disorders, particularly psychosis or schizophrenia-like syndrome (Bidaki et al., 2012; Jukić, Titlić, Tonkić, Dodig, & Rogosić, 2006; Kontaxakis, Stefanis, Markidis, & Tserpe, 1988; Krstić, Antonijević, & Špirić, 2014; Matarazzo, 2002; Shah & Vankar, 2003; Stiller, Kassubek, Schönfeldt-Lecuona, & Connemann, 2002), mainly characterized by persecutory delusion. Hallucinations (mostly auditory) have been rarely reported and are typically associated with delusion of reference or persecution (Bidaki et al., 2012; Kontaxakis et al., 1988; Matarazzo, 2002). WD presentation with psychotic manifestation also encompassed the rare syndrome of catatonia in youth (Nayak et al., 2012; Sahoo, Avasthi, Sahoo, Modi, & Biswas, 2010) and even in paediatric age (Davis & Borde, 1993).

Despite the interest on the association between WD and schizophrenia-like disorders, the occurrence of WD with bipolar disorder (BD) spectrum symptoms at its onset (with manic/hypomanic episodes, over-activity, irritability, aggressive behaviour, disinhibition, suicide attempts) has been most frequently described in case reports (Aravind, Krishnaram, Neethiarau, & Srinivasan, 2009; Chand & Murthy, 2006; Keller, Torta, Lagget, Crasto, & Bergamasco, 1999; Machado et al., 2008; McDonnell & Esmonde, 1999; Müller, 1999; Nazariah, Aisah, Anita, Yeoh, & Ng, 2011; Vale, Caramelli, & Teixeira, 2011). As shown below, this association was further confirmed by epidemiological studies on the course of WD.

However, a number of case reports also described WD onset with depression (Araújo-de-Freitas, Rocha, Gondim, Quarantini, & Miranda-Scippa, 2014; Chan et al., 2005; Stiller et al., 2002; Walter & Lyndon, 1997), in some cases highlighting a very late (Ala, Borjigin, Rochwarger, & Schilsky, 2005; Sechi et al., 2007) or a very early onset (Chakraborty, Sanyal, & Bannerjee, 2015; Krishnakumar & Riyaz, 2005), or an atypical symptomatology (Crumley, 1990; Woerwag-Mehta, Hindley, Hedderly, & Dhawan, 2011). Such reports queried whether depression in WD could be considered 'organic', rather than due to demoralization secondary to a chronic disease.

Also, other authors, warning of the possibility of atypical onset of WD in paediatric or juvenile age, reported cases of WD presenting with irritability and suicidal ideation (Millard, Zimbrean, & Martin, 2015), obsessive-compulsive disorder (Kumawat, Sharma, Tripathi, Ralot, & Dixit, 2008), Attention-Deficit/

Table 4. Case reports on psychiatric comorbidity in WD (alphabetical order).

