Neuroendocrinology Letters Volume 42 No. 3 2021
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

Management of 201 individuals with emotionally unstable personality disorders: A naturalistic observational study in real-world inpatient setting

Homayun Shahpesandy[1], Rosemary Mohammed-Ali[1], Michael Oakes[2], Tarik Al-Kubaisy[3], Anna Cheetham[4], Moses Anene[5]

1 The Hartsholme Centre, Long Leys Road, Lincoln, LN1 1FS, Lincolnshire NHS Foundation Trust, United Kingdom
2 University of Wolverhampton- Research Institute of Information and Language Processing- Reader in Computational Linguistics- Wolverhampton- United Kingdom, Research Institute of Information and Language Processing- Reader in Computational Linguistics, Wolverhampton, United Kingdom
3 Early Intervention Psychosis Team; Meridian House, Normanby Road, Scunthorpe, North Lincolnshire, DN15 8QZ, Rotherham, Doncaster and South Humber NHS Foundation Trust, United Kingdom
4 Sycamore Centre, Beaconfield Site, Beacon Lane. Grantham NG31 9DF. Lincolnshire NHS Partnership Foundation Trust, United Kingdom
5 Connolly Ward Peter Hodgkinson Centre, Greetwell Road, Lincoln, LN2 5UA, Lincolnshire NHS Partnership Foundation Trust, United Kingdom

Correspondence to: Dr Homayun Shahpesandy, MD, MSc, PhD.
The Hartsholme Centre, Long Leys Road, Lincoln, LN1 1FS, Lincolnshire NHS Partnership Foundation Trust, United Kingdom.
tel.: 0044 1522307332;
e-mail: Shahpesandy@hotmail.com, homayun.shahpesandy@nhs.net

Submitted: 2021-05-09 Accepted: 2021-06-03 Published online: 2021-06-03

Key words: **emotionally unstable personality disorder; borderline personality disorder; trauma; co-morbidity; symptomatology; pharmacotherapy**

Neuroendocrinol Lett 2021; **42**(3):200–212 **PMID:** XXXXXXXX NEL420321XXX

Abstract

BACKGROUND: Emotionally unstable personality disorder (EUPD) is a challenging condition with a prevalence of 20% in inpatient services. Psychotherapy is the preferred treatment; nevertheless, off-license medications are widely used.
OBJECTIVES: To identify socio-demographics, clinical and service-delivery characteristics of people with EUPD admitted to inpatient services between 1st January 2017 and 31st December 2018.
METHODS: A retrospective review using data from patients' records. Individuals, age 18–65 were included. Statistical analysis was conducted by the Mann-Whitney-Wilcoxon test and Chi-squared test with Yates's continuity correction.
RESULTS: Of 1646 inpatients, 201 (12.2%); had the diagnosis of EUPD; 133 (66.0%) women, 68 (44.0%). EUPD was significantly ($P < .001$) more prevalent in women (18.2%) than men (7.4%). EUPD patients were significantly ($P < .001$) younger (32.2 years) than patients without EUPD (46 years), and had significantly ($P < .001$) more admissions (1.74) than patients without EUPD (1.2 admission). 70.5% of patients had one and 17.0% two Axis-I psychiatric co-morbidities. Substance use was significantly ($P < .001$) more often in men (57.3%) than in women (28.5%). Significantly ($P = 0.047$) more women (68.4%) than men (53.0%) reported sexual abuse. 87.5% used polypharmacy. Antidepressants were significantly (P = 0.02) often prescribed to women (76.6%) than men (69.1%). Significantly (P = 0.02)

more women (83.5%) than men (67.6%) were on antipsychotics. 57.2% of the patients were on anxiolytics, 40.0% on hypnotics and 25.8% on mood stabilisers.
CONCLUSION: EUPD is a complex condition with widespread comorbidity. The term EUPD, Borderline Personality Disorder is unsuitable, stigmatising and too simplistic to reflect the nature, gravity and psychopathology of this syndrome.

INTRODUCTION

EUPD has an estimated prevalence of 1% to 2% in the general population; and 10% in community psychiatric services (APA, 2001). Data on the prevalence of EUPD in inpatient services differ; some studies (Doering, 2019) estimate it between 9% and 14%, however, others (Gunderson *et al.* 2018) report higher figures between 15% and 28%. This disorder is largely diagnosed in women, with an estimated female to male ratio of 3:1(Oldham, 2005).

According to ICD 10 (WHO, 1992), the key feature of the EUPD is emotional instability; in addition, the patient's own self-image, and internal preferences (including sexual) are often disturbed. There are usually chronic feelings of emptiness. A liability to become involved in intense and unstable relationships may cause repeated emotional crises and may be associated with excessive efforts to avoid abandonment and a series of suicidal threats or acts of self-harm. The diagnosis of EUPD in the Statistical Manual of Mental Disorders, Fifth Edition (APA, 2013), is based on the evidence of (1) a pervasive pattern of instability of interpersonal relationships, self-image, and affects, and (2) marked impulsivity beginning by early adulthood and present in a variety of contexts, including frantic efforts to avoid real or imagined abandonment,; unstable and intense relationships; identity disturbance; impulsivity that is potentially self-damaging in at least two of the following areas such as spending, sex, substance abuse, reckless driving, binge eating; recurrent suicidal gestures or threats, or self-mutilation; marked mood reactivity; chronic feelings of emptiness; frequent displays of inappropriate or intense anger; and stress-related paranoid ideation or severe dissociative symptoms.

The aetiology of EUPD incorporates the conception of a biological predisposition along with psychological and environmental factors. There is a sufficient body of evidence of genetic factors contributing to the progress of EUPD (Torgersen *et al.* 2008). Patients with EUPD report many negative life events, including a history of childhood sexual or/and physical abuse (Paris, 2007). Childhood sexual abuse is an important risk factor for EUPD and predicts more severe clinical presentation and poorer prognosis (de Aquino Ferreira, *et al.* 2018). Therefore, an interaction between biological and psychosocial factors will probably provide the best explanation of how the EUPD develops (Gabbard, 2005).

People with EUPD are at an increased risk of suicide (Cheng *et al.* 1997), with up to 85% engaging in attempting suicidal behaviours (Timäus *et al.* 2019). The rate of completed suicide has been estimated to be approximately 10% (Oldham, 2006), however, recent data (Temes *et al.* 2019) report lower, around 6% of suicide rate. There is a well-documented association between EUPD and other psychiatric conditions (Wetterborg *et al.* 2015). Because of a considerable overlap between EUPD and mood disorders, it has been suggested that EUPD should be classified in the context of mood disorders. Likewise, its association with past trauma, and similarities of its presentation with post-traumatic stress disorder (PTSD), has led some to suggest that EUPD should be regarded as a form of delayed PTSD (Yen & Shea, 2001).

In terms of management of the EUPD, in the United Kingdom, no medication is particularly licensed for EUPD, and the National Institute for Health and Clinical Excellence (NICE) recommends medication only for co-morbid mental disorders (NICE, 2009). The American Psychiatric Association's practice guidelines (APA, 2005) in line with NICE recommend psychotherapy as the main treatment; however, in contrast to NICE, APA considers pharmacotherapy as an adjunctive component of treatment that targets state symptoms during periods of acute decompensation. Earlier findings (Lieb *et al.* 2010) suggested that antidepressants such as selective serotonin reuptake inhibitors (SSRI's) and serotonin and noradrenalin reuptake inhibitors (SNRI's) are being effective for treatment of aggression, irritability, depression and self-mutilation. Also, drugs such as mood stabilisers (MS's) and second-generation antipsychotics (SGAs) (Bridler *et al.* 2015, Paolini *et al.* 2017) may be effective for symptoms of anger, aggression, impulsivity and disruptive behaviours. Notwithstanding recent data demonstrate limited efficacy of psychotropic drugs (Stoffers-Winterling *et al.* 2020), especially on core EUPD symptoms such as chronic feelings of emptiness, identity disturbance and abandonment (Bozzatello *et al.* 2020).

METHODS AND OBJECTIVES

Individuals aged 18-65 with a diagnosis of EUPD, using the ICD-10 code of F60.30 and F60.31 (WHO, 1992) admitted to Lincolnshire NHS Foundation Trust (LPFT) inpatient services between 1st January 2017 and 31st December 2018 were included. Individuals with organic mental disorders and co-morbid schizophrenia-spectrum, major depressive disorder and bipolar affective disorders were excluded. This is a retrospective cohort examination, and data for the study were collected from patients' medical records.