References	Psychiatric symptoms/disorder	Occurrence/topic
Ala et al. (2005)	depression	onset
Araújo-de-Freitas et al. (2014)	depression	onset
Aravind et al. (2009)	mania	onset
Bidaki et al. (2012)	psychosis	onset
Carr and McDonnell (1986)	adjustment disorder	onset
Chakraborty et al. (2015)	depression	onset
Chan et al. (2005)	depression/personality disorder/suicide attempt	onset
Chand and Murthy (2006)	mania	onset
Crumley (1990)	depression	onset
Davis and Borde (1993)	catatonia	onset
Grover et al. (2014)	psychosis	treatment
Jukić et al. (2006)	psychosis	onset
Keller et al. (1999)	mania	onset
Kenar and Menteseoglu (2014)	mania	in course
Kontaxakis et al. (1988)	psychosis	onset
Krishnakumar and Riyaz (2005)	depression	onset
Krstić et al. (2014)	psychosis	onset
Kulaksizoglu and Polat (2003)	mania	treatment
Kumawat et al. (2008)	obsessive-compulsive disorder	onset
Leggio et al. (2007)	anxiety	in course
Lin et al. (2006)	Attention Deficit Hyperactivity Disorder (ADHD)	onset
Lingam et al. (1987)	conduct disorder	onset
Litwin, Chabik, and Członkowska (2013)	depression	treatment
Litwin et al. (2016)	mania	treatment
Loganathan et al. (2008)	mania	in course
Machado et al. (2008)	mania	onset
Matarazzo (2002)	psychosis	onset
McDonald and Lake (1995)	psychosis	treatment
McDonnell and Esmonde (1999)	bipolar disorder	onset
Millard et al. (2015)	irritability/suicidal ideation	onset
Mitra et al. (2014)	mania	in course
Modai et al. (1985)	schizophrenia-like psychosis	treatment
Müller (1999)	psychosis/change in mood/aggressive behaviour/suicide attempt	onset
Nayak et al. (2012)	catatonia	onset
Nazariah et al. (2011)	mania	onset
Negro and Louzá Neto (1995)	depression	treatment
Özcan & Selimoğlu (2009)	behaviour disorder	in course
Rich and Lajoie (2012)	psychosis	in course
Rodrigues et al. (2004)	catatonia	treatment
Rybakowski et al. (2013)	bipolar disorder	in course
Sahoo et al. (2010)	catatonia	onset
Sahu et al. (2013)	obsessive-compulsive disorder	in course
Sechi et al. (2007)	depression	onset
Shah and Kumar (1997)	psychosis	treatment
Shah and Vankar (2003)	psychosis	onset
Silva et al. (2011)	Attention Deficit Hyperactivity Disorder (ADHD)/phobias	onset
Sorbello et al. (2011)	psychosis	treatment
Spyridi et al. (2008)	delusional disorder, alcohol abuse	in course
Stiller et al. (2002)	depression/psychosis	onset
Vaishnav and Gandhi (2013)	psychosis	treatment
Vale et al. (2011)	bipolar disorder/suicide attempt	onset
Varghese et al. (2008)	mania	treatment
Volpe and Tavares (2000)	psychosis	in course
Walter and Lyndon (1997)	depression	onset
Wichowicz et al. (2006)	delusional disorder	in course
Woerwag-Mehta et al. (2011)	depression/obsessive-compulsive disorder	onset
Zimbrean and Schilsky (2015)	psychosis	in course

Hyperactivity Disorder (ADHD) (Lin, Lin, Wang, & Wong, 2006; Silva, Nobre, Campos, Vasconcelos, & Gonçalves, 2011), adjustment disorder (Carr & McDonnell, 1986), and conduct disorder (Lingam, Wilson, Nazer, & Mowat, 1987).

No distinction can be made clinically between the psychiatric symptoms of WD and psychiatric symptoms due to an actual psychiatric disorder. Therefore, the diagnosis of WD cannot be ascertained based on the psychiatric presentation. Thus, a pure psychiatric presentation, which often is unspecific (for instance, poor scholastic performance in adolescence), can lead to a delay in an appropriate diagnosis and treatment (Prashanth et al., 2004).

Comorbid psychiatric disorders in course of WD

Previous reviews categorized psychiatric manifestation in WD into five (cognitive impairment; personality disorders; affective disorders; psychosis; other psychiatric alterations) (Akil & Brewer, 1994) or four clusters (affective, behavioural, schizophrenia-like, and cognitive symptoms) (Dening, 1985). A number of comorbid psychiatric disorders have been identified in WD, which encompass all psychopathological aspects. However, even recently, not all researchers assessed psychiatric symptoms by means of standardized clinical interviews, thus the exact prevalence of comorbid psychiatric disorders from cohort studies was hard to establish. Moreover, such studies were mostly dedicated to describing in general the symptomatology and the outcomes of WD, and an in-depth psychiatric evaluation was generally lacking. Table 2 synthetizes the findings from cohort studies (Beinhardt et al., 2014; Bem et al., 2011; Członkowska, Tarnacka, Litwin, Gajda, & Rodo, 2005; Kumar et al., 1996; Lin et al., 2014; Litwin, Gromadzka, & Członkowska, 2012; Machado et al., 2006; Medici et al., 2005; Oder et al., 1991; Pellecchia et al., 2003; Prashanth et al., 2004; Soltanzadeh et al., 2007; Srinivas et al., 2008; Svetel et al., 2009; Taly et al., 2007; Tatsumi et al., 2010).