Tab. 1. Demographic

	Total (n=201)	Women (n=133)	Men (n=68)
Ethnicity			
White British	198 (98.5%)	130 (98.0%)	68 (100.0%)
Another White	3 (1.5%)	3 (2.0%)	0
Family status			
Single	136 (67.6%)	85 (64.0%)	51 (75.0%)
Married & cohabited	42 (20.8%)	34 (25.5%)	8 (11.7%)
Divorced & separated	21 (10.4%)	13 (10.0%)	9 (13.2%)
Widow	1 (0.5%)	1 (1.0%)	0.0%
Education			
Basic	149 (74.0%)	96 (72.0%)	53 (78.0%)
Higher	31 (15.4%)	23 (17.3%)	8 (11.7%)
Academic	13 (6.4%)	10 (7.5%)	3 (4.4%)
Not stated	8 (4.0%)	4 (2.0%)	4 (6.0%)
Employment			
Employed	48 (24.0%)	34 (25.6%)	14 (20.6%)
Unemployed	152 (75.6%)	98 (73.6%)	54 (79.4%)
Retired	1 (0.5%)	1 (0.75%)	0
Sexual orientation			
Heterosexual	160 (79.6%)	103 (77.4%)	57 (83.8%)
LGBT	26 (13.0%)	21 (15.7%)	5 (7.3%)
Not stated	15 (7.5%)	9 (7.0%)	6 (9.0%)

Tab. 2. Hospital admission

	Total (n=201)	Women (n=133)	Men (n=68)
Average number of admissions/two years	1.7 times	1.5 times	2.0 times
One admission	116 (57.7%)	82 (61.6%)	34 (50.0%)
Two admissions	48 (23.8%)	32 (24.0%)	16 (23.5%)
3≥ admissions	37 (18.4%)	19 (14.2%)	18 (26.4%)
LOS	96 days	123.3 days *P=0.005	42.8 days

Statistical analysis was conducted by the Mann-Whitney-Wilcoxon test and Chi-squared test with Yates's continuity correction.

The principal objective of this paper is to identify socio-demographics, clinical and service-delivery characteristics of persons with EUPD.

RESULTS

Of 1646 individuals (731 women, 915 men), 267 (16.2%) were initially identified with EUPD, ICD 10, F60.30/31. 66 (24.7%) were excluded; 35 (13.1%) with co-morbid schizophrenia-spectrum disorders, and 31 (11.6%) with bipolar affective and recurrent depressive disorders. 201 (12.2%); 133 women (66%) and 68 men (34%) were included to the observation. EUPD was significantly (P < .001) more frequent in women (18.6%); than in male patients (7.4%). Moreover, significantly (P < .001) more women (89.5%) than men (56%) were diagnosed with EUPD, borderline type. The impulsive type of the EUPD was in contrast diagnosed in only 10.5% of women but 44% of men.

When comparing the cohort of patients with EUPD with those without EUPD; EUPD patients were significantly (P < .001) younger (32.2 years) than those without EUPD (46 years). Moreover, individuals with EUPD had significantly (P < .001) more admissions (1.74) than those without EUPD (1.2 admission). The average length of stay (LOS) for patients with EUPD was 96 days and 85.6 days for those without EUPD.

Tab. 3. Self-harm, suicide attempts, attendances at the A&E, and suicide

	Total (n=201)	Women (n=133)	Men (n=68)
Any suicide attempt	170 (84.5%)	113 (85%)	57 (84%)
One attempt	63 (31.3%)	41 (31%)	22 (32.5%)
Two attempts	31 (15.4%)	20 (15%)	11 (16%)
3≥ attempts	76 (37.8%)	52 (39%)	24 (35.3%)
Any attendance at A& E	168 (83.5%)	112 (84.2%)	56 (82.3%)
One attendance at A & E	68 (33.8%)	48 (36%)	20 (29.5%)
Two attendances at A & E	33 (16.4%)	21 (15.8%)	12 (17.6%)
3≥ attendances	67 (33.3%)	43 (32.3%)	24 (35.3%)
Death by suicide	4 (2.0%)	1 (0.75%)	3 (4.4%)
Overdose	3 (1.5%)	1 (0.75%)	2 (2.9%)
Hanging	1 (0.5%)	0	1 (1.5%)

Tab. 4. Early childhood trauma

	Total (n=201)	Women (n=133)	Men (n=68)
Any abuse	179 (89.0%)	124 (93.2%)	55 (81.0%)
Physical abuse	52 (26.0%)	33 (25.0%)	19 (28.0%)
Sexual abuse	127 (63.2%)	91(68.4%) *$P = 0.047$	36 (53.0%)

Tab. 5. Psychiatric and medical co-morbidities

	Total (n=201)	Women (n=133)	Men (n=68)
Physical co-morbidity	105 (52.2%)	72 (54.0%)	33 (48.5%)
1 psychiatric co-morbidity	142 (70.5%)	93 (70.0%)	49 (72.0%)
2 psychiatric co-morbidity	34 (17.0%)	23 (17.2%)	11 (16.2%)
Substance-use disorders	71 (35.3%)	38 (28.5%)	39 (57.3%) *$P < .001$
Alcoholism	30 (15.0%)	20 (15.0%)	10 (14.5%)
Polysubstance abuse	41 (20.4%)	18 (13.5%)	29 (42.6%) *$P < .001$
Neurotic & stress-related disorders	63 (31.3%)	47 (35.3%)	16 (23.5%)
Eating disorders	13 (6.5%)	12 (9.0%)	1 (1.5%)
LD	9 (4.5%)	8 (6.0%)	1 (1.5%)
ASD	4 (2.0%)	2 (1.5%)	2 (3.0%)

Patient demographics

Of 201, 198 (98.5%) patients were White British and three (1.5%) of other White origin. 67.6% were single, 20.8% married (relatively more married women 25.5%, than men 11.7%), 10.4% were separated and/or divorced, and one (0.5%) patient was widowed. With regards to education; 74.0%, had basic; 15.4% higher, and 6.4% academic education. In terms of employment; 24.4% were employed; and 75.6% were unemployed. 79.5% identified themselves as heterosexuals; 13.0% as lesbian, gay, bisexual or transsexual (LGBT), and 7.5% did not disclose their sexual orientation; table 1.

Admission and length of stay

The average number of admissions during the two-year period was 1.7. 57.7% of patients had one admission, 23.7% two and 18.4% 3≥ admissions. The average LOS for the whole group was 96 days, nonetheless, women had significantly ($P = 0.005$) longer (123.3 days) admission than men (42.8 days); table 2.

Tab. 6. Pharmacotherapy

	Total (n=201)	Women (n=133)	Men (n=68)
No medications used	5 (2.5%)	2 (1.5%)	3 (4.5%)
On medication	196 (97.5%)	131 (98.5%)	65 (95.5%)
Monotherapy	20 (10.0%)	13 (9.7%)	7 (10.3%)
Polypharmacy	176 (87.5%)	118 (88.7%)	58 (85.3%)
Two medications	37 (18.4%)	21 (15.7%)	16 (23.5%)
Three medications	43 (21.3%)	29 (21.8%)	14 (20.5%)
4≥ medications	96 (47.7%)	68 (51.0%)	28 (41.2%)
ANTIDEPRESSANTS			
One AD	149 (74.0%)	102 (76.6%) *P = .026	47 (69.0%)
Two AD's	21 (10.5%)	15 (11.0%)	6 (9.0%)
TCA	2 (1.0%)	2 (1.5%)	0
SSRI'	68 (34.0%)	40 (30.0%)	28 (41.2%)
SNRI's	40 (20.0%)	34 (25.6%) *P = .002	6 (9.0%)
Mirtazapine	39 (19.4%)	26 (19.5%)	13 (19.0%)
Antipsychotics			
One AP's	157 (78.0%)	111 (83.5%) *P = 0.02	46 (67.6%)
Two AP's	34 (17.0%)	25 (19%)	9 (13.2%)
FGA	20 (10.0%)	16 (12.0%)	4 (6.0%)
Haloperidol	6 (3.0%)	4 (3.0%)	2 (3.0%)
Trifluperazine	1 (0.5%)	1 (0.75%)	0
Zuclopenthixol	8 (4.0%)	8 (6.0%)	0
Chlorpromazine	5 (2.5%)	3 (2.2%)	2 (3.0%)
SGAs	137 (68.0%)	95 (71.4%) *P = 0.035	42 (61.8%)
Amisulpride	6 (3.0%)	4 (3.0%)	2 (3.0%)
Aripiprazole	33 (16.4%)	29 (22.0%) *P = .002	4 (6.0%)
Clozapine	3 (1.5%)	2 (1.5%)	0
Olanzapine	24 (12.0%)	13 (9.8%)	11 (16.2%)
Quetiapine	58 (29.0%)	43 (32.3%)	15 (22.0%)
Risperidone	14 (7.0%)	4 (3.0%)	10 (14.7%)
Depot AP's	15 (7.5%)	10 (7.5%)	5 (7.3%)
Aripiprazole	2 (1.0%)	1 (0.75%)	1 (1.5%)
Paliperidone/Risperdal Consta	5 (2.5%)	0	3 (4.4%)
Haloperidol	1 (0.5%)	0	1 (1.5%)
Zuclopenthixol	7 (3.5%)	7 (5.2%)	0
ANXIOLYTICS			
One anxiolytic	115 (57.2%)	75 (56.4%)	40 (58.8%)
Two anxiolytics	34 (17.0%)	24 (18.0%)	10 (14.7%)
BDZ's	82 (40.7%)	53(40.0%)	29 (42.6%)
Clonazepam	14 (7.0%)	12 (9.0%)	2 (3.0%)
Diazepam	33 (16.4%)	21 (15.8%)	12 (17.5%)

	Total (n=201)	Women (n=133)	Men (n=68)
Lorazepam	35 (17.4%)	20 (15.0%)	15 (22.0%)
Pregabalin	33 (16.4%)	22 (16.5%)	11 (16.2%)
HYPNOTICS			
Any hypnotic drug	81 (40.3%)	53 (40.0%)	28 (41.2%)
BDZ's hypnotics	5 (2.5%)	5 (4.0%)	0
Nitrazepam	4 (2.0%)	4 (3.0%)	0
Temazepam	1 (1.0%)	1(1.0%)	0
'Z' hypnotics	50 (25.0%)	29 (22.0%)	21 (31.0%)
Zopiclone	46 (23.0%)	25 (19.0%)	21 (31.0%)
Zolpidem	4 (2.0%)	4 (3.0%)	0
Other hypnotics	26 (13.0%)	19 (14.2%)	7 (10.3%)
Melatonin	2 (1.0%)	2 (1.5%)	0
Promethazine	24 (12.0%)	17 (13.0%)	7(10.3%)
MOOD STABILISERS			
Any mood stabiliser	52 (26.0%)	36 (27.0%)	16 (23.5%)
Lithium	4 (2.0%)	3 (2.2%)	1 (1.5%)
Antiepileptic mood stabilisers	48 (24%)	33 (25.0%)	15 (22.0%)
Carbamazepine	4 (2.0%)	2 (1.5%)	2 (3.0%)
Gabapentin	2 (1.0%)	1 (0.7%)	1 (1.5%)
Lamotrigine	29 (14.5%)	20 (15.0%)	9 (13.2%)
Topiramate	5 (2.5%)	5 (4.0%)	0
Valproate	8 (4.0%)	5 (4.0%)	3 (4.4%)

History of self-harm and suicide

84.5% of patients had a history of self-harm and suicidal behaviours prior to their admission, which required treatment at the accident and emergency (A&E) department. Of 201 patients, four (2.0%) died of suicide; drug overdose was the method of suicide in three patients, and strangulation in one patient; table 3.

Early childhood trauma

Childhood trauma was reported by 179 (89.0%) patients; 26.0% reported physical abuse, whereas sexual abuse was reported by 63.2%, however, significantly (P = 0.047) more often by women (68.4%) than men (53.0%); table 4.

Clinical manifestation and co-morbidities

In terms of medical co-morbidities; 52.2% of patients had at least one medical co-morbidity. However, 70.5% have had at least one and 17.0% two axis-I psychiatric co-morbidities. Substance abuse was detected in 35.3% of all, but significantly (P < .001) more often in men (57.3%) than in women (28.5%). Similarly, multiple substance abuse was significantly (P = 0.001) more prevalent in men (42.6%) than in women (13.5%). Neurotic disorders were diagnosed in 31.3%, but more frequently in women (35%) than men (23.5%). Eating disorders were identified in 6.5% (9.0% of women, 1.5% of men), mild learning disabilities (LD) in 4.5% and autistic-spectrums disorders (ASD) in 2.0%; table 5.

Psychopharmacological management

Of 201 patients, 196 (97.5%) were prescribed a medication; 20 (10.0%) were on monotherapy, but 176 (87.5%) on polypharmacy; 37 (18.4%) were on two drugs, 43 (21.3%) on three, and 96 (47.7%) on 4≥ medications concomitantly. More women (51.0%) than men (41.2%) used 4≥ medications.

In terms of antidepressants (AD's), 74.0% of patients were on one, and 10.5% on two AD's concomitantly. AD's, were significantly (P=.26) more often prescribed to women (76.6%) than men (69.0%). SSRI's were the most common AD's prescribed in 34.0% of patients, followed by SNRI's (20.0%) and Mirtazapine (19.4%). Furthermore, SNRI's were significantly (P = 0.002) more often prescribed to women (25.6%) than men (9.0%). Tricyclic AD's (TCA) plus SSRI's or SNRI's and Mirtazapine plus SSRI's/SNRI's were the most common combination of AD's.

Similarly, 78% of all patients, but significantly (P = 0.02) more women (83.5%) than men (67.5%)

were on AP's. Moreover,17.0% of patients were on two AP's. Whilst 10.0% used first generation antipsychotics (FGA), though, 68.0% were prescribed SGA's, which were significantly (P = 0.035) more often utilised by women (71.4%) than men (62%). Amongst the SGAs, Quetiapine (29.0%), aripiprazole (16.4%) and olanzapine (12.0%) were the most frequently prescribed drugs; nonetheless, aripiprazole was significantly (P = .002) more prescribed to women (22.0%) than to men (6.0%). Additionally, 7.5% of the patients were prescribed depot AP's; in 5.5% in combination with an oral AP's.

In terms of anxiolytics, 57.2% were prescribed at least one and 17.4% two anxiolytic drugs. Benzodiazepines (BDZ's) were the most common anxiolytics (40.7%) followed by pregabalin (16.4%).

As far as the hypnotics are concerned, eighty-one patients (40.3%) were prescribed a hypnotic medication; of whom 50 (25.0%) were prescribed 'z'-hypnotics (zolpidem and zopiclone), five (2.5%) BDZ's hypnotics, and 26 (13.0%) other hypnotics.

With regards to the MS's; 52 (26.0%) patients were prescribed MS's; four (4.0%) were prescribed lithium and 48 (24.0%) antiepileptic drugs, mostly lamotrigine (14.5%); table 6.

Psychological interventions

47.7% of patients were provided psycho-education on their diagnosis and treatment alternatives; 43.2% received structured dialectical behavioural therapy (DBT).

DISCUSSION

In our study, of 1646 inpatients, 201 (12.2%) were diagnosed with EUPD, which correspond to findings of Doering, 2019 who reports the prevalence of EUPD among psychiatric inpatients between 9% and 14%. In our examination EUPD was significantly (P < .001) more prevalent in women (18.2%) than men (7.4%), and of 221 patients, 133 (66.0%) were female, which indicates a female to male ratio of 2:1. Furthermore, in our cohort, significantly (P < .001) more women (89.5%) than men (56.0%) were identified with EUPD, borderline type. Our results are comparable to results of Tadić *et al.* 2009 and Sher, *et al.* 2019, but dissimilar with outcomes of Oldham, 2005 estimating female to male ratio 3:1, or Koch et al, 2019 suggesting an even higher ratio of 4:1. It is assumed that EUPD is largely (75%) diagnosed in women, however, there is no significant difference in the lifetime prevalence of this disorder between men and women. This discrepancy of gender prevalence, therefore is anticipated to be resulting from the fact that women with EUPD are more likely to contact services and seek treatment than men (Canadian Agency for Drugs and Technologies in Health, 2017).

Our patient group consisted of mostly single, young individuals, with the average age of 32.2 years; unambiguously of White background. Our results are comparable with literature signifying people with EUPD consist of young single individuals of White background (Oldham, 2006, Yen *et al.* 2021).