Results from larger cohorts showed an overall prevalence of psychiatric disturbances in the course of WD, ranging from ∼4% (Srinivas et al., 2008) to 15% (Litwin et al., 2012; Taly et al., 2007), with the exception of the study by Dening and Berrios (1989a) reporting a very high prevalence and a detailed psychiatric symptoms description by using the glossary of the Association of Methodology and Documentation in Psychiatry, partially modified by the authors. However, the last study was carried out on patients mostly affected by the neurological form of WD, in which, according to other similar studies, the prevalence of psychiatric manifestations was higher, varying between 24% (Soltanzadeh et al., 2007) and 67% (Machado et al., 2006).

Behavioural disturbances (including disinhibition, agitation, and aggression) and personality change were frequently reported (Bem et al., 2011; Dening & Berrios, 1989a; Kumar et al., 1996; Lin et al., 2014; Machado et al., 2006; Pellecchia et al., 2003; Taly et al., 2007), as well as irritability (Bem et al., 2011; Dening & Berrios, 1989a; Kumar et al., 1996; Machado et al., 2006; Soltanzadeh et al., 2007), but unfortunately such symptoms are widespread, and can overlap with a variety of psychiatric disorders, like anxiety, mood (both polarity), and psychotic disorders, besides some personality disorders.

A clinically relevant depression was recognized in several studies, but with very low prevalence (ranging from ∼1–12% of the cases) (Dening & Berrios, 1989a; Kumar et al., 1996; Lin et al., 2014; Machado et al., 2006; Medici et al., 2005; Oder et al., 1991; Prashanth et al., 2004; Soltanzadeh et al., 2007; Svetel et al., 2009). Also, the diagnosis of BD was frequently reported (Bem et al., 2011; Dening & Berrios, 1989a; Kumar et al., 1996; Machado et al., 2006; Oder et al., 1991; Prashanth et al., 2004; Srinivas et al., 2008; Taly et al., 2007) with a prevalence of ∼2.5–3%.

Psychotic symptoms were reported, with delusions, hallucinations, or a most complex schizophrenia-like syndrome (Dening & Berrios, 1989a; Kumar et al., 1996; Lin et al., 2014; Medici et al., 2005; Oder et al., 1991; Prashanth et al., 2004; Soltanzadeh et al., 2007; Srinivas et al., 2008; Taly et al., 2007), generally affecting ∼0.5–1% of the samples. Higher prevalence of ∼6% for psychotic symptoms was reported in the studies by Kumar et al. (1996) and Oder et al. (1991).

Impaired cognition, generally mild, was reported in a low percentages of patients (Dening & Berrios, 1989a; Machado et al., 2006; Srinivas et al., 2008), with a high prevalence of 45% among the neurological WD sample by Kumar et al. (1996).

Noticeably, suicide attempts were disclosed by Dening and Berrios (1989a) and Oder et al. (1991), with prevalence of, respectively, 3% and 15%, and suicide acts were reported with prevalence of 0.4% out of 229 (Beinhardt et al., 2014), 2.8% out of 142 (Svetel et al., 2009), and 6.6% out of 30 individuals (Tatsumi et al., 2010). Moreover, among 20 subjects who died from a cohort of 164, mood disorders (mainly BD) were reported as a complication and cause of death in three, and suicide in one individual (Członkowska et al., 2005).

Given the rarity of WD, samples in case-control and cross-sectional studies were generally small. However, a number of studies assessed psychiatric comorbidity by means of standardized interviews (Carta, et al., 2015; Carta, Sorbello, et al., 2012; Lang, Müller, Claus, & Druschky, 1990; Shanmugiah et al., 2008; Svetel et al., 2009), thus conferring on results greater validity.

Case-controlled studies evidenced higher lifetime prevalence of mood disorders (both Major Depressive Disorder (MDD) and Bipolar Disorder (BD)) in persons with WD compared to healthy controls (Carta, Sorbello, et al., 2012; Lang et al., 1990), and suggested

the presence of an organic origin for mood disturbances in WD. People with hepatic, neurological, and psychiatric involvement displayed early abnormal patterns of brain perfusion in the temporal cortex and basal ganglia at 99Tcm-ethyl cysteinate dimer (ECD) single photon emission computer tomography (SPECT) compared with healthy age-gender matched controls, with an individual with depression and anxiety also showing pathological magnetic resonance imaging (MRI) findings on images of putamen, midbrain, and pons (Piga, et al., 2008). This hypothesis was further confirmed by the evidence of a higher frequency of brain damage (detected using MRI), particularly in the basal ganglia ($p < .001$), and in the overall brain ($p < .003$), and total brain damage ($p = .003$) in patients with comorbid WD and BD compared to both comorbid WD and MDD, and WD without mood disorders (Carta et al., 2015).