The average number of admission for our patients was 1.7 admissions, and the average LOS was 96 days. Nonetheless, women had significantly (P = .005) longer (123.3 days) LOS than men (42.8 days). Data from Austria (Koch *et al.* 2019), Australia (Wong & Tye, 2005), Germany (Kaess *et al.* 2017), and United States (Patel *et al.* 2019) unanimously associate the diagnosis EUPD with prolonged inpatient treatment, mainly because of high risk of suicide. 84.5% of our subjects had a history of self-harm and/or suicide attempts prior to their admission. This is almost identical with the findings of Soloff *et al.* 2002 who reported suicidal behaviours in 84% of patients with EUPD. Likewise, our outcomes are consistent with previous findings of Hull, *et al.* 1996, suggesting suicidal behaviours were the most common triggers leading to patients' admission. Opinions regarding hospitalisation of people with EUPD vary amongst professionals. Nonetheless, the consensus is that hospital resources should be used to carry out specific aspects of treatment that cannot be provided in the community (Paris, 2002, Bateman & Fonagy, 1999). Improved access to psychological therapies can reduce inpatient admissions, and fewer prescriptions for antidepressants, resulting in an estimated 9%-53% reductions in short, medium and long-term costs. Furthermore, if patients with personality disorders are treated in the community, i.e. under the crisis and home treatment teams instead of hospital, this would have reduced the LOS and hospital cost up to £600 per admission (McCrone *et al.* 2008).

We have found widespread co-morbidities amongst our patients; 70.5% had at least one and 17% two Axis-I co-morbidities. In a similar study, Timäus *et al.* 2019 reported that 79.3% of the EUPD inpatients had at least one, 46.0% two and 28.7% three or more psychiatric co-morbidities. There is a body of evidence (Wetterborg *et al.* 2015) reporting a prevalent co-morbidity amongst people with EUPD, and individuals with EUPD being twice as likely to receive a diagnosis of three or more Axis-I disorders, compared with those without EUPD (Zimmerman & Mattia, 1999). Substance abuse was the most common co-morbidity detected in 35.0% of our patients, but significantly (P < .001) more often in men (57.0%) than in women (28.5%). Likewise, poly-substance abuse was significantly (P = 0.001) more widespread in men (42.6%) than in women (13.5%). Evidence indicate higher levels of alcohol and drugs abuse in individuals with EUPD (Tadić *et al.* 2009, Sher *et al.* 2019). Neurotic and stress-related mental disorders were observed in 31.3% of all, but relatively more in women (35%) than men (23.5%). Our findings mirror previous research (Timäus *et al.* 2019, Tadić *et al.* 2009, McCormick *et al.* 2007) reporting stress-related disorders are amongst the most common

co-morbidities found in people with EUPD. Eating disorders were identified in 9% of women and 1.5% of men. Tadić *et al.* 2009 reported eating disorders in 13% of their sample. 4.5% of our subjects had mild LD. Data from the Netherlands (Wieland *et al.* 2015) reported higher frequency of personality disorders in people with borderline intellectual functioning. ASD were detected in 2.0% of our patients, which is relatively lower in comparison to literature that estimates ASD in approximately 10% of people with EUPD (Bringmann & Maidman, 2019). Besides, evidence suggests that EUPD patients have elevated autistic traits, suggesting an overlap between EUPD and ASD (Dudas *et al.* 2017). The presence of ASD traits has also been associated with higher suicidality in patients with EUPD (Chabrol & Raynal, 2018). A recent study from the UK (Fok *et al.* 2019) examining records of 7677 individuals with personality disorders concluded that people with personality disorders, compared to general population had an increased admission rate for several conditions, including cardiovascular, respirator, digestive, nervous and musculoskeletal system disorders. The extensive co-morbidity among individuals with EUPD results in a substantial increase and extensive use of services (Cailhol *et al.* 2015, Bender *et al.* 2006) resulting in higher total healthcare costs (Rendu *et al.* 2002) 46 compared with people with other personality disorders; major depression, or general anxiety disorder (Soeteman *et al.* 2008).

Almost 90% of our patients reported a history of childhood trauma, whereas the history of sexual abuse was reported, significantly (P = .047) more by women (68.4%) than men (53.0%). Childhood sexual abuse has been reported in 40% to 70% of inpatients with EUPD (Zanarini *et al.* 2006). The history of childhood sexual abuse is strongly associated with the higher risk of suicidal behaviours, increased hostility, severity of the illness and feelings of hopelessness (Brodsky *et al.* 1997, Soloff *et al.* 2002, Yen *et al.* 2021). Additionally, the history of childhood abuse has been linked with a 5-fold increase in the rate of lifetime suicide attempts relative to individuals with no history of abuse (Kaplan *et al.* 2016). In a systematic review of 37 studies, with a total of 253719 participants, Hughes *et al.* 2017 demonstrated that individuals with a history of adverse childhood experiences (ACEs) were at higher risk of mental health problems, compared with individuals with no ACEs. Similarly, a meta-analysis of 97 studies comparing persons with EUPD to individuals with other mental disorders and controls revealed that people with EUPD were 3.15 times more likely to report ACEs than other psychiatric groups, and 13.9 times more likely to report ACEs than non-clinical controls (Porter *et al.* 2020).

In our study, 4.4% of men, and 0.75% of women died because of suicide. In a 24-year prospective study of 290 patients with EUPD and 72 non-EUPD cohort, Temes *et al.* 2019 reported a total of 5.9% of borderline patients and 1.4% of control subjects died by suicide. Risk factor for completed suicide in people with EUPD include older age, previous suicide attempts, co-morbid alcoholism or substance abuse (Brodsky *et al.* 1997), and interpersonal problems (Gvion & Levi-Belz, 2018). Moreover, it has been reported that men with EUPD are at higher risk of dying by suicide than women (Sher *et al.* 2019).

In our study, 87.5% of patients were on polypharmacy; 18.4% were on ≥ 2 drugs, 21.3% on ≥ 3 drugs and 47.7% on ≥ 4 drugs. Our results are in line with literature (Aguglia *et al.* 2019) reporting a widespread polypharmacy among people with EUPD. A study from Italy (Paolini *et al.* 2017) reported 83.5% of their inpatients with EUPD were on polypharmacy. Data from the European Drug Safety Project (Bridler *et al.* 2015) analysing information on medication in 2195 inpatients with EUPD found that 90% received at least one, 80% ≥ 2 and 54% ≥ 3 psychotropic medications concomitantly. In a naturalistic study of 226 individuals with EUPD Pascual *et al.* 2010 reported that 97.4% of the patients were on medications; 56% taking ≥ 3 drugs and 30% ≥ 4 drugs.

In our study 74.0% of patients were on ADs, and 10.5% on two AD's. Moreover, AD's were significantly (P = .02) more often prescribed to women (76.6%) than men (69.0%). Our findings are almost identical with the findings of Bridler *et al.* 2015 who reported 70% of patients with EUPD were medicated with AD's. In our study, SSRI's (34%) were the most common group of AD', followed by SNRI's (20%) and mirtazapine (25%). Furthermore, SNRI's were significantly (P = 0.002) more often prescribed to female patients (25.6%) than their male counterparts (9.0%). In similar study, Timäus *et al.* 2019 reported SSRI's (52.3%) being the most frequent medication group, followed by mirtazapine (31.8%) and TCA's (13.6%).

Correspondingly, 78.0% of patients were on AP's, but significantly (P = 0.02) more women (83.5%) than men (67.5%). Our outcomes are comparable with the findings of Bridler *et al.* 2015 who reported AP's use in 70% and Paolini *et al.* 2017 in 78.7% of individuals with EUPD. We found Quetiapine (29.0%), aripiprazole (16.4%) and olanzapine (12.0%) the most common drugs used by our subjects. Nevertheless, in our study, aripiprazole was significantly (P = .002) more often prescribed to women (22.0%) than to men (6.0%). A study from Italy, Aguglia *et al.* 2019 reported a similar trend, indicating olanzapine, quetiapine and aripiprazole being the most common antipsychotics prescribed for people with EUPD. Similarly, a study from Austria (Riffer, *et al.* 2019) found quetiapine the most common SGA prescribed in EUPD. Strong evidence supporting use of SGA in EUPD is lacking (Wasylyshen & Williams, 2016), although they have proven to be efficacious in managing anger, aggression (Tadić *et al.* 2009, Sher *et al.* 2019) and in reducing cognitive-perceptual symptoms (Vita *et al.* 2011). Amongst SGA aripiprazole seems

to be having a much larger effect on anger than another AP's (Mercer *et al.* 2009).