Cross-sectional studies also showed an association between WD and major mood disorders, such as depression (Lang et al., 1990; Shanmugiah et al., 2008; Svetel et al., 2009), dysthymia (Shanmugiah et al., 2008; Svetel et al., 2009), and, above all, BD (Carta, Sorbello, et al., 2012; Shanmugiah et al., 2008; Svetel et al., 2009); these conditions were diagnosed through standardized clinical tools. In addition, other mood disturbances, such as hypomania (Lang et al., 1990; Svetel et al., 2009), irritability (Lang et al., 1990; Svetel et al., 2009), and suicidal behaviour (Lang et al., 1990), were recognized with high frequency in WD. This result is particularly interesting in regard of BD spectrum, since it might suggest a psychopathological pattern ascribable to sub-threshold manic symptoms. Moreover, an association was shown between WD and anxiety (Svetel et al., 2009), and psychotic symptoms (Lang et al., 1990; Piga et al., 2008), the last evidenced in individuals with both psychiatric and neurologic involvement.

Case reports (see Table 4) mostly reported psychosis, with parkinsonism and delusion of though insertion (Zimbrean & Schilsky, 2015), with persecutory delusion (Wichowicz, Cubała, & Sławek, 2006), and also with impulsivity and conduct disturbances (Spyridi et al., 2008; Volpe & Tavares, 2000).

A number of case reports focused on bipolar disorder in the course of WD, presenting after discontinuance of penicillamine (Kenar & Menteseoglu, 2014), or improving with chelation only (Mitra, Ray, & Roy, 2014), or responsive to lithium (Loganathan et al., 2008; Rich & Lajoie, 2012; Rybakowski, Litwin, Chlopocka-Wozniak, & Czlonkowska, 2013). Rarely, it was reported in the course of WD as an obsessive-compulsive disorder (Sahu, Singhi, & Malhotra, 2013), behaviour disorder (Özcan & Selimoğlu 2009), and anxiety (Leggio et al., 2007).

Pathogenesis of psychiatric disorders in WD

It has been supposed that the high prevalence of psychiatric presentation, and that of psychiatric comorbidity, mostly along with neurological involvement, could be caused in WD by the brain damage determined by copper accumulation. Early studies hypothesized an association between the psychopathological symptoms and specific neurological ones, in particular concerning bradykinesia and gait disturbances (Dening & Berrios, 1989b), dysartria (Dening & Berrios, 1990), and tremor (Kumar et al., 1996).

MRI abnormalities, specially described in basal ganglia, pons, and subcortical area, have been shown in neuropsychiatric forms of WD in almost 90–100% of cases and hypothesized to be correlated with copper deposits (Dusek, Litwin, & Czlonkowska, 2015). Such typical WD MRI brain abnormalities in basal ganglia and white matter were shown, with a higher frequency in subjects with co-morbid BD compared with both co-morbid MDD and WD without mood disorders (Carta et al., 2015). Moreover, irritability and aggression, previously described as 'personality changes' or 'behavioural disturbances' (Akil et al., 1991; Dening & Berrios, 1989a; Oder et al., 1991; Walshe & Yealland, 1992), were associated with neurological signs of WD, such as dyskinesia and dysarthria, and with the presence of lesions of putamen and pallidum (Lang et al., 1990; Oder et al., 1993). Noticeably, in a large cohort study recently published, all individuals with psychiatric presentation had also neurologic symptoms (Beinhardt et al., 2014). However, behavioural abnormalities might not always be matched with structural pathological signs detectable with MRI, but rather through a more sensitive method to functional alterations such as SPECT (Piga et al., 2008).

SPECT findings suggested an organic origin of depression in WD, with the evidence of presynaptic serotonin transporter density in some brain regions (thalamus-hypothalamus and midbrain-pons regions) inversely correlated with the severity of depression (Eggers et al., 2003). Interestingly, such findings are more consistent with those reported in primary BD than in depression: in fact, a decrease of serotonin transporter in midbrain regions has been found also in depressive episodes in the course of BD (Oquendo et al., 2007) and in euthymic subjects with BD-I (Chou et al., 2010), while SPECT in individuals with

depression generally showed a reduction in cerebral blood flow in the prefrontal area (Nagafusa et al., 2012). Moreover, serum copper (among other trace elements) has been shown to be significantly higher in subjects with BD compared with healthy controls (González-Estecha, et al., 2011). Copper is hypothesized to determine the brain damage in WD via oxidative stress. In BD, oxidative stress markers, mostly lipid peroxidation, have been found significantly increased compared to healthy subjects (Brown, Andreazza, & Young, 2014), and a decrease in lipid peroxidation has been associated with response to treatment with lithium (de Sousa et al., 2014). It has been hypothesized that earlier research and case reports, using unspecific psychiatric assessments, could have stressed the occurrence of 'schizophrenia-like psychosis' in WD, while recently the current psychiatric diagnostic criteria, and the use of standardized diagnostic tools and case-control design, strongly support the evidence of a specific correlation between WD and BD, which might share a similar pathogenesis due to brain oxidative damage and consequent neurodegeneration determined by trace-metals accumulation (Carta, Sorbello, et al., 2012).

The high rate of depression in the course of WD was also hypothesized to be associated with the severity of functional impairment; however, a higher prevalence of depression was shown in WD than in persons suffering by other chronic diseases with a similar level of disability, like rheumatic arthritis (Ehmann, Beninger, Gawel, & Riopelle, 1990), and similar to the rates of depression in other basal ganglia disorders (Rosenblatt & Leroi, 2000). The co-presence of neurological symptoms could be an obstacle to the psychiatric examination, and lead to both under-diagnosed (because of the tendency to give a reactive explanation) and over-diagnosis (in the case of neurologic symptoms overlapping with depression, such as apathy, psychomotor slowness, sleep disturbances) (Rosenblatt & Leroi, 2000); furthermore, it was hypothesized that WD lesions of the basal ganglia could mediate the denial of disease (Seniów, Mroziak, Członkowska, & Jedryka-Góral, 2003).

Recently, Ferenci et al. (2015) suggested that 'minor' psychopathological symptoms (such as apathy, irritability, and emotional lability) could be due to a mild hepatic encephalopathy. A liver involvement in neurologic presentation of WD has been shown in a large percentage of those affected, with liver cirrhosis in 34% of them (Beinhardt et al., 2014), and it has been postulated that every person with WD has some degree of hepatic disease (Brewer, 2001). On the contrary, early-treated subjects with pure hepatic WD presentation did not differ from healthy controls in MRI findings, or in neuropsychiatric and neuropsychological assessment (all normal) (Dubbioso et al., 2016). All considered findings seemed to confirm the early observation by Dening and Berrios (1989a), which stated that 'the connection between neurologic and psychiatric aspect seems genuine', (Dening & Berrios, 1989a, p. 1132) and such an association 'strongly suggest that psychopathology has a considerable organic component' (Dening & Berrios, 1989a, p. 1132).

Psychosocial burden of WD

WD is characterized by a lifetime course, generally presenting in young age, and by the need of chronic life-saving therapies; if treatment is initiated early, however, life expectancy is comparable with that of unaffected persons, thus compliance represents the key in managing WD (Rodriguez-Castro et al., 2015). Psychiatric symptoms, along with neurological disability, were recognized among the strongest prediction of poor outcome (Dening & Berios, 1989a), because they complicate the course of WD, worsen Quality of Life (QoL) (Carta, Mura et al., 2012), and may impact with an adequate adherence to therapy. Few papers have reported the impact of WD on psychosocial outcomes from the person's point of view (i.e. assessing self-report wellbeing, as in the case of questionnaires on QoL); however, undirected indicators, such as psychosocial outcomes, could be traced from the literature. Table 5 shows the findings of studies on the burden of WD on QoL and other psychosocial outcomes.

Self-reported QoL, which reflects a subjective point of view on the whole wellbeing, encompasses physical, emotional, and social domains of general life satisfaction. Individual's perception of QoL has become a key outcome in chronic diseases, particularly in those that eventually determine disability and require long-term medications, as in the case of neurological and rheumatologic ones (Fernández-Jiménez & Arnett, 2015; Mura, Bhat, Pisano, Licci, & Carta, 2012). Studies on QoL in persons with WD generally indicated an inverse correlation between neurological impairment and QoL in the physical domain, with individuals with impaired physical ability (Dening & Berrios, 1990; Kumar, et al., 2008), and people with neuropsychiatric involvement compared with the ones with a pure hepatic form of WD (Svetel, et al., 2011), particularly for those with a bipolar spectrum comorbidity

Table 5. Quality-of-life and other psychosocial outcomes in WD.