7.5% of our patients were prescribed a depot AP's; 5.5% in combination with another AP's. Evidence on use and efficacy of long acting AP's in people with EUPD is vague. Though, in a six-month small study of 12 patients with severe EUPD Díaz-Marsá *et al.* 2008 report a significant clinical and functional improvement in patients. Likewise, in a 12-week study of 16 patients with EUPD treated with paliperidone palmitate Palomares *et al.* 2015 reported a significant decrease in impulsivity, disruptive behaviour and improvement in patients' psychosocial functioning. In another six-month study of 49 patients with EUPD treated with long acting risperidone Carrasco *et al.* 2012 reported a significant decrease in symptoms of anxiety and aggression as well as improvement in patients' level of psychosocial functioning. In a case-study of a 40-year old patient suffering from EUPD with co-morbid bipolar disorder, and substance abuse, Martínez and Caballero, 2017 reported the patient was successfully treated with aripiprazole long acting injection.

Likewise, 57.2% of the patients in our study were on at least one, and 17% on two anxiolytic drugs. Furthermore, 40% used hypnotic medications. Use of anxiolytics has been reported in about 30% of inpatients with EUPD (Bridler *et al.* 2015, Bender *et al.* 2006), nonetheless, a study from Italy (Paolini *et al.* 2017) reported that 85.2% of their inpatients were prescribed benzodiazepine anxiolytics and hypnotics.

26.0% of our patients were also on MS's; 24.0% on anticonvulsants and 2.0% on lithium. Corresponding to our results, Bridler *et al.* 2015 reported use of anticonvulsants in 33% and lithium in 4% of people with EUPD. Likewise, Bender *et al.* 2006 reported use of MS's in 27% of their subjects with EUPD. Nonetheless, Paolini *et al.* 2017 stated higher, 70% use of MS's in their inpatients with EUPD. Despite their frequent use, there are opposing interpretations on efficacy of MS's in the management of EUPD. Earlier evidence, supported use of MS's for management of anger and depressive symptomatology. However, Hancock-Johnson *et al.* 2017 in a systematic review of 15 pharmacological studies challenged the efficacy of MS's implying there is little evidence to support use of these drugs in patients with EUPD. Furthermore, Crawford *et al.* 2018 in the RCT of up to 200 mg of lamotrigine per day compared to placebo in a cohort of 196 individuals with EUPD concluded that lamotrigine was not clinically effective. Moreover, recent evaluation of seven RCT studies found no effect of lamotrigine, a common MS prescribed to people with EUPD (Stoffers-Winterling *et al.* 2020).

Whilst most of our patients received pharmacotherapy, only 43.2% received structured DBT. This could be associated with several factors; firstly, most patients with EUPD struggle to engage with psychological interventions and view pharmacological interventions as more effective and rather a 'quick fix'. Secondly, from the service-provider point of view, most psychologists would refuse to accept a patient with EUPD who is suicidal or uses alcohol or other substances. Besides, limited psychological therapies could reflect inadequate services. Psychotherapies are the treatment of choice for people with EUPD (NICE, 2009, Verheul & Herbrink, 2007). Psychodynamic psychological interventions such as mentalisation-based therapy (MBT) and transference-focused therapy (TFT) and cognitive-behavioural based therapies such as dialectical–based therapy (DBT) and scheme-focused therapies (SFT) have been shown to be effective, particularly, in reducing the self-destructive behaviour (Zanarini, 2009). However, recent opinions on the efficacy of psychological therapies are not as optimistic. Stoffers, *et al.* 2012 in a systematic review of twenty-eight studies involving a total of 1804 participants with EUPD reported psychotherapies, such as DBT, MBT and TFT beneficial, nonetheless, they concluded none of the therapies had a robust evidence base, and raised concerns about the quality of the individual studies. In a literature review of sixteen randomised clinical trials, analysing effects of DBT, SFT cognitive behavioural therapy (CBT) and manual-assisted cognitive therapy, Marques *et al.* 2017 reported that from all the above psychological interventions, especially DBT and SFT showed beneficial effects by reducing the severity and frequency of self-harm, and by improving the overall social, interpersonal and global functioning. In a similar literature review of twenty studies with 1375 participants, Oud *et al.* 2018 concluded that DBT and MBT and TFT compared to treatment as usual (TAU) were effective in reducing overall symptomatology and severity of EUPD, however, their effects were small to medium. Similarly, Cristea *et al.* 2017 in a Cochrane review of thirty-three trials with 2256 participants, come to assumption that psychotherapies, especially DBT and psychodynamic approaches were effective for EUPD symptoms, nonetheless, these effects were small, inflated by risk of bias and publication bias, and predominantly unstable in follow-up. In a most recent Cochrane review of 75 RCT with 4507 participants, comparing sixteen different psychological interventions with TAU, Storebø *et al.* 2020, found no evidence of a difference in effects estimates between the different types of psychological therapies. Though, compared to TAU, DBT was more effective in the reduction of EUPD severity, self-harm and psychosocial functioning and, for MBT, more efficacious on self-harm, suicidality and depression. Nonetheless, the authors of the study expressed an opinion that these findings were based on low quality evidence.

CONCLUSIONS

People with EUPD tend to represent one of the most challenging groups of patients, with multiple needs and complex presentation. Polypharmacy and co-morbidities are very widespread. They are one of the most

recurrent clients of emergency services, requiring urgent medical care.

No psychotropic drug is specifically licensed for EUPD, and the choice of medications is largely based upon the predominant axis-I comorbid condition17. Opinion from the United States (APA, 2001, APA, 2005) and Europe (Lieb *et al.* 2010) recommend psychotherapy as the principal treatment for this disorder, nonetheless, they also support a symptom-targeted pharmacotherapy. The NICE agrees with the use of psychotherapy, but is against the use of psychotropic medication for individual symptoms of EUPD. In addition, where there are depressive or psychotic symptoms, or affective instability, that fall short of diagnostic criteria for mental disorder, the use of psychotropic drugs is largely 'off-label'. Prescribing off-label places additional responsibilities on the prescriber and may increase liability if there are adverse effects. The Royal College of Psychiatrists recommends that the patient be informed that the drug prescribed is not licensed for the indication for which it is being used, and the reason for its use and potential side effects fully explained (Baldwin & Kosky, 2007).

There are several factors why individuals with EUPD are prescribed multiple medications despite their limited evidence. One of the major issues is the fact that patients with EUPD have several crises, and each crisis can be very distressing. At times of crisis, few patients would engage in psychotherapies, and hence both patients and professionals are left with no other alternative than to use pharmacotherapy. Hence each time they are presented at the crisis assessment settings or admitted to hospital; they are prescribed a new medication. The most likely reason for this seems to be that patients and their relatives but also prescribers assume that previous recommended medicines were ineffective; hence, to enhance their efficacy or/and prevent further deterioration, they prescribe an additional drug. Besides, there are many clinicians, who believe pharmacological therapies are effective and should be prescribed for individual symptoms of EUPD. On the contrary there are clinicians prescribing medication not because they are convinced of their efficacy, nonetheless feel pressurised by patients and their families as they fear complaints and negative criticism. Likewise, lack of specialised services for people with personality disorders, and the absence of the availability of psychological services is another factor for polypharmacy.

The introduction of specialised services for people with EUPD that will offer individualised and trauma-focused psychotherapies is one of the most effective ways to tackle the issue of medication over-prescription. Besides it will also lead to effective management these individuals in the community, reduce their length of admission and overall improve the quality of life for people with personality disorders.

In the light of existing practice and evidence from research, we believe current NICE guidance of EUPD is out of date and not fit for purpose. The future NICE guidance should revise the pharmacotherapy of EUPD and should consider symptom-targeted pharmacotherapy. Moreover, the new guidance would also need to expand beyond DBT and should consider other methods of psychological therapies such as MBT, TFT, SFT and eye-movement desensitization and reprocessing therapy.