Reference	Sample size	Design	Observation period	Outcome(s)	Results
Bem et al. (2011)	36	Retrospective	1971–2010	Marriage, have children, employment/study	Married: 53.8% Had children: 57.2% Employed: 38.9% Studying 8.3%
Carta, Sorbello, et al. (2012)	23 WD 92 CTRL	Case-control		Quality-of-Life (SF-12)	SF-12: 33.76 ± 9.0 (WD) vs 38.14 ± 6.4 (CTRL) ($p = .008$)
Dening and Berrios (1990)	129	Prospective		General health (GHQ: General Health Questionnaire)	GHQ 'cases': 32%, significant correlations between GHQ and impaired walking and GHQ and serum levels of ALT
Kumar et al. (2008)	30	Longitudinal		Quality-of-Life (WHO-BREF)	WHO-QoL-BREF domains (mean scores ± SD): physical (3.65 ± 0.55), psychological (3.53 ± 0.75), social relations (3.93 ± 0.95), and environmental (3.47 ± 0.62). The physical domain had a significant correlation with the duration of treatment ($p < .01$) and Neurological Symptom Score ($p < .05$).
Pellecchia et al. (2003)	30	Retrospective	1970–2000	Marriage, employment	Married: 33% Employed: 50%
Sutcliffe et al. (2003)	24 LT for WD vs normed scores of SF-36	Prospective	92 months mean follow-up period	Quality-of-Life (SF-36)	SF-36 scores comparable with those of normative sample. No significant difference in either physical or mental domains of SF-36 with respect to sex, clinical presentation, or presence of major adverse events (reoperation or re-transplantation). Significant correlation between physical component score and social function, bodily pain, and vitality.
Svetel et al. (2011)	60	Cross-sectional		Quality-of-Life (SF-36)	Lower SF-36 scores in patients with neurological WD vs hepatic WD, and in psychiatric WD vs non-psychiatric WD. Significant inverse correlations between SF-36 domains and delay from onset and treatment initiation, MMSE and HDRS scores, and different domains of the GAS for WD.
Taly et al. (2007)	282 (for 225 follow-up data available)	Retrospective	1970–2000	Employment/study	72.8% resumed work or school.

ADL: activities of daily living; CTRL: controls; GAS: Global Assessment Scale for WD; GHQ: General Health Questionnaire; HDRS: Hamilton Depression Rating Scale; LT: liver transplantation; MMSE: Mini Mental State Examination; SF-12: Short-Form 12-Item Health Survey; SF-36: Short-Form 36-Item Health Survey; WD: Wilson's disease; WHO-QoL-BREF: World Health Organization Quality of Life questionnaire-26 questions.

(Carta, Sorbello, et al., 2012), most likely to perceive a poor QoL. However, Sutcliffe et al. (2003) reported QoL in persons who have undergone liver transplantation for WD comparable with age- and gender-matched healthy subjects. The last study was carried out in patients with severe liver disease, the only indication for liver transplantation. Noticeably, another study that investigated clinical outcomes of individuals with WD who underwent liver transplantation underlined that psychiatric symptoms were associated with poorer outcome compared with subjects with liver disease only, and stated that severe neuropsychiatric disturbances represent a contraindication for liver transplantation (Medici et al., 2005).

Other longitudinal studies looked at social outcomes in individuals with WD, such as being married, having children, and employment or education. These outcomes do not obviously reflect a subjective satisfaction in life; however, they could be useful to give an idea of the individual's social functioning. A high percentage of individuals with treated WD who resumed work or studies (72.8%) has been shown in the largest study by Taly et al. (2007), with other studies in smaller samples reporting percentages of ~50% of employment/study (Bem et al., 2011; Pellecchia et al., 2003), and similar percentages for those married and having children (Bem et al., 2011).