We believe the term EUPD causes stigma to patients, does not reflect the true nature, gravity and psychopathology of this illness. The is a large body of evidence demonstrating that people with EUPD experience stigma because of their illness, which in some cases limits their access to health services, quality of their care, and their potential to achieve optimal health and well-being (Klein, *et al.* 2021). The term borderline personality disorder is out of date, incorrect and too simplistic to reflect the true nature, gravity and psychopathology of this compounded syndrome. Instead, enduring personality changes, ICD 10 F62, or tardive and complex PTSD, should be considered. We warmly welcome the ICD 11 diagnosis of Complex posttraumatic disorder, 6B41 that better captures symptoms of the EUPD, is not stigmatising, and most of all considers the traumatic nature of this condition (WHO, 2020).

ACKNOWLEDGEMENT

The authors acknowledge the help of the Lincolnshire NHS Partnership Trust and colleagues including Dr Timothy Carlton, Dr Joseph Verghese and Dr Grahame Worwood.

GOVERNANCE, ETHICS AND DATA PROTECTION

Using the Health Research Authority (HRA) Decision Tool, this work is not defined as research. It does not therefore require HRA review (or NHS ethics review). Only employees of LPFT have retrieved data and this is for quality purposes only (evaluation/audit/service review). The work is not research (which is a secondary use of data) and consent has not therefore been required. No personal identifiable information has been shared outside of the Trust. All information within this publication is anonymous.

REFERENCES

1 Aguglia A, Serafini G, Nebbia J, Salvi V, Martinotti G, Corbo M, Signorelli MS, Mineo L, Mencacci C, Di Sciascio G, Biggio G, Aguglia E, Amore M. Off-Label Use of Second-Generation Antipsychotics in Borderline Personality Disorder: A Survey of Italian Psychiatrists. J Pers Disord. 2019 Oct **14**: 1–15. doi: 10.1521/pedi_2019_33_445. Epub ahead of print. PMID: 31609189.

2 American Psychiatric Association Practice Guidelines. Practice guideline for the treatment of patients with borderline personality disorder. American Psychiatric Association. Am J Psychiatry. 2001 Oct; **158**(10 Suppl): 1–52. PMID: 11665545.

3 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. 5th ed. Arlington, VA: American Psychiatric Association; 2013. **663**: 6.

4 American Psychiatric Association. Practice Guidelines for the Treatment of Patients with Borderline Personality Disorder: Guideline Watch. 2005. Washington, DC.

5 Baldwin, D., & Kosky, N. Off-label prescribing in psychiatric practice. Advances in Psychiatric Treatment. 2007; **13**(6): 414–422. doi:10.1192/apt.bp.107.004184.

6 Bateman A, Fonagy P. Effectiveness of partial hospitalization in the treatment of borderline personality disorder: a randomized controlled trial. Am J Psychiatry. 1999 Oct; **156**(10): 1563–9. doi: 10.1176/ajp.156.10.1563. PMID: 10518167.

7 Bender DS, Skodol AE, Pagano ME, Dyck IR, Grilo CM, Shea MT, Sanislow CA, Zanarini MC, Yen S, McGlashan TH, Gunderson JG. Prospective assessment of treatment use by patients with personality disorders. Psychiatr Serv. 2006 Feb; **57**(2): 254–7. doi: 10.1176/appi.ps.57.2.254. PMID: 16452705; PMCID: PMC2705621.

8 Bozzatello P, Rocca P, De Rosa ML, Bellino S. Current and emerging medications for borderline personality disorder: is pharmacotherapy alone enough? Expert Opin Pharmacother. 2020 Jan; **21**(1): 47–61. doi: 10.1080/14656566.2019.1686482. Epub 2019 Nov 6. PMID: 31693423.

9 Bridler R, Häberle A, Müller ST, Cattapan K, Grohmann R, Toto S, Kasper S, Greil W. Psychopharmacological treatment of 2195 in-patients with borderline personality disorder: A comparison with other psychiatric disorders. Eur Neuropsychopharmacol. 2015 Jun; **25**(6): 763–72. doi: 10.1016/j.euroneuro.2015.03.017. Epub 2015 Apr 11. PMID: 25907249.

10 Bringmann SA, Maidman PE. De diagnose van autismespectrum-stoornis bij vrouwen met suïcidaliteit en kenmerken van een borderline-persoonlijkheidsstoornis [Diagnosis of autism spectrum disorder in women with suicidality and characteristics of borderline personality disorder]. Tijdschr Psychiatr. 2019; **61**(2): 121–125. Dutch. PMID: 30793273.

11 Brodsky BS, Malone KM, Ellis SP, Dulit RA, Mann JJ. Characteristics of borderline personality disorder associated with suicidal behavior. Am J Psychiatry. 1997 Dec; **154**(12): 1715–9. doi: 10.1176/ajp.154.12.1715. PMID: 9396951.

12 Cailhol L, Thalamas C, Garrido C, Birmes P, Lapeyre-Mestre M. Utilisation des services de soin par les patients hospitalisés, présentant un trouble de personnalité borderline en Midi-Pyrénées [Mental health service utilization among borderline personality disorder patients inpatient]. Encephale. 2015 Apr; **41**(2): 115–22. French. doi: 10.1016/j.encep.2014.10.008. Epub 2014 Dec 17. PMID: 25526809.

13 Canadian Agency for Drugs and Technologies in Health. Aripiprazole for Borderline Personality Disorder: A Review of the Clinical Effectiveness [Internet]. Ottawa (ON); 2017 Feb 3. PMID: 28825781.

14 Carrasco JL, Palomares N, Marsá MD. Effectiveness and tolerability of long-acting intramuscular risperidone as adjuvant treatment in refractory borderline personality disorder. Psychopharmacology (Berl). 2012 Nov; **224**(2): 347–8. doi: 10.1007/s00213-012-2880-0. Epub 2012 Oct 11. PMID: 23052570.

15 Chabrol H, Raynal P. The co-occurrence of autistic traits and borderline personality disorder traits is associated to increased suicidal ideation in nonclinical young adults. Compr Psychiatry. 2018 Apr; **82**: 141–143. doi: 10.1016/j.comppsych.2018.02.006. Epub 2018 Feb 15. PMID: 29486417.

16 Cheng AT, Mann AH, Chan KA. Personality disorder and suicide: a case-control study. Br J Psy 1997; **170**: 441–6.

17 Crawford MJ, Sanatinia R, Barrett B, Cunningham G, Dale O, Ganguli P, Lawrence-Smith G, Leeson VC, Lemonsky F, Lykomitrou-Matthews G, Montgomery A, Morriss R, Munjiza J, Paton C, Skorodzien I, Singh V, Tan W, Tyrer P, Reilly JG. Lamotrigine for people with borderline personality disorder: a RCT. Health Technol Assess. 2018 Apr; **22**(17): 1–68. doi: 10.3310/hta22170. PMID: 29651981; PMCID: PMC5925438.

18 Cristea IA, Gentili C, Cotet CD, Palomba D, Barbui C, Cuijpers P. Efficacy of Psychotherapies for Borderline Personality Disorder: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2017 Apr 1; **74**(4): 319–328. doi: 10.1001/jamapsychiatry.2016.4287. PMID: 28249086.

19 de Aquino Ferreira LF, Queiroz Pereira FH, Neri Benevides AML, and Aguiar Melo MC. Borderline personality disorder and sexual abuse: a systematic review. Psychiatry Res. 2018 Apr; **262**: 70–77.

20 Díaz-Marsá M, Galian M, Montes A, Fernández R, Arza R, López-Ibor J, Carrasco J. Risperidona intramuscular de acción prolongada en el trastorno límite de la personalidad resistente al tratamiento. Un estudio piloto [Long-acting injectable risperidone in treatment resistant borderline personality disorder. A small series report]. Actas Esp Psiquiatr. 2008 Mar-Apr; **36**(2): 70–4. Spanish. PMID: 18365787.

21 Doering S. Borderline Personality Disorder in Patients with Medical Illness: A Review of Assessment, Prevalence, and Treatment Options. Psychosom Med. 2019 Sep; **81**(7): 584–594. doi: 10.1097/PSY.0000000000000724. PMID: 31232916.

22 Dudas RB, Lovejoy C, Cassidy S, Allison C, Smith P, Baron-Cohen S. The overlap between autistic spectrum conditions and borderline personality disorder. PLoS One. 2017 Sep 8;12(9): e0184447. doi: 10.1371/journal.pone.0184447. Erratum in: PLoS One. 2018 Jan 2; **13**(1): e0190727. PMID: 28886113; PMCID: PMC5590952.

23 Fok ML, Chang CK, Broadbent M, Stewart R, Moran P. General hospital admission rates in people diagnosed with personality disorder. Acta Psychiatr Scand. 2019 Mar; **139**(3): 248–255. doi: 10.1111/acps.13004. PMID: 30689214.

24 Gabbard GO. Mind, brain, and personality disorders. Am J Psychiatry; 2005; **162**: 648–55.

25 Gunderson JG, Herpertz SC, Skodol AE, Torgersen S, Zanarini MC. Borderline personality disorder. Nat Rev Dis Primers. 2018 May 24; **4**: 18029. doi: 10.1038/nrdp.2018.29. PMID: 29795363.

26 Gvion Y, Levi-Belz Y. Serious Suicide Attempts: Systematic Review of Psychological Risk Factors. Front Psychiatry. 2018 Mar 7; **9**: 56. doi: 10.3389/fpsyt.2018.00056. PMID: 29563886; PMCID: PMC5845877.

27 Hancock-Johnson E, Griffiths C, Picchioni M. A Focused Systematic Review of Pharmacological Treatment for Borderline Personality Disorder. CNS Drugs. 2017 May; **31**(5): 345–356. doi: 10.1007/s40263-017-0425-0. PMID: 28353141.

28 Hughes K, Bellis MA, Hardcastle KA, Sethi D, Butchart A, Mikton C, Jones L, Dunne MP. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. Lancet Public Health. 2017 Aug; **2**(8): e356–e366. doi: 10.1016/S2468-2667(17)30118-4. Epub 2017 Jul 31. PMID: 29253477.

29 Hull JW, Yeomans F, Clarkin J, Li C, Goodman G. Factors associated with multiple hospitalizations of patients with borderline personality disorder. Psychiatr Serv. 1996 Jun; **47**(6): 638–41. doi: 10.1176/ps.47.6.638. PMID: 8726493.

30 Kaess, M, Herpertz SC, Plener, PL, and Schmahl C. Borderline personality disorder. Z Kinder Jugenpsychiatr Psychother. 2017 Sep; **45**(5): 403–13.

31 Kaplan C, Tarlow N, Stewart JG, Aguirre B, Galen G, Auerbach RP. Borderline personality disorder in youth: The prospective impact of child abuse on non-suicidal self-injury and suicidality. Compr Psychiatry. 2016 Nov; **71**: 86–94. doi: 10.1016/j.comppsych.2016.08.016. Epub 2016 Sep 5. PMID: 27649322; PMCID: PMC5201161.

32 Klein P, Fairweather AK, Lawn S, Stallman HM, Cammell P. Structural stigma and its impact on healthcare for consumers with borderline personality disorder: protocol for a scoping review. Syst Rev. 2021 Jan 11; **10**(1): 23. doi: 10.1186/s13643-021-01580-1. PMID: 33423674; PMCID: PMC7798332.

33 Koch M, Vyssoki B, Wippel A, Gmeiner A, Pruckner N, Oberndorfer R. Deskriptive Untersuchung der stationären Aufenthalte von Patienten mit emotional instabiler Persönlichkeitsstörung in Österreich zwischen 2001 und 2016 mit besonderer Berücksichtigung von Alter, Geschlecht und Aufenthaltsdauer [Descriptive examination of inpatient stays of patients with emotionally unstable personality disorder in Austria between 2001 and 2016 with special consideration of age, gender and length of stay]. Neuropsychiatr. 2019 Dec; **33**(4): 191–197. German. doi: 10.1007/s40211-019-0308-3. Epub 2019 Apr 2. PMID: 30941735.

34 Lieb K, Völlm B, Rücker G, Timmer A, Stoffers JM. Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. Br J Psychiatry; 2010; **196**: 4–12.

35 Marques S, Barrocas D, Rijo D. Intervenções Psicológicas na Perturbação Borderline da Personalidade: Uma Revisão das Terapias de Base Cognitivo-Comportamental [Psychological Treatments for Borderline Personality Disorder: A Review of Cognitive-Behavioral Oriented Therapies]. Acta Med Port. 2017 Apr 28; **30**(4): 307–319. Portuguese. doi: 10.20344/amp.7469. Epub 2017 Apr 28. PMID: 28555557.

36 Martínez JS, Caballero AR. Long-Acting Aripiprazole in Comorbid Bipolar Disorder and Borderline Personality Disorder and Substance Abuse. J Clin Psychopharmacol. 2017 Apr;37(2):266-267. doi: 10.1097/JCP.0000000000000653. PMID: 28145998.

37 McCormick B, Blum N, Hansel R, Franklin JA, St John D, Pfohl B, Allen J, Black DW. Relationship of sex to symptom severity, psychiatric comorbidity, and health care utilization in 163 subjects with borderline personality disorder. Compr Psychiatry. 2007 Sep-Oct; **48**(5): 406–12. doi: 10.1016/j.comppsych.2007.05.005. Epub 2007 Jul 5. PMID: 17707247.

38 McCrone, P, Dhanasiri, S, Patel, A. (2008) Paying the price: the cost of mental health care in England to 2026. London: King's Fund. Available at: http://www.kingsfund.org.uk/sites/files/kf/Paying-the-Price-the-cost-of-mental-health-care-England-2026-McCrone-Dhanasiri-Patel-Knapp-Lawton-Smith-Kings-Fund-May-2008_0.pdf (accessed 11 July 2013).

39 Mercer D, Douglass AB, Links PS. Meta-analyses of mood stabilizers, antidepressants and antipsychotics in the treatment of borderline personality disorder: effectiveness for depression and anger symptoms. J Pers Disord. 2009 Apr; **23**(2): 156–74. doi: 10.1521/pedi.2009.23.2.156. PMID: 19379093.

40 National Institute for Health and Clinical Excellence. Borderline personality disorder. Treatment and management. 2009. NICE clinical guideline 78.

41 Oldham JM. Borderline personality disorder and suicidality. Am J Psy 2006; **163**: 20–6.

42 Oldham, JM. Guideline Watch: Practice Guideline for the Treatment of Patients with Borderline Personality Disorder. Arlington, VA: American Psychiatric Association. 2005; 1–9.

43 Oud M, Arntz A, Hermens ML, Verhoef R, Kendall T. Specialized psychotherapies for adults with borderline personality disorder: A systematic review and meta-analysis. Aust N Z J Psychiatry. 2018 Oct; **52**(10): 949–961. doi: 10.1177/0004867418791257. Epub 2018 Aug 9. PMID: 30091375; PMCID: PMC6151959.

44 Palomares N, Montes A, Díaz-Marsá M, Carrasco JL. Effectiveness of long-acting paliperidone palmitate in borderline personality disorder. Int Clin Psychopharmacol. 2015 Nov; **30**(6): 338–41. doi: 10.1097/YIC.0000000000000095. PMID: 26230268.

45 Paolini E, Mezzetti FA, Pierri F, Moretti P. Pharmacological treatment of borderline personality disorder: a retrospective observational study at inpatient unit in Italy. Int J Psychiatry Clin Pract. 2017 Mar; **21**(1): 75–79. doi: 10.1080/13651501.2016.1235202. Epub 2016 Sep 27. PMID: 27669762.

46 Paris Joel. The nature of borderline personality disorder: multiple dimensions, multiple symptoms, but one category. J Pers Disord; 2007; **21**: 457–73.

47 Paris, Joel. Commentary on the American Psychiatric Association guidelines for the treatment of borderline personality disorder: evidence-based psychiatry and the quality of evidence. Journal of Personality Disorders, 2002; **16**: 130–134.

48 Pascual JC, Martín-Blanco A, Soler J, Ferrer A, Tiana T, Alvarez E, Pérez V. A naturalistic study of changes in pharmacological prescription for borderline personality disorder in clinical practice: from APA to NICE guidelines. Int Clin Psychopharmacol. 2010 Nov; **25**(6): 349–55. doi: 10.1097/YIC.0b013e32833e23ed. PMID: 20838221.

49 Patel RS, Manikkara G, Chopra A. Bipolar Disorder and Comorbid Borderline Personality Disorder: Patient Characteristics and Outcomes in US Hospitals. Medicina (Kaunas). 2019 Jan 14; **55**(1): 13. doi: 10.3390/medicina55010013. PMID: 30646620; PMCID: PMC6358827.