Treatments of psychiatric disorders in WD

Contrary to what happens in most of the rare inherited fatal diseases, a number of treatments are

currently available for WD, allowing an overall survival rate of ∼90% (Bem et al., 2011). Specific treatment with anti-copper drugs should be initiated in WD once the diagnosis has been made, even in subjects who were asymptomatic at presentation. This treatment needs to be continued lifelong. Treatment is based on chelating agents, which increase urinary copper excretion (cupriuretic copper chelators: D-penicillamine, trientine) or both urinary and intestinal excretion (tetrathiomolybdate), and/or the use of zinc salts to blocking the intestinal copper absorption; international guidelines recommend chelating agents in symptomatic subjects as first line agents, followed by either reduced doses of chelating agents or zinc salts for maintenance (European Association for the Study of the Liver, 2012; Roberts & Schilsky, 2008). Available therapies should be integrated with a dietary modification that reduces the foods rich in copper, and by supplementation with vitamin E because of its antioxidant power. Liver transplantation represents the ultimate therapeutic option in the case of acute/chronic liver disease where medications failed. The prognosis in early treated WD is excellent, while those with long delay before diagnosis, or who discontinued anti-copper treatments (Rodriguez-Castro et al., 2015), or with liver cirrhosis at diagnosis (Beinhardt et al., 2014) showed poor outcomes. Both D-penicillamine and zinc sulphate, the two most used de-coppering treatments, have been showed to determine a decrease in copper metabolism, a normalization of copper homeostasis, and to improve (but not normalize) antioxidant capacity parameters (Gromadzka et al., 2014). A retrospective analysis on 380 individuals with WD treated with D-penicillamine and trientine showed comparable outcomes for the two drugs, although penicillamine had been shown to be burdened with more adverse effects, but less frequent neurologic deterioration than trientine (Weiss et al., 2013), and a randomized controlled trial showed the superiority of tetrathiomolybdate over trientine for preserving neurologic function in subjects with neurologic WD presentation (Brewer, et al., 2006).

Impact of anti-copper treatments upon psychiatric symptoms in WD

The impact of specific WD therapies on psychiatric symptoms has been examined in a few observational studies; however, a number of conclusions can be drawn from case reports. Dening and Berrios (1989a) reported that treatment with D-penicillamine showed greater response rates in subjects with better general clinical conditions and incongruous behaviour, while depression and irritability did not improve; moreover, non-responders with psychiatric symptoms were more likely to have dysartria. A more recent longitudinal study on outcomes of subjects undergoing long-term treatment with D-penicillamine showed a resolution of psychiatric symptoms in all affected individuals (Lowette et al., 2010). Treatment with D-penicillamine is thought to determine a rapid mobilization of hepatic copper into the blood stream and its distribution in brain, causing an initial worsening of neurological symptoms in subjects with neurologic WD (Brewer, Terry, Aisen, & Hill, 1987), and even in previously asymptomatic individuals (Brewer, Turkay, & Yuzbasiyan-Gurkan, 1994; Glass, Reich, & DeLong, 1990). The frequent presence of concomitant neurologic symptoms should be considered in treating psychotic symptoms with neuroleptics and certain atypical antipsychotics, which could contribute to the worsening of extra-pyramidal signs. Some cases evidenced a resolution of psychosis with chelation therapy (Modai, Karp, Liberman, & Munitz, 1985), other ones showed the worsening of psychotic symptoms during penicillamine titration (Grover, Sarkar, Jhanda, & Chawla, 2014; McDonald & Lake, 1995).

As stated above, several symptoms of depression overlap with neurologic symptoms of WD, thus it could be argued that chelating agents might determine a psychopathological improvement via neurologic positive changes, as shown by some reports (Brewer, 1994; Chan et al., 2005; Krishnakumar & Riyaz, 2005; Stiller et al., 2002; Walter & Lyndon, 1997). Neuropsychiatric symptoms were shown to improve with zinc therapy in all cases in the study by Medici et al. (2006).

Liver transplantation was both reported as useful (Sorbello, Riccio, Sini, Carta, & Demelia, 2011) and unbeneficial for psychiatric symptoms in the course of WD, so that it was stated that psychopathological symptoms should be considered as a partial contraindication for liver transplantation (Medici et al., 2005).