50 Porter C, Palmier-Claus J, Branitsky A, Mansell W, Warwick H, Varese F. Childhood adversity and borderline personality disorder: a meta-analysis. Acta Psychiatr Scand. 2020 Jan; **141**(1): 6–20. doi: 10.1111/acps.13118. Epub 2019 Nov 18. PMID: 31630389.

51 Rendu A, Moran P, Patel A, Knapp M, Mann A. Economic impact of personality disorders in UK primary care attenders. Br J Psychiatry. 2002 Jul; **181**: 62–6. doi: 10.1192/bjp.181.1.62. PMID: 12091265.

52 Riffer F, Farkas M, Streibl L, Kaiser E, Sprung M. Psychopharmacological treatment of patients with borderline personality disorder: comparing data from routine clinical care with recommended guidelines. Int J Psychiatry Clin Pract. 2019 Sep; **23**(3): 178–188. doi: 10.1080/13651501.2019.1576904. Epub 2019 May 29. PMID: 31140337.

53 Sher L, Rutter SB, New AS, Siever LJ, Hazlett EA. Gender differences and similarities in aggression, suicidal behaviour, and psychiatric comorbidity in borderline personality disorder. Acta Psychiatr Scand. 2019 Feb; **139**(2): 145–153. doi: 10.1111/acps.12981. Epub 2018 Nov 12. PMID: 30353921.

54 Soeteman DI, Hakkaart-van Roijen L, Verheul R, Busschbach JJ. The economic burden of personality disorders in mental health care. J Clin Psychiatry. 2008 Feb; **69**(2): 259–65. doi: 10.4088/jcp. v69n0212. PMID: 18363454.

55 Soloff PH, Lynch KG, Kelly TM. Childhood abuse as a risk factor for suicidal behavior in borderline personality disorder. J Pers Disord. 2002 Jun; **16**(3): 201–14. doi: 10.1521/pedi.16.3.201.22542. PMID: 12136678.

56 Stoffers JM, Völlm BA, Rücker G, Timmer A, Huband N, Lieb K. Psychological therapies for people with borderline personality disorder. Cochrane Database Syst Rev. 2012 Aug 15; **2012**(8): CD005652. doi: 10.1002/14651858.CD005652.pub2. PMID: 22895952; PMCID: PMC6481907.

57 Stoffers-Winterling J, Storebø OJ, Lieb K. Pharmacotherapy for Borderline Personality Disorder: An Update of Published, Unpublished and Ongoing Studies. Curr Psychiatry Rep. 2020 Jun 5; **22**(8): 37. doi: 10.1007/s11920-020-01164-1. PMID: 32504127; PMCID: PMC7275094.

58 Storebø OJ, Stoffers-Winterling JM, Völlm BA, Kongerslev MT, Mattivi JT, Jørgensen MS, Faltinsen E, Todorovac A, Sales CP, Callesen HE, Lieb K, Simonsen E. Psychological therapies for people with borderline personality disorder. Cochrane Database Syst Rev. 2020 May 4; **5**(5): CD012955. doi: 10.1002/14651858.CD012955.pub2. PMID: 32368793; PMCID: PMC7199382.

59 Tadić A, Wagner S, Hoch J, Başkaya O, von Cube R, Skaletz C, Lieb K, Dahmen N. Gender differences in axis I and axis II comorbidity in patients with borderline personality disorder. Psychopathology. 2009; **42**(4): 257–63. doi: 10.1159/000224149. Epub 2009 Jun 12. PMID: 19521142.

60 Temes CM, Frankenburg FR, Fitzmaurice GM, Zanarini MC. Deaths by Suicide and Other Causes Among Patients with Borderline Personality Disorder and Personality-Disordered Comparison Subjects Over 24 Years of Prospective Follow-Up. J Clin Psychiatry. 2019 Jan 22; **80**(1): 18m12436. doi: 10.4088/JCP.18m12436. PMID: 30688417.

61 Timäus C, Meiser M, Bandelow B, Engel KR, Paschke AM, Wiltfang J, Wedekind D. Pharmacotherapy of borderline personality disorder: what has changed over two decades? A retrospective evaluation of clinical practice. BMC Psychiatry. 2019 Dec 12; **19**(1): 393. doi: 10.1186/s12888-019-2377-z. PMID: 31830934; PMCID: PMC6909459.

62 Torgersen S, Czajkowski N, Jacobson K, Reichborn-Kjennerud T, Røysamb E, Neale MC, Kendler KS. Dimensional representations of DSM-IV cluster B personality disorders in a population-based sample of Norwegian twins: a multivariate study. Psychol Med:2008; **38**: 1617–25.
63 Verheul R, Herbrink M. The efficacy of various modalities of psychotherapy for personality disorders: a systematic review of the evidence and clinical recommendations. Int Rev Psychiatry. 2007 Feb; **19**(1): 25–38. doi: 10.1080/09540260601095399. PMID: 17365156.
64 Vita A, De Peri L, Sacchetti E. Antipsychotics, antidepressants, anticonvulsants, and placebo on the symptom dimensions of borderline personality disorder: a meta-analysis of randomized controlled and open-label trials. J Clin Psychopharmacol. 2011 Oct; **31**(5): 613–24. doi: 10.1097/JCP.0b013e31822c1636. PMID: 21869691.
65 Wasylyshen A, Williams AM. Second-generation antipsychotic use in borderline personality disorder: What are we targeting? Ment Health Clin. 2016 Mar 8;6(2):82-88. doi: 10.9740/mhc.2016.03.82. PMID: 29955452; PMCID: PMC6007581.
66 Wetterborg D, Långström N, Andersson G, Enebrink P. Borderline personality disorder: Prevalence and psychiatric comorbidity among male offenders on probation in Sweden. Compr Psychiatry. 2015 Oct; **62**: 63–70. doi: 10.1016/j.comppsych.2015.06.014. Epub 2015 Jun 26. PMID: 26343468.
67 Wieland J, Van Den Brink A, Zitman FG. The prevalence of personality disorders in psychiatric outpatients with borderline intellectual functioning: Comparison with outpatients from regular mental health care and outpatients with mild intellectual disabilities. Nord J Psychiatry. 2015; **69**(8): 599–604. doi: 10.3109/08039488.2015.1025836. Epub 2015 Apr 2. PMID: 25832758.
68 Wong MT, Tye C. Low hospital inpatient readmission rate in patients with borderline personality disorder: a naturalistic study at Southern Health, Victoria, Australia. Aust N Z J Psychiatry. 2005 Jul; **39**(7): 607–11. doi: 10.1080/j.1440-1614.2005.01633. x. PMID: 15996142.
69 World Health Organization. ICD 11 – Mortality and Morbidity Statistics (version:9/2020). icd.who.int.
70 World Health Organization. The ICD-10 classification of mental and behavioural disorders. Clinical descriptions and diagnostic guidelines. World Health Organization, Geneva, 1992.
71 Yen S, Peters JR, Nishar S, Grilo CM, Sanislow CA, Shea MT, Zanarini MC, McGlashan TH, Morey LC, Skodol AE. Association of Borderline Personality Disorder Criteria with Suicide Attempts: Findings from the Collaborative Longitudinal Study of Personality Disorders Over 10 Years of Follow-up. JAMA Psychiatry. 2021 Feb 1; **78**(2): 187–194. doi: 10.1001/jamapsychiatry.2020.3598. PMID: 33206138; PMCID: PMC7675214.
72 Yen, S. & Shea, MT. Recent developments in research of trauma and personality disorder. Current Psychiatry Reports, 2001; **3**: 52–58.
73 Zanarini MC, Frankenburg FR, Hennen J, Reich DB, Silk KR. Prediction of the 10-year course of borderline personality disorder. Am J Psychiatry. 2006 May; **163**(5): 827–32. doi: 10.1176/ajp.2006.163.5.827. PMID: 16648323.
74 Zanarini MC. Psychotherapy of borderline personality disorder. Acta Psychiatr Scand. 2009 Nov; **120**(5): 373–7. doi: 10.1111/j.1600-0447.2009.01448. x. PMID: 19807718; PMCID: PMC3876885.
75 Zimmerman M, Mattia JI. Axis I diagnostic comorbidity and borderline personality disorder. Compr Psychiatry. 1999 Jul-Aug; **40**(4): 245–52.