The use of psychotropic medications for psychiatric symptoms in WD

Lithium is often the preferred medication in treatment of mania and hypomania in WD, because it is not metabolized by the liver (Loganathan et al., 2008; Rybakowski et al., 2013; Woerwag-Mehta et al., 2011). However, hepatic failure and the possibility of tubular acidosis in some subjects hardly challenge the therapeutic choices, preventing the use of lithium, valproate, and carbamazepine (Varghese, Narayanan, & Dinesh,

2008). Moreover, lithium might worsen tremor and impair cognition, and copper chelation therapy has only been shown to reduce manic symptoms (Loganathan et al., 2008; Machado et al., 2008; Mitra et al., 2014). Some authors reported a good response of manic symptoms with atypical antipsychotics, such as olanzapine (Litwin, Dzieżyc, Karliński, Szafrański, & Członkowska, 2016), and quetiapine (Kulaksizoglu & Polat, 2003; Zimbrean & Schilsky, 2015). Traditional neuroleptics, such as haloperidol, could determine the occurrence of extrapyramidal symptoms in individuals both with BD (Varghese et al., 2008) and with psychotic symptoms in WD (Nayak et al., 2012). Risperidone carries the same risk (Vaishnav & Gandhi, 2013). Changes in dopamine D2 receptors (reduced density in striatum) and disruption of dopaminergic neurotransmission have been observed in WD (Litwin, Chabik, & Członkowska, 2013; Litwin, Gromadzka, Samochowiec, Grzywacz, Członkowski, & Członkowska, 2013), and these modifications could be related with early neurological deterioration, often irreversible, associated with the use of antidopaminergic drugs, such as neuroleptics (Litwin et al., 2015).

A good response to depression has been obtained with SSRIs (escitalopram and sertraline) (Chakraborty et al., 2015). SSRIs (fluoxetine), along with chelating agents, have also been shown to be safe and rapidly acting in obsessive-compulsive disorder in WD (Kumawat et al., 2008; Sahu et al., 2013). Acute dystonia was reported following treatment with tricyclic antidepressant (clomipramine) (Litwin, Chabik, et al., 2013).

Few reports showed the efficacy of electro-convulsive therapy (ECT) on catatonia (Sahoo et al., 2010), psychosis (Rodrigues, Dalgalarrondo, & Banzato, 2004; Shah & Kumar, 1997; Vaishnav & Gandhi, 2013), and severe depression (Negro & Louzá Neto, 1995).

To our best knowledge, no study reported the treatment of psychiatric symptoms in WD with individual or family psychotherapy. Because treatments often begin at a young age and have to be undertaken lifelong, patient's compliance and education are essential requisites for the survival, and it was suggested that psychoeducation could be useful in management of WD, improving awareness and adherence to treatment (Chahine & Chemali, 2006).

Conclusions

A high frequency of psychiatric disorders was confirmed in WD that may both present as psychic disturbances in previous asymptomatic individuals, and as a psychiatric symptomatology in the course of disease. A pure psychiatric presentation is rare, confounding, and often characterized by mild psychic disturbances, such as poor scholastic performance, or changes in behaviour. More frequently, some neurological signs can be traced together with psychiatric disorders. Because of the relative rarity of WD, cohort studies were generally carried out on small samples, and psychiatric assessment on onset symptoms was mostly clinical and retrospective.

Psychiatric comorbidity in WD is characterized by a high prevalence of mood disorders, and particularly interesting is the association with bipolar spectrum disorders. Such an association explained the frequent report of psychopathological features like mood swings, irritability, over-activity, and aggressiveness, and is related with neurological symptoms and abnormal imaging findings on MRI and SPECT. Moreover, suicidal risk should not be under-estimated in persons with WD suffering from psychiatric disorders.

Quality-of-life and psychosocial outcomes are shown to be worse than those in the general population, and related with both neurological disability and psychiatric comorbid disorders. However, it should be underlined that specific therapies for WD lead to a good life expectancy, and adherence to medicaments and clinical monitoring warrant excellent outcomes. Compliance with therapies represent nowadays one of the major challenges for clinicians who deal with WD, and a multidisciplinary approach, including a hepathologic, neurologic, and psychiatric careful evaluation represents the best option for managing this chronic disease. Moreover, education of those affected and their relatives could be implemented to improve the insight of disease and awareness of the need for lifelong therapies.

Further research is needed to clarify the pathogenesis of psychiatric disturbances in WD, and to lead clinicians to establish individually tailored treatments.

Disclosure statement

No potential conflict of interest was reported by the authors.

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